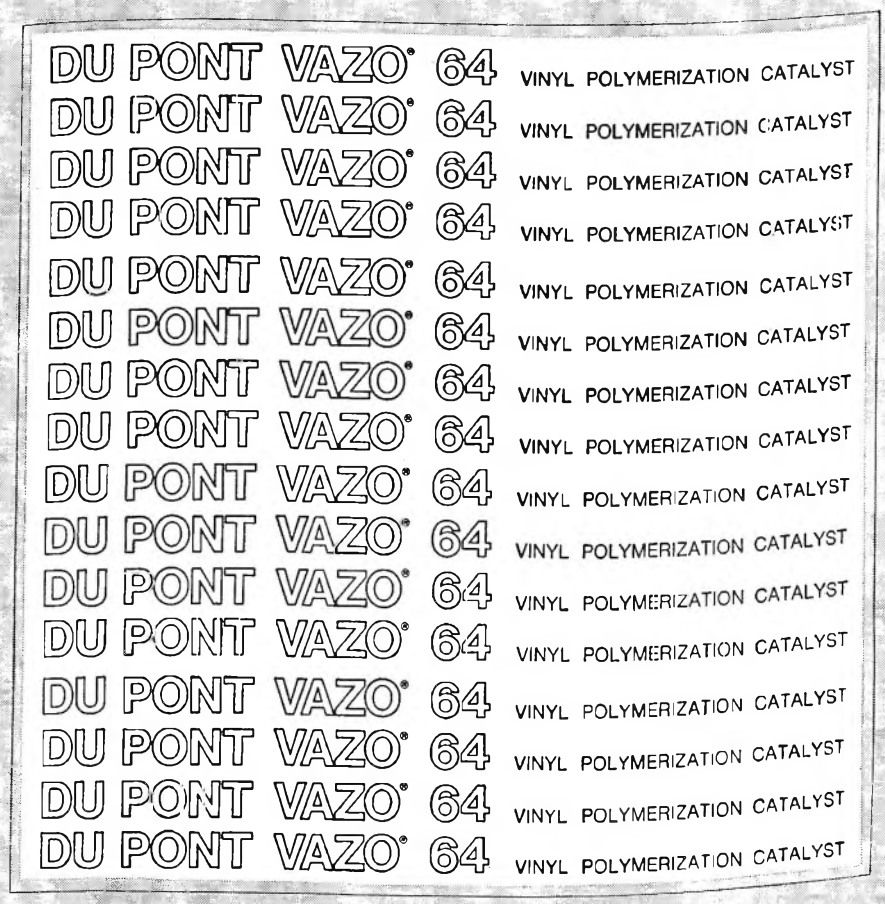
VOLUME 35 MAY 1970 NUMBER 5 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY

Send for your free copy...

A BIBLIOGRAPHIC REVIEW OF 2,2'-AZOBIS(ISOBUTYRONITRILE)



...we'll also include a product bulletin on VAZO® 64.

Send coupon or write to Du Pont, Room 8710, Wilmington, DE. 19898

DuPont Company
Room 8710
Wilmington, DE. 19898

☐ Please send me your bibliography and product information bulletin on DuPont VAZO 64

☐ Have a representative call

Name_____

Company_____

Street_____

City_____ State_____ Zip_____

Telephone_____

DU PONT VAZO 64

REG. U.S. PAT. OFF.

*REG. U.S. PAT. OFF.

THE JOURNAL OF Organic Chemistry

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

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

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

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

Business and Subscription Information

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

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

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

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

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

Subscription rates for 1970: $16.00 per volume to members of the ACS and $32.00 per volume to all others. Add $4.50 per subscription for Canada and countries belonging to the Postal Union, and $5.50 for all other countries.

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

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

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

PUT THE TRI·SIL® FAMILY TO WORK IN YOUR LAB

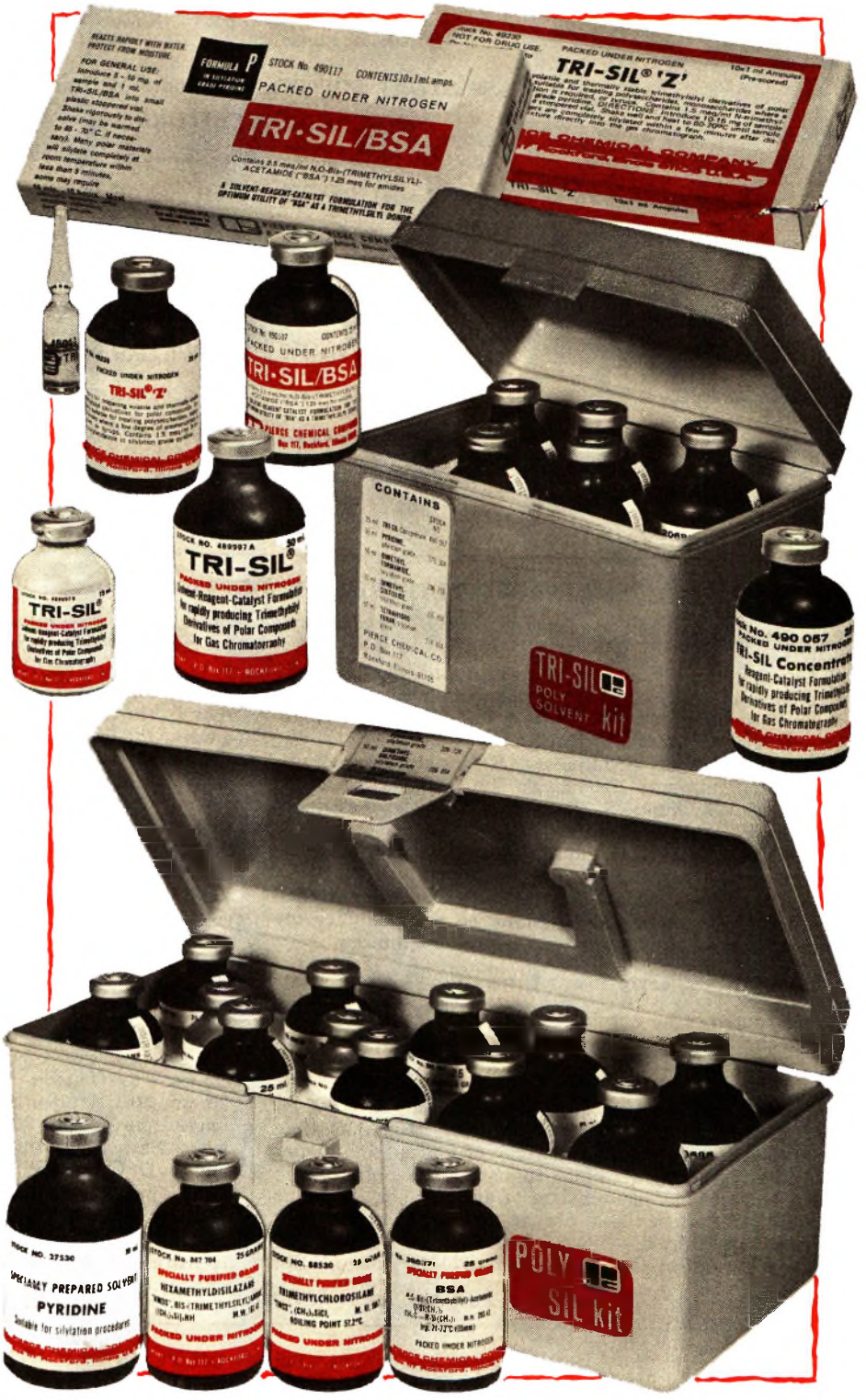
This accomplished family of reagents has eased the problems of thousands engaged in research, quality control, process monitoring and other fields of investigation and analysis.

By quickly forming volatile and thermally stable derivatives of polar compounds these reagents make light work and tight determinations of formerly difficult gas phase analyses.

In fact, quite a few analytical problems that were practically impossible before have been resolved by silylation of samples preparatory to GLC or Mass Spec. Many of these procedures are now routine, practical and economical.

We have just published a 60 page "Handbook of Silylation" that is a gold mine of information on silylation and other special techniques of gas phase analysis. It contains a wealth of practical suggestions, methods, references, data on reagents and accessories with current prices.

"Handbook of Silylation" is free, but you wouldn't take anything for your copy after you've looked it over. If you haven't received yours yet drop use a note—today.



THE JOURNAL OF Organic Chemistry

Volume 35

MAY–AUGUST 1970

(Pages 1241–2848)

THE JOURNAL OF Organic Chemistry®

VOLUME 35, NUMBER 5 MAY 1970

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 35, NUMBER 5

MAY 1970

Studies on the Bromination and Acetylation of the Isomeric Cyclooctadienes[1]

SUNG MOON AND CHARLES R. GANZ[2]

Department of Chemistry, Adelphi University, Garden City, New York 11530

Received August 18, 1969

Allylic bromination and subsequent silver acetate acetylation of 1,3-, 1,4-, and 1,5-cyclooctadiene (COD) were studied. 1,3-COD yielded bicyclo[3.3.0]oct-3-en-2-yl acetate in addition to the expected 2,4-cyclooctadien-1-yl acetate. The latter, as well as its alcohol and ketone derivatives, was found to undergo facile 1,5-hydrogen shifts under thermal conditions. 1,4-COD afforded the same bromide and acetate products as did 1,3-COD. This points to a common intermediate during bromination. 1,5-COD led to nonrearranged as well as allylic rearrangement products. Possible mechanisms for the various conversions are discussed.

In connection with projected studies, it was of interest to us to prepare various bicyclo[4.2.0]oct-7-en-2-yl derivatives. Cope and coworkers[3] have reported that photolysis of 2,4-cyclooctadien-1-yl acetate (**1**) provides a convenient route to bicyclo[4.2.0]oct-7-en-2-yl acetate. This reaction appeared to offer a good means of entry into the systems desired in our work.

The appearance of anomalous results upon preparing **1** by Cope's procedure prompted us to reinvestigate the reaction pathways leading to **1**. Described below are the results of this work as well as an extension of this research to include the corresponding reactions of the isomeric 1,4- and 1,5-cyclooctadiene.

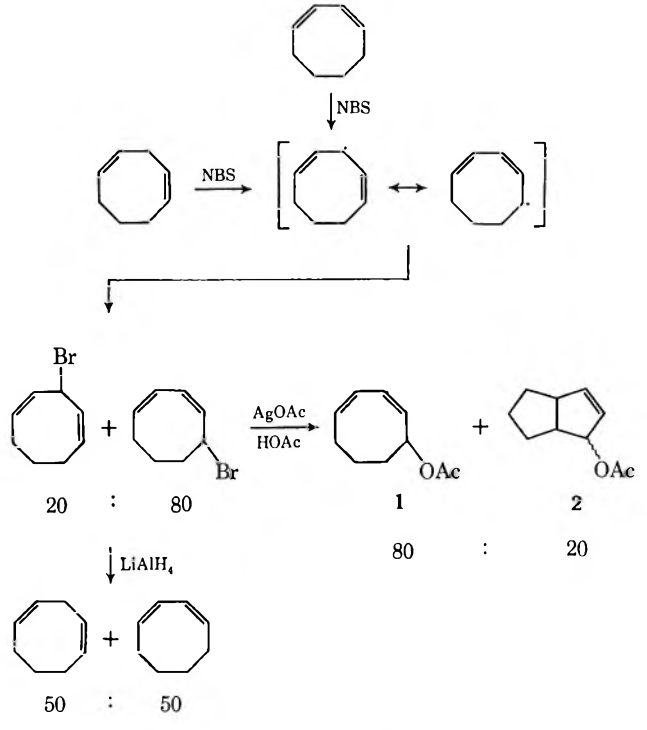
Results and Discussion

The reaction of 1,3-cyclooctadiene (COD) with N-bromosuccinimide followed by treatment of the bromination product with silver acetate in acetic acid gave two products. Gas chromatography (glpc) showed them to be in the ratio of 20:80 (Scheme I).

The major product was assigned the structure **1** by virtue of its uv, ir, and nmr spectra. The minor product was shown by its ir and nmr spectra to also be an unsaturated acetate. The absence of uv absorption above 210 mμ, however, indicated that it did not contain a conjugated diene chromophore.

The acetate mixture was subjected to catalytic hydrogenation to determine whether the minor product resulted from a simple double-bond reorganization or from a skeletal rearrangement. The appearance of two saturated acetates in the hydrogenation product indicated that two-carbon skeletons were present. The one present in the greater amount was shown to be cyclooctyl acetate by comparison of its spectral properties with those of an authentic sample.

SCHEME I



As will be subsequently described, the formation of the rearranged product was found to take place during the step involving the carbonium ion (acetylation). Inspection of models of 1,3-COD suggested that inter-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Petroleum Research Fund Fellow, 1968–1969.

(3) A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *J. Amer. Chem. Soc.*, **84**, 4865 (1962).

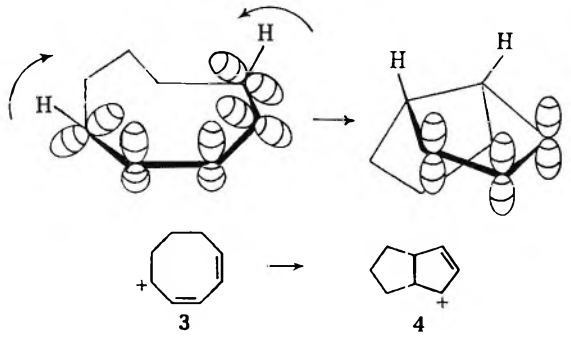


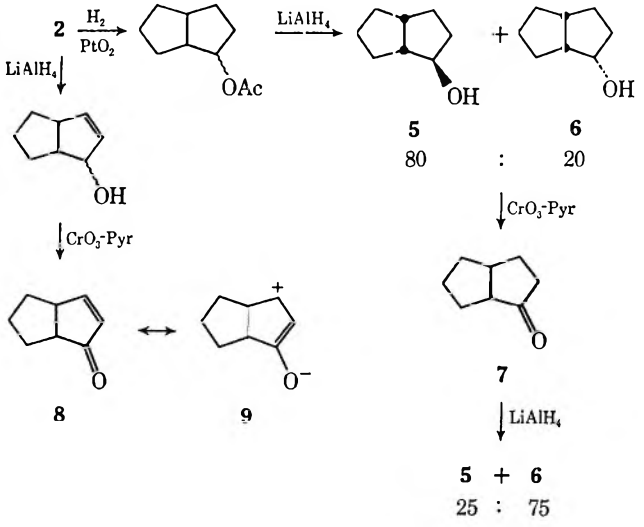
Figure 1.—Transformation of 2,4-cyclooctadien-1-yl cation to bicyclo[3.3.0]oct-3-en-2-yl cation.

action between a carbonium ion p orbital at the allylic position and the p orbital at the opposite end of the diene system was geometrically quite feasible. The bicyclo[3.3.0] system appeared, therefore, to be a likely candidate for the rearranged carbon skeleton. In addition, the nmr spectrum of the unknown unsaturated acetate was compatible with that expected for bicyclo[3.3.0]oct-3-en-2-yl acetate (**2**). This transformation is illustrated schematically in Figure 1.

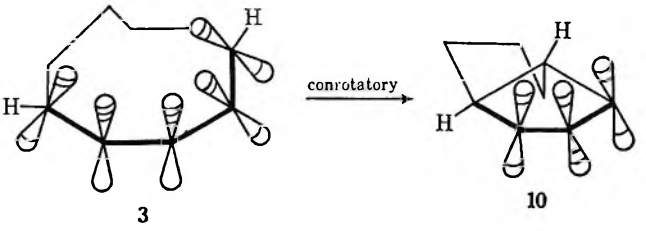
The bicyclic structure, the *cis* ring junction, and the stereochemistry of the acetate group (a mixture of *exo* and *endo* isomers) in **2** were established by conversion of the unsaturated acetate into the known saturated alcohols. Thus, hydrogenation of **2** followed by lithium aluminum hydride reduction of the resultant material afforded two alcohols. The major constituent (~80% of the mixture) was identified as *exo,cis*-bicyclo[3.3.0]-octan-2-ol (**5**) by comparison of its ir spectrum with that of an authentic sample.[4] The minor product could not be obtained in sufficient purity for direct characterization. However, the formation of a single ketone **7**, upon oxidation of the alcohol mixture, indicated that the minor component was probably the *endo* alcohol **6**. Brown and Hammar[5] have reported that $LiAlH_4$ reduction of ketone **7** gives a 75:25 mixture of **6** and **5**, respectively. In agreement with Brown's report, the major component (~75%) from our reduction of **7** was identified as the *endo* alcohol **6** by comparing its ir spectrum to that of an authentic sample.[4] The retention time of this *endo* alcohol was identical with that of the minor alcohol obtained from the hydrogenation and subsequent reduction of **2**. This permitted assignment of structure **6** to the minor alcohol.

Conversion of **2** into the corresponding ketone gave a product whose spectral properties (see Experimental Section) were in good agreement with those reported for 2-cyclopentenone.[6] Of particular interest was the nmr spectrum which revealed a marked difference in the chemical shifts of the two vinyl protons (τ 2.67 *vs.* τ 4.05). The large downfield shift of the 3 proton can be attributed to a planar conformation of the enone ring[7] and thus a sizable contribution of resonance form **9** to the electron distribution in **8**. The formation of an α,β-unsaturated ketone indicated that the acetate group was α to the olefinic moiety thus providing further confirmation for the structural assignment of **2**. The reaction sequences used in the structure determination of **2** are outlined in Scheme II.

SCHEME II



As far as can be determined, a ring closure of carbonium ion **3** to cation **4** is without literature precedent. A possible reason for this is the fact that the formation of a *cis* ring junction, as in **4**, is contrary to that predicted by orbital symmetry considerations.[8] Thus the conversion of the pentadienyl carbonium ion to the cyclopentenyl cation is expected to proceed in a conrotatory manner. It is readily seen that an analogous conrotatory ring closure in **3** would lead to a strained *trans* ring junction.



Several lines of reasoning can be used to interpret the observed contradiction. The basis for the first of these is a corollary to the Woodward–Hoffmann Rules which asserts that, if a symmetry-allowed product is geometrically of high energy, as is **10**, then the symmetry rules may be overcome and formation of the forbidden product may be possible.[9] This, however, usually requires much more energetic conditions than those necessary for the allowed process. Since the formation of **2** occurs at room temperature, an explanation based on this postulate becomes somewhat tenuous.

A second rationale for the observed phenomenon can be found in the fact that a reaction must be concerted in order to be governed by the orbital symmetry rules.[8] Inspection of a molecular model of **3** indicates that a good deal of ring strain as well as several unfavorable nonbonded interactions exist when the double bonds and the carbonium ion center are made coplanar. This

(4) A. C. Cope, R. W. Gleason, S. Moon, and C. H. Park, *J. Org. Chem.*, **32**, 942 (1967).
(5) H. C. Brown and W. J. Hammar, *J. Amer. Chem. Soc.*, **89**, 1524 (1967).
(6) (a) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, pp 12, 41; (b) J. Wieman, P. F. Casals, and S. Resse, *Bull. Soc. Chim. Fr.*, 1281 (1963).
(7) (a) N. Heap and G. H. Whitman, *J. Chem. Soc., B*, 164 (1966); (b) H. L. Goering, R. W. Greener, and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1391 (1961).
(8) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).
(9) G. B. Gill, *Quart. Rev.* (London), **22**, 338 (1968).

factor could cause a concerted reaction, involving overlap of the five p orbitals, to be somewhat difficult in which case the Woodward–Hoffmann Rules may no longer apply. On the other hand, Stapp and Kleinschmidt[10] have found that the 2,4-cyclooctadien-1-yl anion is converted, in good yield, by a symmetry-allowed disrotatory process, into the *cis*-bicyclo[3.3.0]-oct-3-en-2-yl anion. It therefore appears that 1,3-cyclooctadienyl systems may be capable of concerted reactions in spite of adverse geometric requirements.

Although the above explanations cannot be completely rejected, it is most tempting to view the formation of cation **4** as resulting from the presence of silver ion in the reaction medium. It has been demonstrated[11] that transition metal ions may, through mixing of substrate and metal energy levels, cause a symmetry-forbidden process to become symmetry allowed. Of particular note is the work of Merk and Pettit[12] in which added silver ion was shown to make a thermally disallowed reaction facile, even at room temperature. In addition, as will be noted below, there is some evidence that **2** will not form in the absence of silver ion.

Throughout the foregoing discussion it was assumed that rearrangement to the bicyclo[3.3.0] system occurred in the carbonium ion step (acetylation) and not in the radical step (bromination). Somewhat surprisingly, careful examination of the nmr spectrum of the bromination product indicated that the signal at τ 5.15, presumably due to an allylic proton on a bromine-bearing carbon, integrated for less than the expected one proton. It was assumed that this signal was due to 2,4-cyclooctadien-1-yl bromide and it was thereby calculated that the mixture was comprised of only about 80% of this material. No nmr signal consistent with either of the bridgehead protons in bicyclo[3.3.0]oct-3-en-2-yl bromide could be found.

Removal of both allylic and nonallylic bromines, in good yield, by reduction with $LiAlH_4$, is well documented.[13] This method offered a possible means of identifying the unknown bromides through the corresponding olefins, provided that the latter could be separated.

Treatment of the bromination product with $LiAlH_4$ yielded approximately a 50:50 mixture of two olefins. One of the products was identified as 1,3-COD. The nmr spectrum of the second olefin indicated that it was not bicyclo[3.3.0]oct-2-ene but rather 1,4-COD. Comparison of the latter with an authentic sample[14] confirmed this belief.

The formation of 1,4-COD can be explained by invoking an allylic rearrangement of the initially formed radical from the NBS reaction[15] (see Scheme I). Winstein and coworkers[16] have carried out the bromination and $LiAlH_4$ reduction of 1,3-COD with similar results. Winstein's group contends, however, based on a publication by Jefford, *et al.*,[17] that the rearrangement is an S_N2' process which occurs during $LiAlH_4$ reduction. From the product ratios found in our bromide mixture and then in our olefin mixture, it now appears that both a free-radical allylic rearrangement and an S_N2' reaction are operating here. The allylic rearrangement is apparent, not only from nmr evidence, but also from the fact that NBS bromination of 1,4-COD gave a bromide mixture whose nmr spectrum was identical with that of the bromides obtained from 1,3-COD. Conversion of the 1,4-COD bromide mixture into the corresponding acetates, with silver acetate and acetic acid, as well as to the olefins with $LiAlH_4$ afforded essentially the same product mixtures as those derived from 1,3-COD. Both of these reactions provide further confirmation that the two bromide products were the same. Furthermore, the change in product ratios going from the bromides to the olefins is indicative of an S_N2' process during $LiAlH_4$ reduction.

From the preceding it is clear that the bicyclo[3.3.0] system was not formed during the NBS bromination. It is interesting that no acetate corresponding to 2,7-cyclooctadien-1-yl bromide was found in the acetylation product. This difference between the free-radical and carbonium ion reactions may simply reflect different conformational requirements for stabilization of the two species.[18] However, there is not sufficient evidence available to make a definitive statement with regard to more subtle factors which may be operating here.

An investigation of the properties of 2,4-cyclooctadien-1-yl acetate (**1**) and its analogs (see Scheme III) demonstrated that facile thermal rearrangements occurred in virtually all of the dienes studied. In fact this portion of our study was initiated by just such a finding in the dienyl acetate system. Thus, the mixture of **1** and **2** was distilled through a spinning-band column. An nmr spectrum of the fraction presumably containing **1**, however, revealed an absorption (τ 5.2, triplet of triplets) not previously present in the nmr spectrum of **1** or **2**. In addition subtle changes in the multiplet structure of the other absorption bands were evident. Crandall[19] has suggested that cyclooctadienyl acetates can undergo thermal 1,5-hydrogen shifts. In order to explore the possibility that thermal conversions could account for the observed changes in the nmr spectrum, a carbon tetrachloride solution of **1** (isolated by glpc at 90°, prior to spinning-band distillation, and later found to contain 30% of **11**) was placed in a sealed nmr tube and heated at about 110°. Periodic recordings of the nmr spectrum of the solution showed an increase in the relative area of the τ 5.2 absorption, thereby confirming that a thermal rearrangement was indeed taking place. The product mixture, however, showed only a single peak on gas chromatography (EGA) with the same retention time as **1**.

Comparison of the chemical shift of the τ 5.2 absorp-

(10) P. R. Stapp and R. F. Kleinschmidt, *J. Org. Chem.*, **30**, 3006 (1965).

(11) (a) F. D. Mango and J. H. Schachtschneider, *J. Amer. Chem. Soc.*, **89**, 2484 (1967); (b) H. Hogeveen and H. C. Volger, *ibid.*, **89**, 2486 (1967).

(12) W. Merk and R. Pettit, *ibid.*, **89**, 4787, 4788 (1967).

(13) (a) C. W. Jefford, *Proc. Chem. Soc.*, 64 (1963); (b) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 34.

(14) We wish to thank Dr. E. Ciganek for supplying the spectra of 1,4-cyclooctadiene.

(15) S. Moon and C. Ganz, *J. Org. Chem.*, **34**, 465 (1969).

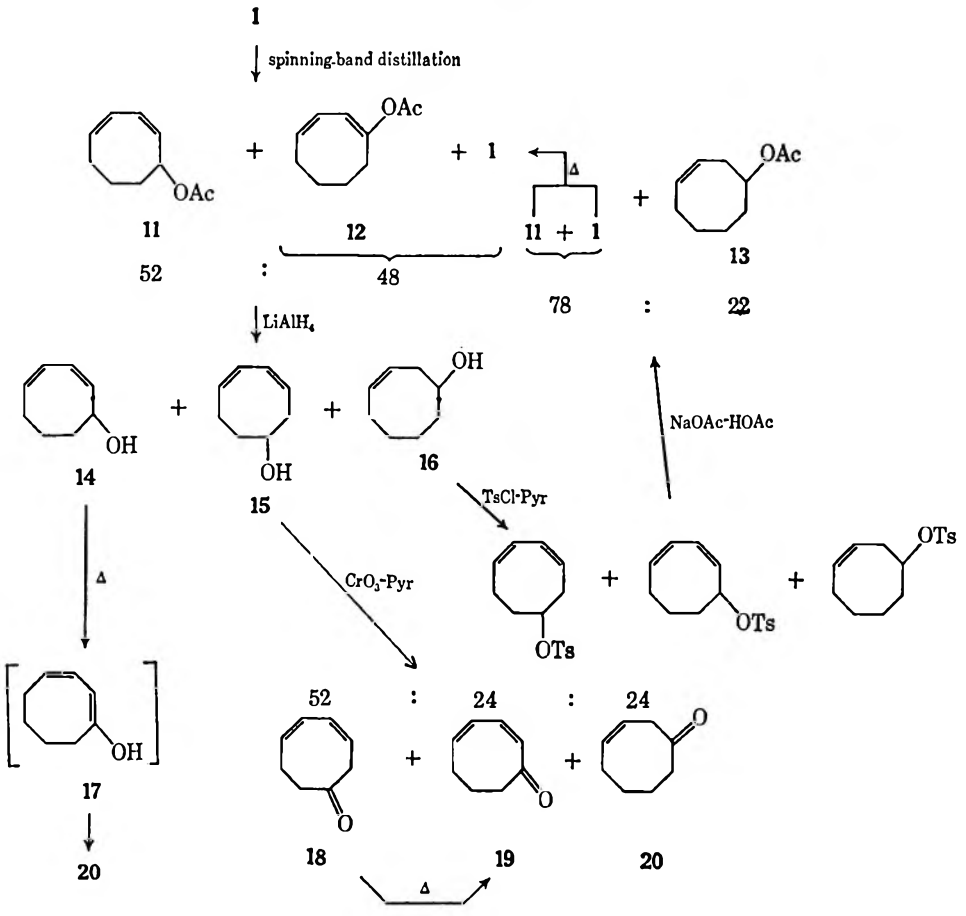
(16) D. S. Glass, R. S. Boickess, and S. Winstein, *Tetrahedron Lett.*, 999 (1966).

(17) C. W. Jefford, S. Makajan, J. Gunsher, and B. Waegell, *ibid.*, 2333 (1965).

(18) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Co., New York, N. Y., 1968, pp 129, 155.

(19) J. K. Crandall and L. H. Chang, *J. Org. Chem.*, **32**, 532 (1967).

SCHEME III



tion with that exhibited by the allylic 2 proton (τ 4.75) in the bicyclic acetate **2** suggested that the unknown signal was due to a proton α to an acetoxy group but not allylic. Of the isomers of **1**, derived from a 1,5-hydrogen shift, only 3,5-cyclooctadien-1-yl acetate (**11**) has a proton which would be expected to appear at about τ 5.2. Additional support for the homoallylic structure can be found in the triplet of triplets exhibited by the absorption in question. This multiplet structure is indicative of a proton flanked on either side by methylene groups with different chemical shifts and is thus quite compatible with **11**.

The approximate percentage of **11** present at various time intervals during the thermal study was calculated by comparing the relative integrated area of the τ 5.2 absorption with that of the entire spectrum. It was thereby calculated that the fraction of **11** reached a value of about 60% after 26 hr of heating. Further heating showed only a slight change in this percentage. In a similar manner it was calculated that the spinning-band distillate (heated for 7 days at ~80°) contained about 52% of **11**.

From spectral analysis alone it was extremely difficult to obtain the structural details of all the compounds, other than **11**, which were present in the thermally rearranged product. The single glpc peak obtained from the thermolysis mixture, however, indicated that the isomeric acetates **1** and **12** were likely prospects for the other components. The spinning-band distillate was subjected to $LiAlH_4$ reduction in an attempt to identify the unknown acetates through their corresponding alcohols. The nmr spectrum of the crude reduction product clearly showed signals due, mainly, to homoallylic alcohols. No signal consistent with a proton both allylic and α to a hydroxyl group was visible. However, it is quite probable that an absorption of this type may well have been obscured by the vinyl signal (τ 3.9–5.1). In the first place, a marked downfield shift would be expected for a proton on the hydroxyl-bearing carbon going from a homoallylic to an allylic alcohol. Secondly, a model of 2,4-cyclooctadien-1-ol (**14**) strongly suggests that the allylic proton is thrust into the deshielding region of the 4,5 double bond. This would lower still further the expected chemical shift of the allylic proton. Nevertheless, it could be discerned that the homoallylic alcohol **15** was the major component due to the fact that certain features of the crude nmr spectrum were quite compatible with those reported by Crandall[19] for a compound to which he assigned the structure 3,5-cyclooctadien-1-ol (**15**).

Gas chromatographic analysis of the crude alcohol mixture gave three components which were identified by comparison with authentic samples as 3-cyclooctenl-one (**20**), 3-cyclooctenl-ol (**16**), and a mixture of **20** and unidentified alcohols. Crandall and Chang[19] have reported that **14** undergoes a thermal 1,5-hydrogen shift to afford **20**. Since an ir spectrum of the crude alcohols showed essentially no carbonyl band, **20** and the mixture of **20** and the unknown alcohols were presumed to have resulted from thermal 1,5-hydrogen shifts upon gas chromatography. Thus alcohol **15** was converted into alcohol **14** and then into ketone **20** (*via* **17**). Also, any **14** which was already present was

changed to **17** and then to **20**. Reinjection of the mixture of **20** and the alcohols converted the latter almost completely into the ketone.

The presence of **16** in the $LiAlH_4$ reaction mixture can be explained by assuming that the enol acetate **12** was present in the acetate mixture and was reduced to **16** by $LiAlH_4$. Such a reaction has ample precedent.[20] In addition, close inspection of an ir spectrum of the spinning-band fraction, containing the dienyl acetate mixture, revealed a weak shoulder on the major carbonyl band at approximately 1755 cm^{-1}. The position of this absorption is compatible with those reported[21] for enol acetate carbonyl groups. This lends support to the proposed mechanism.

It was of interest to determine the relative amounts of the alcohols **14**, **15**, and **16** present in the reduction mixture. However, owing to the thermal interconversions of the dienols and ketone **20**, a direct glpc estimate was not feasible. An attempt to overcome this difficulty was made, by oxidizing the alcohol mixture to the corresponding ketones with chromic trioxide–pyridine complex. The product was shown (glpc) to be a 24:76 mixture of two constituents. The minor component was identified as ketone **20**, while uv, ir, and nmr data from the remaining glpc-isolated material suggested it to be about a 30:70 mixture of a nonconjugated and a conjugated dienone, respectively. Surprisingly, it was found, by ir and nmr spectral analysis, that the ratio of nonconjugated to conjugated dienone in the crude mixture was in direct contrast to that indicated by the spectra of the material exposed to the glpc. Thus, apparent in the nmr spectrum of the crude ketone product was a large doublet at about τ 7.0. This absorption is characteristic of a methylene group both allylic and α to a carbonyl group. The relative area of the τ 7.0 signal demonstrated that the major product in the crude material was the homoallylic rather than the allylic dienone. The same doublet was also noticeable in the nmr spectrum of the material isolated by gas chromatography but at greatly diminished relative intensity. That these results were due to another thermal rearrangement on the gas chromatograph was confirmed by heating a solution of the sample isolated by gas chromatography in carbon tetrachloride in a sealed nmr tube (110°). A recording of the nmr spectrum, after 6 hr of heating, showed a decrease of almost 50% in the relative area of the τ 7.0 doublet. It was also clear, from comparing the spectra of the crude product with those of the sample isolated by gas chromatography and the heated sample, that the characteristics of the nmr spectrum were progressively approaching those reported by Heap and coworkers[22] for pure 2,4-cyclooctadien-1-one. By analogy to our previous findings, a 1,5-hydrogen shift, transforming **18** to **19**, can be invoked to explain the observed thermal rearrangement.

(20) (a) W. G. Dauben and J. F. Eastham, *J. Amer. Chem. Soc.*, **73**, 3260 (1951); (b) W. G. Dauben and J. F. Eastham, *ibid.*, **75**, 1718 (1953); (c) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Wiley–Interscience, New York, N. Y. 1956, pp 533, 963; (d) one of the referees pointed out that the formation of **16** does not necessarily indicate the existence of **12**, since the formation can be explained by the route **14** → **17** → **20** — **16**.

(21) (a) N. J. Leonard and F. H. Owens, *J. Amer. Chem. Soc.*, **80**, 6039 (1953); (b) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 44.

(22) N. Heap, G. E. Green, and G. H. Whitham, *J. Chem. Soc., C*, 160 (1969).

The approximate percentages of ketones **18**, **19**, and **20** present in the crude mixture, were calculated from both gas chromatographic data as well as from well-separated nmr signals which could now be assigned, with some confidence, to **18** and **19**. The nmr absorptions used to calculate **18** and **19** were a two-proton doublet at τ 6.96 and a three-proton vinyl signal centered at τ 3.83, respectively. It was thus determined that the ratio of **18** to **19** to **20** was 52:24:24. The 52% calculated for the homoallylic dienone **18** is in close agreement with that previously calculated for the corresponding homoallylic acetate **11**, directly from an nmr spectrum of the spinning-band-isolated dienyl acetate mixture. Thus the ketone mixture appears to reflect the product ratios present in the acetate mixture from which it was derived.

Conversion of the alcohol mixture into the corresponding tosylates followed by solvolysis of the latter in sodium acetate buffered acetic acid afforded two major products in a 22:78 ratio. An ir spectrum of the minor product was identical with that of 3-cyclooctenyl-1-yl acetate (**13**). Spectral analysis of the major glpc constituent showed it to be very similar to the spinning-band material containing the dienyl acetate mixture but slightly less abundant in acetates **11** and **12**. Apparently, partial thermal equilibrium between the isomeric dienyl acetates was reestablished during isolation of the solvolysis products by gas chromatography. The product ratios found here are in good agreement with those of the ketones obtained from oxidation of the same alcohol mixture.

Noteworthy is the fact that, even though the alcohol mixture appears to have contained about 24% of **14**, none of the bicyclic acetate **2** could be detected in the tosylate solvolysis product. This finding tends to support the proposed role of added silver ion in the formation of **2**.

The results obtained from the 1,3-cyclooctadienyl systems prompted us to investigate the same reaction sequences in the isomeric 1,4- and 1,5-cyclooctadienes.

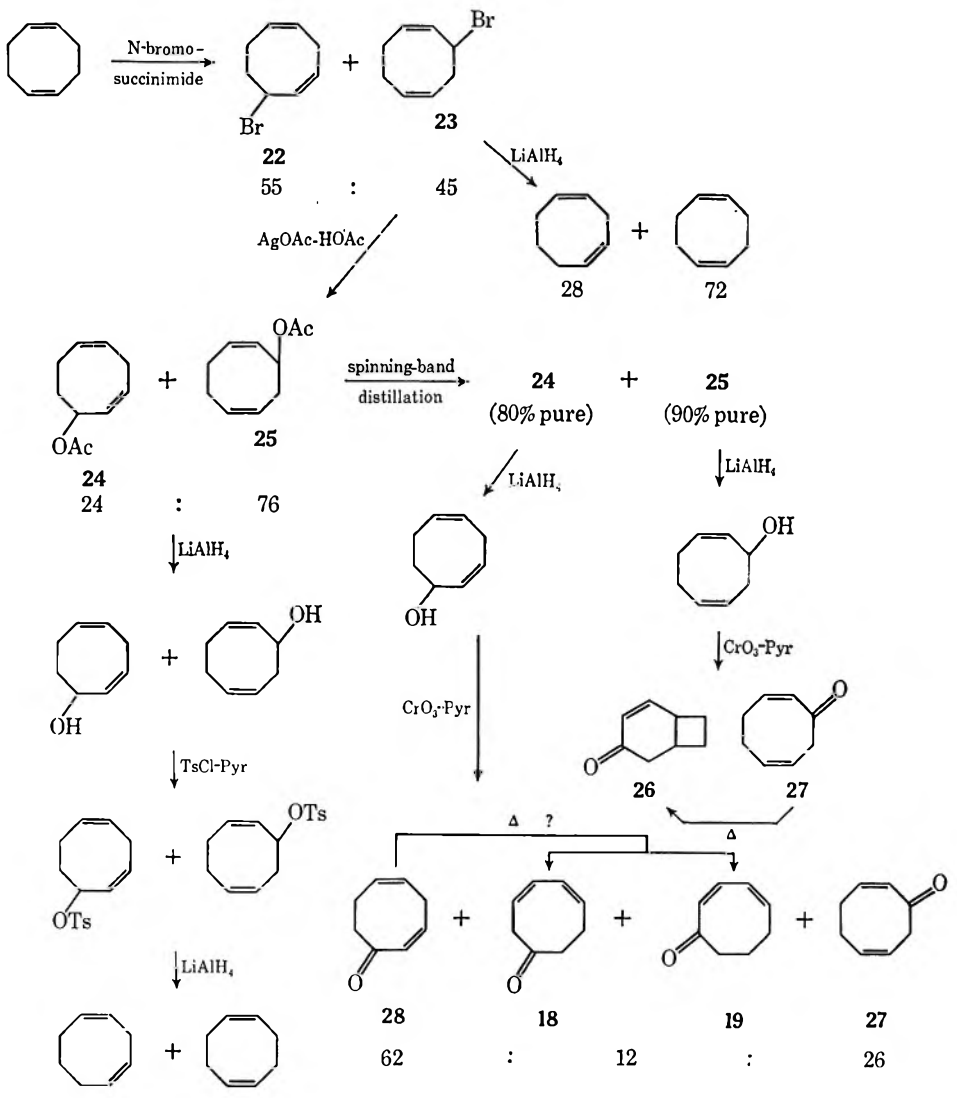
As described above, 1,4-COD gave, upon NBS bromination and subsequent acetylation, bromide and acetate mixtures identical with those obtained from 1,3-COD.

As previously reported by Cope,[23] bromination of 1,5-COD (**21**) afforded two isomeric bromides. A characteristic distorted triplet, similar to the one exhibited by the diallylic protons of 1,4-COD, was clearly visible at τ 7.2 in the nmr spectrum of the bromide mixture. This enabled one of the isomers to be tentatively assigned the structure of the allylic rearrangement product, 2,5-cyclooctadien-1-yl bromide (**22**). A calculation based on the relative area of this absorption indicated that the mixture was made up of approximately 55% of **22** and 45% of another bromide which was assumed to be 2,6-cyclooctadien-1-yl bromide (**23**).

Spectral analysis of a variety of derivatives obtained from the components of the bromide mixture (see Scheme IV) lent considerable support to the assignments of **22** and **23**. In particular, two different routes from **22** and **23** to the parent olefins gave only 1,4- and 1,5-cyclooctadiene.

(23) A. C. Cope and F. Hochstein, *J. Amer. Chem. Soc.*, **72**, 2510 (1950).

SCHEME IV



In all of the isolated derivatives of **22** the distinctive absorption at about τ 7.2 firmly established that the diallylic methylene group of the 1,4-cyclooctadienyl system was present and unsubstituted. That the substituent was also not at the 7 position of 1,4-COD was confirmed by differences found in comparing the nmr spectrum reported[24] for 3,6-cyclooctadien-1-ol with that of the alcohol derived from **22**.

The nmr spectra of the analogs of **23** were compatible with the expected structures. In particular the ketone derivative **27** exhibited a doublet at τ 6.75, characteristic of a methylene group α to a carbonyl group and also allylic.[7a] Uv data (λ_{max} 223, 310 mμ) indicated that the carbonyl group was also α,β-unsaturated and thus permitted the assignment of the expected 2,6-cyclooctadien-1-one (**27**) to the ketone. Farissey and coworkers[25] have assigned the structures **27** and 2,5-cyclooctadien-1-one (**28**) to a pair of ketones derived from air oxidation of 1,5-COD followed by hydrolysis of the resultant hydroperoxides. These workers did not separate these products. They did find, however, that the compound thought to be **27** was converted, upon heating, into bicyclo[4.2.0]oct-2-en-4-one (**26**). Interestingly, in our hands, gas chromatographic isolation of **27** gave rise to a smaller second peak of slightly shorter retention time than **27**. The uv and ir spectra of this material were in good agreement with those expected from **26**. This suggested that the thermal rearrangement found by Farissey may have occurred to some extent on the gas chromatograph.

It is noteworthy that the isomer ratios changed in favor of the 1,5-COD system going from the bromides directly to either the olefins or the acetates. In the former case, by analogy to the $LiAlH_4$ reduction of the bromides derived from 1,3-COD, an S$_N$2′ process can be invoked. Probably owing to variations in steric factors about the bromine-bearing carbon, this type of attack occurs preferentially on the 1,4-diene. On the other hand, the acetate results again appear to reflect differences in the environmental conditions necessary for stabilization of a free radical and a carbonium ion.

The diminished relative concentration of 2,5-cyclooctadien-1-yl acetate (**24**) compared with its bromide counterpart, in addition to the very close boiling points of **24** and its 2,6 isomer (**25**), allowed spinning-band separation of only a small sample of acetate **24** (contaminated with about 15–20% of **25**). A crude mixture of the corresponding alcohols, obtained from $LiAlH_4$ reduction of the impure **24**, exhibited an nmr spectrum,

(24) P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **86**, 1866 (1964).
(25) W. J. Farissey, Jr., R. H. Perry, Jr., F. C. Stehling, and N. F. Chamberlain, *Tetrahedron Lett.*, 3635 (1964).

the gross features of which were quite consistent with that expected for 2,5-cyclooctadien-1-ol. Attempted conversion of this crude material into the ketones yielded a mixture which, when analyzed by gas chromatography, showed a marked decrease in the anticipated amount of ketone **28** relative to **27**. In addition, there appeared a third component (~12%) which was identified as a mixture of **18** and **19** (~30:70, respectively). Several mechanisms for this transformation can be envisioned. A thermal conversion may again be operating since an ir spectrum of a small sample of **28**, collected by gas chromatography, exhibited a carbonyl band (1705 cm^{-1}) compatible with that found for ketone **18**. Unfortunately, difficulties encountered in isolating **28** did not permit either elucidation of its structure or confirmation of its involvement in the formation of **18** and **19**.

Experimental Section[26]

Bromination of 1,3-Cyclooctadiene.—This bromination procedure has been described previously.[15] The nmr spectrum of the distillate showed the following signals:[16] τ 4.25 (m, =CH), 5.15 (m, =CCHBr), 7.8 (m, $=CCH_2$), and 8.0–8.8 (m, CH_2). A calculation of the area of the τ 5.15 absorption relative to the rest of the spectrum showed that it was equivalent to approximately 0.8 proton. On this basis the mixture was assumed to contain 80 ± 5% of 2,4-cyclooctadien-1-yl bromide.

Lithium Aluminum Hydride Reduction of the 1,3-Cyclooctadiene Bromination Product.—The bromination product was treated with lithium aluminum hydride as described previously.[15] The product was found to be a 50:50 mixture of 1,3- and 1,4-cyclooctadiene.

Acetylation of the 1,3-Cyclooctadiene Bromination Product (Formation of 1 and 2).—To 72.8 g (0.39 mol) of the bromide mixture in 170 ml of glacial acetic acid was added, with stirring and external cooling, a slurry of 85 g (0.51 mol) of silver acetate in 170 ml of glacial acetic acid. The mixture was stirred in the dark at room temperature for 48 hr. After filtration, the supernatant liquid was diluted with 50 ml of water. The resultant mixture was extracted with one 400-ml portion and then two 300-ml portions of ether. The combined extracts were washed with two 1-l. portions of water, 1 l. of 10% sodium bicarbonate solution, and water again, and dried ($MgSO_4$). The ether was removed, under reduced pressure, on a rotary evaporator and the residue was distilled through a short-path distillation column to give 46.3 g (72%) of an acetate mixture, bp 42–47° (0.08–0.12 mm). The distillate showed two components on glpc (EGA, 2 ft, 110°) in a ratio of 20:80. The minor component was assigned the structure bicyclo[3.3.0]oct-3-en-2-yl acetate (**2**) and exhibited the following spectral properties: uv: no absorptions above 210 mμ; ir (CS_2): 3040, 2930, 1725, 1250, 1110, 1020, 942, 900, 810, and 730 cm^{-1}; nmr: τ 4.25 (m, 2, =CH), 4.75 (doublet of doublets, 1, J = 5 Hz, J = 2 Hz, =CCHOAc), 6.70 (m, 1, bridgehead =CCH), 7.55 (m, 1, bridgehead CH), 8.03 (s, 3, $O{=}CCH_3$), 8.45 (m, 6, CH_2). The major component was assigned the structure 2,4-cyclooctadien-1-yl acetate (**1**): uv: λ_{max} (95% ethanol) 222 mμ (ε 6225); ir (CS_2): 3000, 2910, 1730, 1250, 1165, 1030, 970, 950, 910, 800, and 690 cm^{-1}; nmr: τ 3.9–4.5 (m, 4, =CH), 4.7 (m, 1, =CCHOAc), 7.4–8.0 (m, 2, $=CCH_2$), 8.01 (s, 3, $O{=}CCH_3$), 8.1–8.8 (m, 4, CH_2).

Hydrogenation of the Acetylation Product (Formation of Bicyclo[3.3.0]octan-2-yl Acetate and Cyclooctyl Acetate).—A mixture of 1 g (6 mmol) of the acetylation product, 100 mg of platinum oxide, and 50 ml of glacial acetic acid was shaken in an atmospheric pressure hydrogenation apparatus for 24 hr. After removal of the catalyst by filtration, the liquid was diluted with water and extracted with ether. The ether extracts were washed with water, 5% sodium carbonate solution, and saturated sodium chloride solution, and dried ($MgSO_4$). Glpc analysis (EGA, 4 ft, 110°) of the residue, after removal of ether under reduced pressure, showed two components in a 13:87 ratio. The disappearance of the ir absorptions in the 3000-cm^{-1} region showed both to be saturated acetates. Based on spectral analysis and the structure proof described below, the minor product was assigned the structure bicyclo[3.3.0]octan-2-yl acetate: ir (CCl_4): 1735 (C=O), 1250 cm^{-1} (CO); nmr: τ 5.3 (m, 1, CHOAc), 7.55 (m, 2, bridgehead CH), 8.07 (s, 3, $O{=}CCH_3$), 7.8–8.9 (m, 10, CH_2). The ir and retention time of the major product were identical with those of an authentic sample of cyclooctyl acetate prepared from cyclooctanol.

Teflon Spinning-Band Distillation of the Acetylation Product.—The acetylation product (46.3 g) was slowly distilled, over 7 days, on a Teflon spinning-band column. Two major fractions, SB-F-1 (7.5 g), bp 56–58° (1.6–1.7 mm), and SB-F-2(24.4 g), bp 65.5° (2.1 mm), both of which were homogeneous on gas chromatography (EGA, 2 ft, 110°), were isolated. The ir and nmr spectra of SB-F-1 were identical with those of the minor acetylation product, **2**. However, SB-F-2 was different from the major acetylation product and showed the following spectral data: nmr: τ 4.35 (m, =CH and =CCHOAc), 5.2 (triplet of triplets, J = 7 Hz, J = 5 Hz, $CH_2CHOAcCH_2$), 7.0–8.8 (m, $=CCH_2$ and CH_2), 8.07 (s, $O{=}CCH_3$); ir (CCl_4): 3005 (=CH), 1755 (=COC=O), 1735 (C=O), 1240 cm^{-1} (CO). Integration of the nmr spectrum showed, based on the τ 5.2 absorption, that this fraction contained about 52% of a compound assigned the structure 3,5-cyclooctadien-1-yl acetate (**11**) and 48% of a mixture of two acetates which were subsequently assigned the structures **1** (24%) and 1,3-cyclooctadien-1-yl acetate (**12**) (24%).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.24; H, 8.49. Found (SB-F-1; **2**): C, 72.14; H, 8.40. Found (SB-F-2): C, 72.08; H, 8.45.

Thermal Rearrangement of 1.—Approximately a 10% carbon tetrachloride solution of **1**, isolated by gas chromatography (EGA, 2 ft, 110°), and shown, by the τ 5.2 absorption in the nmr, to contain about 31% of **11**, was sealed in an nmr tube and heated in an oil bath at 108 ± 4°. Periodic recordings of the nmr spectrum of the solution showed that, after 26 hr, the fraction of **11**, based on the area of the τ 5.2 signal, reached a value of about 60%. Additional heating to a total of 72 hr brought this value to approximately 70%. The final solution showed only a single homogeneous peak on gas chromatography (EGA, 4 ft, 150°) and an ir spectrum very similar to that of the spinning-band fraction, SB-F-2.

Lithium Aluminum Hydride Reduction of Spinning-Band Fraction SB-F-2 (Formation of 14, 15 and 16).—A 2-g sample (12 mmol) of SB-F-2 was treated with 0.6 g (0.16 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether in the manner described above. The crude product (1.15 g, 78%) showed the following spectral properties: ir (CCl_4): 3600 (OH), 3325 (OH), 3000 (=CH), 1060 cm^{-1} (CO); no carbonyl band was present; nmr (external TMS): τ 3.9–5.1 (m, =CH and =CHCHOH), 5.7 (s, OH), 5.9 (s, OH), 6.1 (s, OH), 6.33 (quintet, J = 5.5 Hz, CHOH), 7.3–8.1 (m, $=CHCH_2$), 8.1–8.8 (m, CH_2). From integration of the nmr spectrum and by comparison of it with that reported for 3,5-cyclooctadien-1-ol[19] (**15**), it was discerned that the major alcohol component was **15**. Gas chromatographic analysis (EGA, 4 ft, 150°) showed three constituents which were identified, by comparison with authentic samples, as **20** (~31%), 3-cycloocten-1-ol (~14%), and a mixture of **20** and unidentified alcohols (~55%). Reinjection of **20** and 3-cycloocten-1-ol into the glpc showed no apparent changes. Reinjection of the mixture of **20** and the alcohols converted the latter almost completely into **20**. It was thus apparent that the dienols were thermally converted into **20**.

Conversion of the Crude Alcohol Mixture into the Tosylates.—To 0.5 g of the crude alcohol mixture derived from SB-F-2, in 10 ml of pyridine, was added, with external cooling, 1.55 g of toluenesulfonyl chloride. After standing in a refrigerator overnight, the mixture was poured into ice and the resultant solution extracted with ether. The combined extract was washed with water, 3 *N* hydrochloric acid, and 10% sodium bicarbonate solution, dried ($MgSO_4$), and concentrated. The resultant tosylate mixture (0.59 g, 22%) was used without further purification.

Solvolysis of the Crude Tosylates (Formation of 1, 11, and 13).—To 0.4 g of the crude tosylate mixture was added a solution of

(26) Nmr spectra were determined on a Varian A-60 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Ultraviolet spectra were obtained from a Cary-14 recording spectrophotometer. Gas chromatography was performed on an F & M Model 720 thermal conductivity gas chromatograph using 2- or 4-ft columns containing either 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on Chromsorb P or 20% ethylene glycol adipate (EGA) on Chromosorb W. Boiling points are uncorrected. Unless otherwise specified, nmr spectra were determined as carbon tetrachloride solutions containing tetramethylsilane (TMS) as an internal standard.

0.3 g of sodium acetate in 25 ml of acetic acid. The solution was stirred at room temperature for 18 hr and then poured into 100 ml of water. The resultant mixture was extracted with two 75-ml portions of ether. The combined ether extracts were washed with two 150-ml portions of water, 150 ml of 10% sodium bicarbonate solution, and water again, dried ($MgSO_4$), and concentrated. Gas chromatography (EGA, 4 ft, 175°) showed two major product peaks in the ratio of 22:78 in addition to several components each of which had an area equivalent to less than 5% of the major peak. The smaller of the major components was isolated by gas chromatography and its ir was found to be identical with that of an authentic sample of 3-cycloocten-1-yl acetate (**13**). The major component, also isolated from the glpc, exhibited an nmr spectrum very similar to that of SB-F-2. It was determined, from the τ 5.2 absorption, that this mixture of dienyl acetates contained about 40% of **11**. Partial thermal re-equilibration during isolation of the major component appears to have taken place. One of the trace components had a retention time which was compatible with that expected from the bicyclic acetate, **2**. An ir spectrum of this material demonstrated that it was not **2**, thus precluding the formation of **2** during the solvolysis.

Conversion of the Crude Alcohol Mixture into the Ketones (Formation of 18, 19, and 20).—To 15 ml of pyridine was added, with external cooling, 2 g of chromium trioxide and then 0.5 g of the crude alcohol mixture from SB-F-2. The resultant brown suspension was stirred overnight at room temperature and then poured onto 50 ml of ice. After extraction of the solution with two 75-ml aliquots of ether, the ether layers were combined and washed with two 150-ml portions of water, 150 ml of 3 *N* hydrochloric acid, and water again, and dried ($MgSO_4$). The ether was removed under reduced pressure to give 0.23 g (~47%) of a crude ketone mixture which had the following spectral properties: ir (CCl_4): 3000 (=CH), 1705 (C=O, strong), 1665 cm^{-1} (=C—C=O, medium intensity); nmr: τ 3.5–3.95 (m, =CH), 3.95–4.9 (m, =CH), 6.96 (d, J = 6 Hz, $=CCH_2C=O$), 7.05 (d, J = 4 Hz, $=CCH_2C=O$), 7.15–8.8 (m, $CH_2C=O$, $=CCH_2$ and CH_2). Gas chromatography (EGA, 4 ft, 175°) showed two product peaks in a ratio of 24:76. The minor constituent had the shorter retention time, and, upon isolation by gas chromatography, was found to be identical with an authentic sample of enone **20**. The major glpc-isolated peak gave the following spectral data: uv: λ_{max} (95% ethanol) 220, 274 mμ; ir (CCl_4): 3005 (=CH), 1705 (C=O, medium intensity), 1665 cm^{-1} (=CC=O, strong); nmr: τ 3.5–4.0 (m, =CH), 4.0–4.5 (m, =CH), 6.96 (d, J = 6 Hz, $=CCH_2C=O$), 7.2–7.7 (m, $CH_2C=O$), 7.7–8.3 (m, $=CCH_2$ and CH_2). By comparing the area of the τ 6.96 doublet with that of the total spectrum it was calculated that the major product contained approximately 30% of 3,5-cyclooctadien-1-one (**18**). By comparison with the nmr spectrum reported[22] for 2,4-cyclooctadien-1-one (**19**), the other component (70%) of the major peak was assigned structure **19**. On the other hand, from the relative areas of the τ 3.5–3.95 (assigned to **19**) and the τ 6.96 (assigned to **18**) absorptions in the nmr of the crude ketone mixture, it was determined that, of the 76% of the mixture found by glpc to be dienones, about 52% was **18** and 24% was **19**. Thus the crude mixture was approximately a 52:24:24 mixture of **18**, **19**, and **20**, respectively.

Thermal Rearrangement of 3,5-Cyclooctadien-1-one (18).—A carbon tetrachloride solution of a glpc-isolated sample of the major ketone peak from the alcohol oxidation was sealed into an nmr tube and heated in an oil bath at 110°. After 6 hr of heating, the τ 6.96 doublet, which had already markedly diminished in relative intensity going from the crude to the glpc-isolated material, showed a still further decrease in relative area. In addition the characteristic features of the nmr reported[22] for **19** had become more clearly defined while signals, other than the τ 6.96 doublet, not compatible with structure **19**, seemed to be disappearing. From this evidence it was apparent that ketone **18** was being thermally converted into ketone **19**.

Lithium Aluminum Hydride Reduction of the Spinning-Band Fraction SB-F-1 (Formation of Bicyclo[3.3.0]oct-3-en-2-ol).—The spinning-band fraction assigned structure **2** (SB-F-1) (1 g, 6 mmol) was treated with a suspension of 0.85 g (22 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether as described above. Glpc analysis (EGA, 4 ft, 130°) of the crude product (0.35 g, 54%) yielded a broad major peak. Preparative glpc, isolating either the front or the tail end of this peak, gave materials whose ir spectra were indistinguishable: ir (CCl_4): 3590, 3310, 3040, 1115, 1040, 1010 and 930 cm^{-1}; nmr (crude product): τ 4.42 (m, 2, =CH), 5.75 (doublet of doublets, J ~3 Hz, J ~ 1 Hz, CHOH), 6.0 (s, 1, OH), 6.80 (m, 1, bridgehead =CCH), 7.67 (m, 1, bridgehead CH), 8.58 (m, 6, CH_2). On the basis of spectral data, the major product was assigned the structure bicyclo[3.3.0]oct-3-en-2-ol.

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.71. Found: C, 77.05; H, 9.61.

Oxidation of the Crude Alcohol from SB-F-1 (Formation of Bicyclo[3.3.0]oct-3-en-2-one).—To 40 ml of pyridine was added 4 g of chromium trioxide, the crude bicyclo[3.3.0]oct-3-en-2-ol, and then an additional 8 ml of pyridine. After stirring at room temperature overnight, the mixture was poured onto 50 ml of ice and the resultant liquid extracted with two 150-ml portions of ether. The combined ether layers were washed with 150-ml portions of water, 3 *N* hydrochloric acid, and water, then dried ($MgSO_4$), and concentrated. Glpc analysis (EGA, 4 ft, 170°) showed a single major product. A sample of this product, isolated by glpc, exhibited the following spectral properties: uv: λ_{max} (95% ethanol) 218 mμ (ϵ 9300), 310 (46); ir (CCl_4): 3040, 2950, 1710, 1265 cm^{-1}; nmr: τ 2.67 (doublet of doublets, 1, J = 6 Hz, J = 3 Hz, HC=CC=O), 4.05 (doublet of doublets, 1, J = 6 Hz, J = 2 Hz, =CHC=O), 6.77 (m, 1, bridgehead CHC=O), 7.50 (m, 1, bridgehead =CCH), 7.8–8.9 (m, 6, CH_2). These data were compatible with the structure *cis*-bicyclo[3.3.0]oct-3-en-2-one (**8**).

Anal. Calcd for $C_8H_{10}O$: C, 78.55; H, 8.23. Found: C, 78.61; H, 8.35.

Hydrogenation of the Spinning-Band Fraction SB-F-1 (Formation of Bicyclo[3.3.0]octan-2-yl Acetate).—A mixture of 1 g (6 mmol) SB-F-1, 100 mg of platinum oxide, and 50 ml of glacial acetic acid was stirred for 22 hr in an atmospheric pressure hydrogenation apparatus. The catalyst was removed by filtration and the supernatant liquid diluted with 150 ml of water. After extraction with two 200-ml portions of ether, the ether layers were combined, washed with two 300-ml aliquots of water, 100 ml of 10% sodium bicarbonate solution, and again water, dried ($MgSO_4$), and concentrated. Glpc analysis of the residue (0.49 g, 49%) displayed a single major product which was collected from the glpc (EGA, 4 ft, 130°). The component acetates of this peak were assigned the structures *endo*- and *exo*-bicyclo[3.3.0]octan-2-yl acetate based on the fact that conversion into the corresponding alcohols gave compounds whose ir spectra were identical with those of authentic *endo*- and *exo*-bicyclo[3.3.0]octan-2-ol. The ir and nmr spectra of the product were identical with that of the minor acetate isolated from the hydrogenation of the acetate mixture of **1** and **2**.

Lithium Aluminum Hydride Reduction of the Hydrogenation Mixture (Formation of 5 and 6).—To a suspension of 0.6 g (16 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether was added 0.25 g (1.5 mmol) of the compound assigned the structure bicyclo[3.3.0]octan-2-yl acetate. The resultant mixture was treated in the usual manner. Glpc (EGA, 4 ft, 130°) of the crude product showed two overlapping peaks in an approximate ratio of 20:80. The minor peak which had the shorter retention time could not be isolated in sufficient purity for positive identification. The major peak, collected from the gas chromatograph, exhibited an ir spectrum identical with that of an authentic sample[4] of *exo,cis*-bicyclo[3.3.0]octan-2-ol (**5**); nmr: τ 6.23 (m, 1, CHOH), 7.6 (m, 2, bridgehead CH), 7.6 (s, 1, OH), 7.9–9.0 (m, 10, CH_2).

Oxidation of the Alcohol Mixture Containing 5 and 6.—To 10 ml of pyridine was added, with stirring, 1 g of chromium trioxide and the crude alcohol mixture derived from **2** by hydrogenation and lithium aluminum hydride reduction. The resultant mixture was treated in the manner previously described to give a homogeneous product on glpc (EGA, 4 ft, 125°). The nmr spectrum of the product showed bands centered at τ 7.3 (m, 1, bridgehead CHC=O), 7.3–8.75 (m, 11, CH_2 and bridgehead CH).

Regeneration of Alcohols 5 and 6 from Oxidation Product.—The crude alcohol oxidation product was treated with a suspension of 0.3 g of lithium aluminum hydride in 10 ml of anhydrous ether in the usual way. Glpc of the product showed two overlapping product peaks in about a 75:25 ratio in order of their respective retention times. The retention time of the major peak was identical with that of the unidentified minor peak in the alcohol mixture from which the oxidation product was derived. In addition the ir spectrum of this major peak was identical to that of an authentic sample[4] of *endo,cis*-bicyclo[3.3.0]octan-2-ol (**6**). The minor constituent had a retention time identical with

that of **5**. However it could not be isolated in sufficient purity for positive identification.

Bromination of 1,4-Cyclooctadiene.—A mixture of 2 g (18.5 mmol) of 1,4-cyclooctadiene,[16] 3.5 g (19.7 mmol) of N-bromosuccinimide, 30 mg of benzoyl peroxide, and 30 ml of carbon tetrachloride was refluxed in a nitrogen atmosphere for 3 hr. The reaction mixture was cooled in a refrigerator, filtered, washed with 50-ml portions of water, 10% sodium bicarbonate solution, and water, and dried ($MgSO_4$). The carbon tetrachloride was removed by distillation under reduced pressure and the residue then distilled to give 1.64 g (49%) of a bromide mixture: bp 25–34° (0.07 mm). The nmr spectrum of this product was identical with that of the bromide mixture obtained by similar treatment of 1,3-cyclooctadiene.

Lithium Aluminum Hydride Reduction of the 1,4-Cyclooctadiene Bromination Product.—The bromination product (0.5 g, 2.7 mmol) and a suspension of 0.15 g (4.0 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether were treated in the manner described above. The product showed two peaks in about a 40:60 ratio in order of their retention times. These products were identified as 1,3- and 1,4-cyclooctadiene, respectively, by comparison of their retention times with those of authentic samples.

Acetylation of the 1,4-Cyclooctadiene Bromination Product.—To 1 g (5.4 mmol) of the bromination product in 2 ml of glacial acetic acid was added a slurry of 1.35 g (8.1 mmol) of silver acetate in 5 ml of acetic acid. After stirring in the dark overnight, the mixture was filtered and the filtrate added to 75 ml of water. The resultant solution was extracted with 75- and 25-ml portions of ether; the combined ether layers were washed with 100-ml portions of water, 10% sodium bicarbonate solution, and water, dried ($MgSO_4$), and concentrated with a rotary evaporator. The product (0.67 g, 75%) showed two major product peaks on glpc (EGA) in the approximate ratio of 15:85. The ir spectra and retention times of these materials were identical with those of the acetates **1** and **2** derived from 1,3-cyclooctadiene.

Bromination of 1,5-Cyclooctadiene (Formation of 22 and 23).—A mixture of 108.5 g (1.01 mol) of 1,5-cyclooctadiene, 180 g (1 mol) of N-bromosuccinimide, 0.95 g benzoyl peroxide, and 400 ml of carbon tetrachloride was refluxed, under nitrogen, for 2 hr. The reaction mixture was then cooled in an ice bath and filtered. The filtrate was washed with 600-ml portions of water, 10% sodium bicarbonate solution (twice), and water, and then dried by stirring with $MgSO_4$ for 2 hr. The carbon tetrachloride and unchanged diene were removed by distillation under reduced pressure and the residue was then distilled to give 106 g (57%) of a bromide mixture: bp 27–67° (0.1 mm); nmr: τ 4.1–4.7 (m, =CH), 4.7–5.5 (m, =CCHBr), 7.2 (t, J = 4 Hz, $=CCH_2C=$), 7.3–8.4 (m, $=CCH_2$ and CH_2). By comparison of the integrated area of the τ 7.2 absorption with that of the total spectrum it was discerned that the mixture comprised about 55% of the allylic rearrangement product, 2,5-cyclooctadien-1-yl bromide. The remaining 45% was assumed to be the expected 2,6-cyclooctadien-1-yl bromide.

Lithium Aluminum Hydride Reduction of the 1,5-Cyclooctadiene Bromination Product.—A mixture of 2 g (10.8 mmol) of the 1,5-cyclooctadiene bromination product and a suspension of 0.75 g (19.8 mmol) of lithium aluminum hydride in 25 ml of anhydrous ether was treated in the usual manner. The product showed two glpc peaks in a 28:72 ratio in order of their retention times. These components were respectively identified as 1,4- and 1,5-cyclooctadiene by comparison of their ir spectra and retention times with those of authentic samples.

Acetylation of the 1,5-Cyclooctadiene Bromination Product (Formation of 24 and 25).—The bromination product (43 g, 0.23 mol) in 100 ml of glacial acetic acid was treated with a slurry of 57 g (0.34 mol) of silver acetate in 125 ml of glacial acetic acid in the manner described above to afford 18.2 g (48%) of an acetate mixture (bp 52–57° at 0.1 mm) found by glpc (EGA, 4 ft, 150°) to contain two major components in a 24:76 ratio in order of their retention times. A sample of the major product, isolated by glpc, displayed the following spectral data: ir (CCl_4): 3005, 1740, 1250, 1025, 955, 685, and 650 cm^{-1}; nmr: τ 3.9–4.2 (m, 1, =CCHOAc), 4.2–4.9 (m, 4, =CH), 7.1–8.0 (m, 6, $=CCH_2$), 8.01 (s, 3, $O=CCH_3$). Based on the spectral results, the major acetate was assigned the structure 2,6-cyclooctadien-1-yl acetate (**25**).

Anal. Calcd for $C_{10}H_{14}O_2$ (**25**): C, 72.24; H, 8.49. Found: C, 72.47; H, 8.58.

Similarly, the minor acetate exhibited ir (CCl_4): 3005, 1735, 1250, 1040, 870, 720, and 675 cm^{-1}; nmr: τ 4.0–5.0 (m, 5, =CH and =CCHOAc), 7.17 (m, 2, $=CCH_2C=$), 7.2–8.9 (m, 4, $=CCH_2$ and CH_2). This isomer was assigned the structure 2,5-cyclooctadien-1-yl acetate (**24**).

Anal. Calcd for $C_{10}H_{14}O_2$ (**24**): C, 72.24; H, 8.49. Found: C, 71.94; H, 8.45.

Distillation of 13.3 g of the acetate mixture through an 18-in. Teflon spinning-band column separated it into two major fractions: SB-F-3 (0.73 g, bp 54° at 0.7 mm) and SB-F-4 (9.20 g, bp 62–64° at 0.8 mm). Glpc (EGA, 4 ft, 150°) showed SB-F-3 to contained about 83% of the minor acetate product 2,5-cyclooctadien-1-yl acetate while SB-F-4 contained about 91% of the major acetate product **25**. A trace product (about 1%) appeared in the glpc of SB-F-3 with a slightly shorter retention time than the two identified acetates. This product could not be isolated in sufficient quantity for identification.

Lithium Aluminum Hydride Reduction of SB-F-4 (Formation of 2,6-Cyclooctadien-1-ol).—To a suspension of 0.6 g (16 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether was added 2 g (12 mmol) of SB-F-4. The resultant mixture was treated in the usual manner to give 0.8 g (54%) of a mixture containing about 90% of one alcohol. A glpc-isolated sample (EGA, 4 ft, 175°) of this alcohol showed the following spectral properties: ir (CCl_4): 3600, 3325, 3000, 1080, 1040, 1015, 980, 900, 720, and 650 cm^{-1}; nmr (external TMS): τ 4.2–4.9 (m, 4, =CH), 5.1–5.5 (m, 1, =CCHOH), 7.1–8.1 (m, 6, $=CCH_2$), 8.13 (s, 1, OH). This spectral data is compatible with the structure 2,6-cyclooctadien-1-ol.

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.71. Found: C, 77.67; H, 9.70.

Oxidation of the Alcohol Mixture from SB-F-4 (Formation of 27).—To 15 ml of pyridine was added 2 g of chromium trioxide and a solution of 0.5 g of the alcohol mixture from SB-F-4 in 8 ml of pyridine. The resultant mixture was treated in the usual manner to give a crude ether solution, the glpc (EGA, 4 ft, 160°) of which showed two products in a 15:85 ratio in order of their retention times. Based on spectral data, the major product was assigned the structure 2,6-cyclooctadien-1-one (**27**): ir (CCl_4): 3010, 2950, 1670, 1650, 1235, 1220, 1125, 1080, 830, and 670 cm^{-1}; uv: λ_{max} (95% ethanol) 223 mμ (ϵ 7700), 321 (110); nmr (external TMS): τ 3.4–4.9 (m, 4, =CH), 6.76 (d, 2, J = 6 Hz, $=CCH_2C=O$), 7.1–8.0 (m, 4, $=CCH_2$).

Anal. Calcd for $C_8H_{10}O$ (**27**): C, 78.55; H, 8.23. Found: C, 78.37; H, 8.20.

The minor glpc-isolated product exhibited the following spectral properties: ir: 3030 (=CH), 1675 (=CC=O); uv: λ_{max} (95% ethanol) 233 mμ (ϵ 5000), 317 (s, ϵ 38). The low degree of unsaturation (as determined from the ir spectrum) in addition to the uv data are compatible with the structure bicyclo[4.2.0]oct-3-en-2-one. This may be a product of thermal isomerization[25] on the glpc. A complete structure proof was not carried out.

Lithium Aluminum Hydride Reduction of SB-F-3 (Formation of 2,5-Cyclooctadien-1-ol).—The spinning-band fraction containing mostly 2,5-cyclooctadien-1-yl acetate (SB-F-3, 0.5 g, 3 mmol) was reduced with a suspension of 0.6 g (16 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether, in the usual manner, to afford 0.22 g (59%) of a crude alcohol mixture. Glpc (EGA, 4 ft, 175°) indicated that the product contained about 90% of a single component which was collected from the glpc and showed ir absorptions (CCl_4) at 3600 (OH), 3325 (OH), 3005 (=CH), 1055 cm^{-1} (CO). An nmr spectrum of the crude alcohol mixture showed signals at τ 4.0–5.0 (m, 5.1, =CH), 5.3 (quintet, 1, J = 5 Hz, =CCHOH), 6.2 (s, 1, OH), 7.23 (t, 2, J = 4 Hz, $=CCH_2C=$), 7.0–9.0 (m, 5.7, $=CCH_2$ and CH_2). The somewhat larger than expected integrated areas for the vinyl and methylene regions can be traced to impurities present in the crude material. In general, the ir and nmr spectra are in good agreement with those expected for the anticipated major product, 2,5-cyclooctadien-1-ol.

Attempted Oxidation of the Crude Alcohol Mixture from SB-F-3.—To 10 ml of pyridine was added 1 g of chromium trioxide and a solution of 0.2 g of the crude alcohol mixture in 2 ml of pyridine. The mixture was treated in the usual manner to afford about 50 mg (25%) of a ketone mixture, the glpc (EGA, 4 ft, 140°) of which showed three product peaks in the approximate ratio of 12:62:26 in order of their retention times. The smallest component exhibited an ir spectrum identical with that of the 30:70 mixture of **18** and **19** described above. The peak of longest retention time had an ir spectrum identical with that of

dienone **27**. Only about 1 mg of the major product could be isolated from glpc owing to the significant overlap of this peak and that of **27**. A capillary tube nmr[27] of this sample, after standing at room temperature for several days, showed absorption regions at τ 3.4–4.9 (~4, =CH) and 6.7–8.2 (~6, $CH_2C{=}O$, $=CCH_2$ and $=CCH_2C{=}$). The fine structure of the nmr signals was not discernible. An ir spectrum of this sample displayed bands at 3020 (=CH), 1705 (C=O), and 1665 cm^{-1} (=CC=O). The absorption at 1705 cm^{-1} may indicate that some of **18** was present and was formed either on standing at room temperature or upon collection from the glpc. Since **18** was also found upon glpc analysis, it appears that the latter explanation is more plausible.

Lithium Aluminum Hydride Reduction of the Crude Acetate Mixture from 1,5-Cyclooctadiene (Formation of 2,5- and 2,6-Cyclooctadien-1-ol).—The crude acetate mixture (2 g, 12 mmol) derived from the 1,5-cyclooctadiene bromination product was reduced with a suspension of 0.6 g (15 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether to give 0.72 g (48%) of a crude alcohol product which showed two major glpc components (EGA, 4 ft, 175°) in a 45:55 ratio, in order of their retention times. The ir spectra of samples of the minor and major peaks, collected from the glpc, were identical with those of compounds previously assigned the structures 2,5-cyclooctadien-1-ol and 2,6-cyclooctadien-1-ol, respectively.

Conversion of the Crude Alcohol Mixture into the Tosylates.—To a solution of the crude alcohol mixture (0.5 g) in 10 ml of cold pyridine was added 1.55 g of tosyl chloride. The mixture was isolated as described above to afford an ether solution of a crude tosylate mixture which was not further purified.

Lithium Aluminum Hydride Reduction of the Crude Tosylates.—The crude tosylate mixture was treated with a suspension of 0.3 g of lithium aluminum hydride in 10 ml of anhydrous ether in the usual way to afford two major products in a 56:44 ratio, in order of their retention times. The ir spectra of the major and minor products were identical with those of authentic samples of 1,4- and 1,5-cyclooctadiene, respectively.

Registry No.—**1**, 10095-82-6; **2**, 23346-35-2; **5**, 23359-88-8; **8**, 1122-07-2; **11**, 10095-81-5; **12**, 23346-37-4; **15**, 10095-79-1; **20**, 4734-90-1; **22**, 23359-89-9; **23**, 23346-40-9; **24**, 23346-41-0; **25**, 23346-42-1; **27**, 1460-21-5; bicyclo[3.3.0]octan-2-yl acetate, 23346-44-3; bicyclo[3.3.0]oct-3-en-2-ol, 23346-45-4; 2,6-cyclooctadien-1-ol, 10017-18-2; 2,5-cyclooctadien-1-ol, 10054-74-7.

(27) L. R. Provost and R. V. Jardine, *J. Chem. Educ.*, **45**, 675 (1968).

Molecular Rearrangements. IX.[1a] The Synthesis and Rearrangements of 2-Chlorobicyclo[2.2.2]oct-2-ene Oxide

Richard N. McDonald and Richard N. Steppel[1b,c]

Department of Chemistry, Kansas State University, Manhattan, Kansas 66502

Received September 15, 1969

The synthesis of 2-chlorobicyclo[2.2.2]oct-2-ene oxide (**4**) is reported. Neat, thermal rearrangement of **4** produces 89% 3-chlorobicyclo[2.2.2]octan-2-one (**8**) in addition to nine minor products. Acetolysis of **4** gives as major products **8** (45%) and 3-acetoxybicyclo[2.2.2]octan-2-one (**11**, 40%). Reaction of **4** with anhydrous hydrogen chloride in ether leads to the formation of **8** and 3,3-dichlorobicyclo[2.2.2]octan-2-ol (**10**). The formation of these products is compared with and contrasted to the results from similar studies with 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide.

Our previous investigations of the mechanism of the epoxide–carbonyl rearrangements of α-chloro epoxides have involved peroxidations of α-chlorostilbenes,[2] the intermediacy of α-chloro epoxides being assumed, and studies with the relatively stable α-chloro epoxides, 1-chloro-*cis*- (**1**) and -*trans*-4-methylcyclohexene oxide (**2**),[3] and 2-chloronorbornene *exo*-oxide (**3**).[4,5] The results obtained from these latter α-chloro epoxides have led us to suggest that α-ketocarbonium ion–chloride ion pairs are the principal intermediates in their neat, thermal rearrangements.

A goal of our program in this area of molecular rearrangements has been to study the kinetics of rearrangement of a number of α-chloro epoxides as a function of solvent, added salts, etc., to help us to substantiate or refute the idea of such ion-pair intermediates. The mixture of **1** and **2** did not appear to be suitable for such kinetic studies, since we have been unable to rule out the possibility of a chloronium ion intermediate for the rearrangement of **1**.[3] α-Chloro epoxide **3** was also less suitable than desired, since in neat, thermal rearrangements *ca.* 40% was converted into polymeric material.[4]

The present work reports the synthesis and certain rearrangement studies of 2-chlorobicyclo[2.2.2]octene oxide (**4**), which appears to be a reasonable candidate for the proposed kinetic studies. Epoxide **4** might also allow us to determine the effect of the bicyclic framework on the rearrangement of the analogous bicyclic epoxide, **3**, since **4** has considerably less angle strain than **3**.[6] The *exo–endo* geometric relationship present in **3** is absent in **4**.

Results

The synthesis of **4** began with the Diels–Alder reaction of cyclohexadiene and *trans*-1,2-dichloroethylene. This reaction had been reported by Hine, *et al.*,[7] who stated that "from the boiling point, method of preparation, and analysis, the mixture appeared to contain 5,6-dichlorobicyclo[2.2.2]oct-2-ene (**5**) and a somewhat larger amount of cyclohexadiene dimer." Indeed, separation of **5** from cyclohexadiene dimer was effected only after a careful distillation, and yields of **5** averaged *ca.* 20%. The halogens are believed to be *trans* by analogy to the stereochemistry of the product

(1) (a) Part VIII: R. N. McDonald and D. G. Hill, *Chem. Commun.*, 671 (1969). (b) NDEA Fellow, 1964–1967; NSF Cooperative Fellow, 1967–1968. (c) Taken from the Ph.D. Thesis of R. N. Steppel.

(2) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **85**, 820, 4004 (1963).

(3) R. N. McDonald and T. E. Tabor, *ibid.*, **89**, 6573 (1967).

(4) R. N. McDonald and T. E. Tabor, *J. Org. Chem.*, **33**, 2934 (1968).

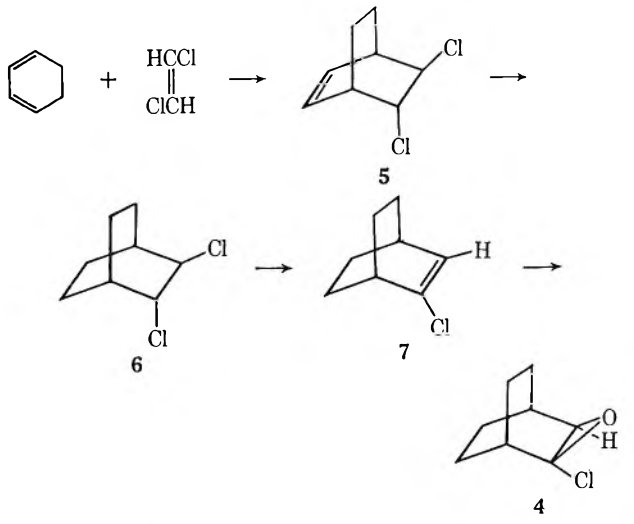
(5) R. N. McDonald and R. N. Steppel, *J. Amer. Chem. Soc.*, **91**, 782 (1969).

(6) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *ibid.*, **83**, 988 (1961).

(7) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner, and M. Hine, *ibid.*, **77**, 594 (1955).

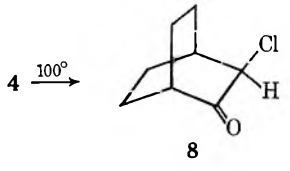
obtained from cyclopentadiene and *trans*-1,2-dichloroethylene.[8]

Hydrogenation of **5** (usually as a mixture with dicyclohexadiene) over 5% palladium on carbon in ethyl alcohol gave *trans*-2,3-dichlorobicyclo[2.2.2]-octane (**6**) in yields of *ca.* 80%. Dehydrochlorination of **6** with potassium *t*-butoxide in *t*-butyl alcohol afforded 2-chlorobicyclo[2.2.2]octene (**7**) in *ca.* 85% yield. Epoxidation of **7** with *m*-chloroperbenzoic acid

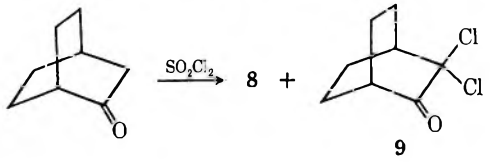


gave a 60% yield of **4** as a crystalline compound, mp 47–48°, which is a reasonably stable α-chloro epoxide.

Neat, thermal rearrangements of **4** were conducted in sealed tubes with a bath temperature of 100°. After 24 hr the samples had not colored and only traces of hydrogen chloride were evident when the tubes were opened. This is in marked contrast to similar attempts with **3** at 60°, where immediate darkening and facile rearrangement (sometimes explosively) occurred and relatively large quantities of hydrogen chloride were noted. The product mixture from **4** was shown by glpc to consist mainly of 3-chlorobicyclo-[2.2.2]octanone (**8**, 89.7%),[9] along with at least nine other components of unknown structure.



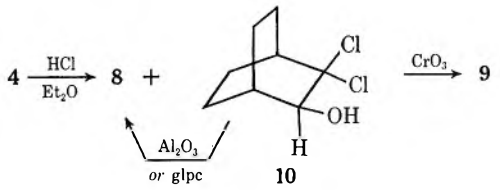
To verify the structure of the major product, **8**, bicyclo[2.2.2]octanone was chlorinated with sulfuryl chloride. From this reaction a mixture of **8** and 3,3-dichlorobicyclo[2.2.2]octanone (**9**) was obtained. When excess sulfuryl chloride was employed, **9** was the only product formed in 83% yield.



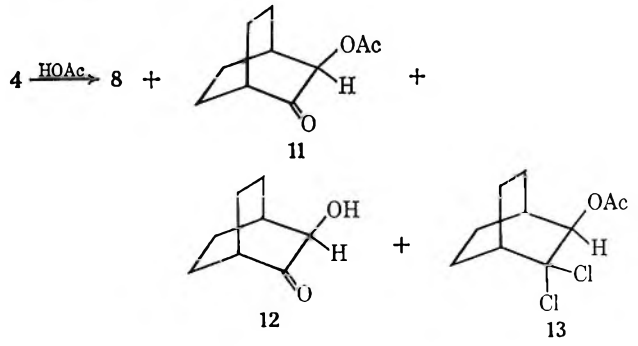
(8) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Amer. Chem. Soc.*, **76**, 5692 (1954).

(9) Glpc integrated per cent.

Treatment of **4** with anhydrous hydrogen chloride in ether gave a mixture of 3,3-dichlorobicyclo[2.2.2]-octan-2-ol (**10**) and **8** in a ratio of 2:1 as determined by nmr spectroscopy. Attempted separation and purification of this mixture by glpc or column chromatography on acidic alumina resulted in substantial or complete conversion of **10** into **8**. Chromic acid oxidation of the 1:2 mixture of **8** and **10** produced a mixture of **8** and **9** in a ratio of 7:3 as analyzed by glpc, thus establishing the presence of **10** in the original mixture. We believe that probably as much as 95% of the reaction between hydrogen chloride and **4** occurs by addition to form **10**, which then eliminates hydrogen chloride and ketonizes to yield **8** to some extent in the work-up.



Acetolysis of **4** produced a mixture of at least 16 components as analyzed by glpc, of which only four integrated for more than 2.0% when a basic wash in the work-up was omitted. The two major products were identified as **8** (44.8%)[9] and 3-acetoxybicyclo[2.2.2]-octan-2-one (**11**, 39.5%).[9] 3-Hydroxybicyclo[2.2.2]-octanone (**12**) was obtained in 0.8%[9] yield, which increased to 12.7% when the acetolysis product was taken up in ether and washed with aqueous base.



A second acetate was obtained as a minor product which, on the basis of its infrared and nmr spectra, was thought to be 2-acetoxy-3,3-dichlorobicyclo[2.2.2]-octane (**13**). Acetate **13** could have been formed by addition of hydrogen chloride (generated in the formation of **11**) to **4** to produce **10** followed by acid-catalyzed esterification.

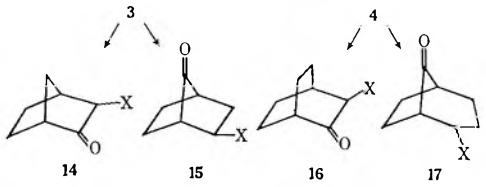
The structures of **11** and **12** were verified by independent synthesis. α-Chloro ketone **8** was heated under reflux with aqueous potassium carbonate to give **12** in *ca.* 90% yield. Acetylation of **12** produced **11**.

Discussion

As pointed out above, the neat, thermal rearrangement of **4** proceeds far more cleanly than that of its [2.2.1] analog, **3**.[4] Little if any rearrangement of **4** to 8-ketobicyclo[3.2.1]oct-2-yl products was observed, whereas Wagner–Meerwein rearrangement of **3** under the same conditions was a major process.[4] These are summarized in Table I.

Table I

Integrated Glpc Percentages of Keto Products in Isolated Rearrangement Products[a]



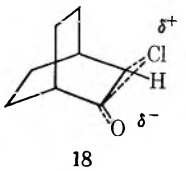
Rearrangement type	14	15	16	17
Neat, thermal	37.4	36.9[b]	89.7	c
HCl, ether	13.0	23.2	33.3[d]	0.0
HOAc	8.5	25.9	85.1	c

[a] X is Cl in neat, thermal, and HCl-catalyzed rearrangements, and Cl, OAc, and OH in acetolysis. [b] This includes 2.0% bicyclo[2.2.1]hept-2-en-7-one. [c] No products containing the [3.2.1] ring system were identified, but it seems likely that several are among the minor components. [d] It is not certain if any of **8** is formed directly or if it arises by dehydrochlorination of **10**.

Solvolyses of bicyclo[2.2.2]octan-2-yl arenesulfonates[6,10] and deamination of 2-aminobicyclo[2.2.2]-octane[10] generally lead to mixtures of [2.2.2] and [3.2.1] products with the [2.2.2] product predominating. We were surprised to find a lack of rearrangement in the major isolated product, especially in the hydrogen chloride catalyzed rearrangement and acetolysis of **4**, where the recovery of products is very good. These two reactions with **3** produced **15** to **14** ratios of 1.8 and 3.0, respectively. The exact ratios of **17** to **16** are unknown but are definitely inverted compared with **15** to **14** ratios, being less than 0.17.

At least two interpretations may be offered to explain this reduced amount of skeletal rearrangement from **4** compared with **3**: (A) a change in mechanism, or (B) the greater stability of the 3-ketobicyclo[2.2.2]oct-2-yl cation relative to the 8-ketobicyclo[3.2.1]oct-2-yl cation compared with that of the 3- and 7-ketonorborn-2-yl cations.

In the neat, thermal rearrangement of **4**, interpretation A could encompass several possibilities, including (a) hydride rather than chloride as the principal migrating group and (b) chlorine migrating *via* a chloronium ion, **18**. Hydride shifts have been shown



18

to be nonexistent in the related rearrangement of **1** and **2**,[3] and to contribute less than 10% of the total rearrangement of **3** to *exo*-3-chloronorcamphor.[5,11] A chloronium ion intermediate is ruled out as a major process with **3** and also is not believed to be occurring in the rearrangement of the mixture of **1** and **2**. Arguing from these analogies, we conclude that a gross change in mechanism in the rearrangement of **4** to **8** is unlikely.

(10) H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1397 (1961).

(11) Multiple hydride shifts (*endo*-3,5, *exo*-5,6, and *endo*-6,2) have been shown to contribute to the extent of 3.1% in the neat, thermal rearrangement of **3**: R. N. Steppel, unpublished results.

Defense of interpretation B may be found in the comment by Sargent "that the rehybridization of C_2 from sp^3 to sp^2, necessitated by the generation of a carbonium ion, must result in a substantially greater increment in angle strain for the norbornyl system than for the bicyclo[2.2.2]octyl system."[12] It would appear that this reduced strain in the [2.2.2] system would become even more significant as we introduce two sp^2-hybridized carbons into an ethano bridge, as would be the case in the 3-ketobicyclo[2.2.2]oct-2-yl cation.[6,13] This explanation could account for the facts that (A) neat, thermal rearrangement of **3** leads to the formation of about equal amounts of *exo*-3-chloronorcamphor and *exo*-2-chloro-7-ketonorbornane[4] while similar treatment of **4** leads to primarily **8**, and (B) acetolysis of **3** gives a small amount of *exo*-2-acetoxy-7-ketonorbornane as the only identified acetoxy ketone[4] while acetolysis of **4** produces a relatively large amount of acetoxy ketone **11**. Chloro ketone **8** has been shown to be stable to the acetolysis conditions.

Another factor which may be of importance in comparing the rearrangements of **3** and **4** is that, when chloride departs from **3**, it leaves from the *endo* face of the [2.2.1] system and must rebond from the *exo* face to give the major products of neat, thermal rearrangement, **14** (*exo*-X = Cl) and **15** (X = Cl).[4,5] Skeletal rearrangement of the suggested intermediate 3-keto- to the 7-ketonorbornyl cation–chloride ion pair could then compete with collapse to products. No such timing delay or motion for chloride ion migration is required in the rearrangement of **4** to **8** in the [2.2.2] system.

Formation of a nonclassical ion pair in the [2.2.1] system and not in the [2.2.2] system is yet another explanation which cannot be ruled out.[5] A more definitive explanation must await further work in this and related systems.

Experimental Section[14]

trans-**5,6-Dichlorobicyclo[2.2.2]oct-2-ene (5).**—In a Carius tube a mixture of 24 g (0.3 mol) of 1,3-cyclohexadiene, 38.8 g (0.4 mol) of *trans*-1,2-dichloroethylene, 200 mg of hydroquinone, and 200 ml of diphenylamine was heated at 180–200° for 30 hr. After cooling to room temperature the tube was opened carefully, since hydrogen chloride is normally present. The excess dichloroethylene was removed in a trap-to-trap distillation under reduced pressure, leaving a dark green residue (*ca.* 35 g) composed mainly of **5** and dicyclohexadiene.

A number of such reaction mixtures were combined and distilled using a 30-cm Vigreux column, collecting the material boiling above 45° (1 mm). Redistillation of 50 ml of this crude product using a Teflon annular spinning-band column gave 7.94 g of pure **5**, bp 56° (1 mm) [lit.[7] bp 90–93° (10 mm)], along with 7.93 g of 84.5% pure product. The yields averaged 20%. The infrared spectrum (neat) of **5** exhibited a broad olefinic absorption at 5.9–6.4 μ with strong absorptions at 3.34, 12.0, 13.4, and 14.7 μ, while the nmr spectrum (CCl_4, internal TMS) showed absorptions centered at τ 3.68 (m, 2), 6.15 (m, 2), 7.23 (m, 2), and 7.7–9.2 (m, 4).

(12) G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966); see p 361.

(13) For discussion of the greater stability of bicyclo[2.2.2]octene compared with norbornene, see R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, **79**, 4116 (1957); H. L. Goering and M. F. Sloan, *ibid.*, **83**, 1992 (1961).

(14) All melting points were taken on a Kofler hot stage (in sealed capillaries) and are corrected; boiling points are uncorrected. Infrared absorption spectra were determined using a Perkin-Elmer Model 137 double-beam recording spectrometer and nmr spectra were obtained using a Varian A-60 recording spectrometer. Gas chromatographic analyses were performed on an F & M Model 500 temperature-programmed gas chromatograph. Microanalyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

trans-2,3-Dichlorobicyclo[2.2.2]octane (6).—A mixture of 41 g of Diels–Alder product containing 37% 5 and dicyclohexadiene dissolved in 60 ml of absolute ethanol was hydrogenated using 3.0 g of 5% palladium on carbon at room temperature in a glass-lined bomb (Magna Dash) with an initial hydrogen pressure of 1100 psi. After 12 hr, the catalyst was removed by filtration and most of the ethanol was distilled under reduced pressure in a short-path distillation (excessive heating causes decomposition). Upon cooling, 16 g of white, crystalline product was obtained. Drying in a desiccator over calcium chloride and sublimation at 50° (5 mm) gave 15.1 g (99%) of pure *trans*-2,3-dichlorobicyclo-[2.2.2]octane, mp 118.5–119.5°. Similar results were obtained using prereduced platinum oxide in a Parr apparatus with yields of about 80%. The infrared spectrum (Nujol) had characteristic, strong absorptions at 10.4, 11.96, 12.25, 12.51, and 14.58 μ (broad). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 5.81 (s, 2), and 7.8–8.8 (m, 10).

2-Chlorobicyclo[2.2.2]octene (7).—Potassium *t*-butoxide was prepared by treating 400 ml of *t*-butyl alcohol with 27.9 g (0.71 g-atom) of potassium. To this stirred solution was added 85.0 g (0.48 mol) of 6 and the mixture was heated under reflux for 40 hr. After cooling, 300 ml of water was added and the mixture was extracted with five 100-ml portions of pentane. The combined pentane extracts were washed with four 500-ml portions of water and dried ($MgSO_4$), and the pentane was removed by distillation. The residue was distilled using a semimicro spinning-band column, which afforded 58.3 g (86%) of 7, bp 108° (102 mm). The infrared spectrum (neat) had characteristic absorptions at 6.18, 9.71, and 14.35 μ, and the nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 3.68 (d of d, 1, J = 7.2 and 2.2 Hz), 7.37 (br s, 2), and 7.8–9.2 [m (a spike at 8.5), 8].

2-Chlorobicyclo[2.2.2]oct-2-ene Oxide (4).—An ice-cold solution of 7.1 g (0.05 mol) of 2-chlorobicyclo[2.2.2]oct-2-ene in 100 ml of methylene chloride was treated with 13.0 g (0.06 mol) of 80%) *m*-chloroperbenzoic acid. After 1 hr the precipitated *m*-chlorobenzoic acid was filtered and washed with small portions of cold methylene chloride. After 48 hr, additional *m*-chlorobenzoic acid was again filtered and similarly washed. The filtrate was washed with cold, saturated aqueous sodium bicarbonate and water and dried over magnesium sulfate. After most of the methylene chloride had been removed under reduced pressure, 150 ml of hexane was added and the work-up was repeated. Careful removal of the hexane under reduced pressure afforded a semisolid, crude product weighing 7.4 g, which was dissolved in 30 ml of hexane and divided into three approximately equal portions. Each portion was chromatographed on 50 g of activity II, neutral alumina. Rapid elution with hexane gave a total of 4.74 g (60%) of 4 after the solvent had been removed by rotatory evaporation (avoiding excessive heating) and evaporation of the last traces of solvent at room temperature and atmospheric pressure (the liquid only crystallizing slowly after the solvent has evaporated), mp 47–48° after sublimation at 40° (100 mm). Column chromatography of larger amounts of epoxide on larger columns resulted in major losses owing to molecular rearrangement during chromatography. 3-Chlorobicyclo[2.2.2]octan-2-one (8) was the major rearrangement product and was eluted with benzene.

The infrared spectrum (neat) of 4 had strong characteristic absorptions at 9.28, 10.05, 10.34, 10.88, 12.0, 12.06, and 13.65 μ. The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions centered at τ 6.56 (d, 1, J = 4.5 Hz) and 7.5–9.0 (m, 10).

Anal. Calcd for $C_8H_{11}OCl$: C, 60.57; H, 6.99. Found: C, 60.30; H, 6.84.

Neat, Thermal Rearrangement of 2-Chlorobicyclo[2.2.2]oct-2-ene Oxide.—Two glass tubes (8-mm bore) were treated with cleaning solution ($Na_2Cr_2O_7$–H_2SO_4), distilled water, ammonium hydroxide, and distilled water, in that order. After drying in an oven at 100° the tubes were allowed to cool in a desiccator. Into each tube was placed 150 mg (95 mmol) of 4, and the tubes were flushed and evacuated several times under nitrogen and sealed under vacuum while cooling the epoxide with a Dry Ice–isopropyl alcohol bath. The two tubes were placed in a bath maintained at 100 ± 0.5°. The epoxide melted immediately. After 24 hr, the tubes were removed and allowed to cool. Upon opening, moist indicator paper signified the presence of a trace amount of hydrogen chloride, which could not be detected by smell. Comparison of the infrared spectrum of the rearrangement mixture with that of 3-chlorobicyclo[2.2.2]oct-2-one indicated the predominance of that compound. Glpc analysis on a 0.25 in. × 12 ft 10% Carbowax 20M on 60–80 Chromosorb W column showed ten peaks. The peaks, retention times (minutes), and integrated percentages follow: 1, 1.3, 0.7%; 2, 1.4, 1.4%; 3, 2.4, 0.5%; 4, 2.7, 0.3%; 5, 3.0, 0.7%; 6, 3.4, 0.4%; 7, 4.2, 1.6%; 8, 5.1, 89.7%; 9, 7.2, 2.5%; and 10, 8.0, 2.2%.

Component 8 was collected and identified as 3-chlorobicyclo-[2.2.2]octan-2-one (8) by comparison of the infrared and nmr spectra and retention time with those of an authentic sample. No attempt was made to identify the smaller components.

The second tube, containing rearrangement products, gave identical results on glpc analysis.

3-Chlorobicyclo[2.2.2]octan-2-one (8).—In an nmr spectral tube were placed 100 mg (0.9 mmol) of bicyclo[2.2.2]octan-2-one, 0.5 ml of carbon tetrachloride, 200 mg of sulfuryl chloride, and *ca.* 10 mg of azobisisobutyronitrile. The nmr spectrum of this reaction mixture just after combining the reagents indicated immediate formation of 3-chlorobicyclo[2.2.2]octan-2-one. After 1.5 hr, analysis by glpc indicated the presence of bicyclo[2.2.2]-octan-2-one, 8, and 3,3-dichlorobicyclo[2.2.2]octan-2-one (9) in the ratio of 3.3:33.3:63.4, respectively. Collection gave 15 mg (36%) of 8 and 55 mg (58%) of 9.

After sublimation at 69° (10 mm), the sample of 8 had mp 133.5–134° and its 2,4-dinitrophenylhydrazone had mp 151–152°, recrystallized from ethanol. The infrared spectrum (Nujol) of 8 had characteristic absorptions of 5.75 (CO), 9.4, 11.6, 11.88, 12.46, and 13.1 μ. The nmr spectrum ($CHCl_3$, internal TMS) exhibited absorptions at τ 5.85 (d of d, 1, J = 2.9 and 1.0 Hz) and 7.5–8.6 [m (major peaks at 7.68 and 8.14, 10].

Anal. Calcd for $C_8H_{11}OCl$: C, 60.57; H, 6.99. Found: C, 60.58; H, 7.07.

3,3-Dichlorobicyclo[2.2.2]octan-2-one (9).—A solution of 0.9 g (7.36 mmol) of bicyclo[2.2.2]octan-2-one in 5 ml of carbon tetrachloride was treated with 4 ml of sulfuryl chloride. Upon addition an exothermic reaction took place with the evolution of a gas. After stirring overnight the excess sulfuryl chloride and carbon tetrachloride were removed under reduced pressure in a trap-to-trap distillation which left a slightly yellow solid. The solid was sublimed at 60° (0.2 mm), which gave a slightly brown-tinted, white solid. The material was resublimed twice and afforded 1.14 g (80%) of 9, mp 190–191°.

The infrared spectrum (CS_2) had characteristic absorptions at 5.68 (CO), 5.72 (CO), 12.0, and 14.5 μ (broad). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 7.0–8.4 (m with two major peaks centered at 7.4 and 8.2).

Anal. Calcd for $C_8H_{10}OCl_2$: C, 49.78; H, 5.22. Found: C, 49.88; H, 5.33.

Acetolysis of 2-Chlorobicyclo[2.2.2]octene Oxide.—A solution of 1.1 g (7 mmol) of 4 in 25 ml of glacial acetic acid was stirred at room temperature for 3 days. The acetic acid was removed by a short-path distillation under reduced pressure, leaving a colorless, liquid reaction product. Analysis by nmr spectroscopy ($CDCl_3$, internal TMS) indicated downfield resonances centered at τ 4.87 and 5.77, with a shoulder on the upfield side of the τ 5.77 peak in the approximate ratio of 3.4:6.2 (including shoulder), as well as other absorptions which included two high-field singlets at τ 7.84 and 7.97. Estimation of the value of the shoulder gave the ratio of 35.4:45.2:19.4 for the two downfield peaks and the shoulder, respectively. The reaction components corresponding to the absorptions at τ 4.87 and the shoulder at τ 5.84 were assigned the structures of 3-acetoxybicyclo[2.2.2]octan-2-one (11) and 3-chlorobicyclo[2.2.2]octan-2-one (8), respectively (see below).

The reaction mixture was taken up in ether, washed with 5% aqueous sodium hydroxide and water, and then dried over magnesium sulfate. The ether was removed under reduced pressure, leaving 0.96 g of reaction product. Analysis of the nmr spectrum ($CDCl_3$, internal TMS) revealed downfield resonances at τ 4.87, 5.84, and 6.03 [assigned as the C_3H in 3-hydroxybicyclo[2.2.2]octan-2-one (see below)], while the peak at τ 5.77, present before base treatment, had completely disappeared. Integration gave the approximate ratio of the three respective peaks as 1.2:10:2.6; these values are only approximate because the integration was not very good. The singlet at τ 7.79 also disappeared, which suggested that it was due to an acetate which had been saponified, since no acid proton could be found. Analysis by glpc on a 0.25 in. × 12 ft 10% Carbowax 20M column showed the presence of six major components and at least eight minor components. The peaks, retention times (min), and integrated percentages follow: 1, 3.05, 0.1%; 2,

3.37, 0.1%; 3, 3.7, 0.3%; 4, 3.9, 0.3%; 5, 5.95, 1.0%; 6, 6.5, 0.4%; 7, 7.1, 4.2%; 8, 8.3, 0.8%; 9, 10.2, 12.7%; 10, 12.8, 60.2%; 11, 17.0, 0.9%; 12, 17.9, 11.6%; 13, 19.2, 2.8%; and 14, 20.8, 4.3%.

Groups of the above peaks were collected and then reinjected under appropriate conditions to effect the separation and collection of several of the individual components. In this manner peaks 9 and 10 were shown to be 3-hydroxy- (**12**) and 3-chlorobicyclo[2.2.2]octan-2-one (**8**), respectively, by comparison of their infrared and nmr spectra with those of authentic samples. Reinjection of **12** (peak 9) showed that it partially decomposed to a yellow solid whose nmr spectrum was identical with that for peak 11.

Peaks 11 and 12 were rechromatographed on a 0.25 in. × 6 ft 10% diisodecylphthalate column. An unidentified yellow solid, corresponding to peak 11, was obtained whose infrared spectrum was characterized by two strong absorptions at 5.73 and 5.81 μ. Its nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions centered at τ 7.2 (br s) and 7.98 (t, J = 1.5 Hz) in a 1:4 ratio. Peak 12 was collected as a white solid and shown to be 3-acetoxybicyclo[2.2.2]octan-2-one (**11**) by comparison of its infrared and nmr spectra with those of an authentic sample.

Peak 13 remained unassigned but may have been 3-acetoxy-3,3-dichlorobicyclo[2.2.2]octane (**13**) based on the strong carbonyl (5.82 μ) and strong acetoxyl (8.12 μ) absorptions in the infrared spectrum, while the nmr spectrum ($CHCl_3$, internal TMS) had absorptions at τ 4.72 (d, J = 2.2 Hz) and 7.4–8.8 (broad multiplet with a singlet absorption at τ 7.82). Reinjection of this material on glpc indicated that either the sample was impure or decomposition was taking place.

A 10-ml aliquot was removed from a second identical acetolysis run. The acetic acid was again removed under reduced pressure, leaving 310 mg of reaction product which was dissolved in 5 ml of acetone. Jones reagent[15] was added at 20–25° until the orange color of the oxidizing reagent persisted. Only a few drops were required, much less than would have been required if an oxidizable secondary alcohol would have been present in any significant amount based on a comparison of the oxidation of 320 mg of bicyclo[2.2.2]octan-2-ol to bicyclo[2.2.2]octan-2-one. After the mixture had stirred for 10 min, 10 ml of water was added to it, followed by saturation with sodium chloride. The mixture was extracted with 100 ml of ether in three portions and the combined extracts were washed with 5% aqueous sodium bicarbonate and water and dried over magnesium sulfate. Removal of the ether left 320 mg of reaction product. Analysis of the nmr spectrum before oxidation again clearly showed the peaks at τ 4.78 and 5.77 with a definite upfield shoulder on the τ 5.77 peak, the size of the τ 4.87 peak being just slightly smaller than the combined τ 5.77 peak and shoulder. Analysis of the nmr spectrum after oxidation indicated that the only discernible missing peak was the one absorbing at τ 5.77. The size of the shoulder (peak now centered at τ 5.84) had increased such that it was now just slightly larger than the peak at τ 4.87.

Finally, glpc (as above) on the remainder of the second acetolysis run after most of the acetic acid had been removed under reduced pressure showed the presence of at least 16 components, not including acetic acid, listed as follows with retention times (min), integrated percentages, and assigned structure where possible: 1, 2.4, 1.9%; 2, 4.1. 0.09%; 3, 4.6, 0.14%; 4, 5.2, 0.14%; 5, 8.6, 0.19%; 6, 9.8, 0.2%; 7, 10.6, 0.18%; 8, 13.1, 0.6%; 9, 16.3, 0.8%, 3-hydroxybicyclo[2.2.2]octan-2-one (**12**); 10, 21.4, 44.8%, 3-chlorobicyclo[2.2.2]octan-2-one (**8**); 11, 23.1, 39.5%, 3-acetoxybicyclo[2.2.2]octan-2-one (**11**); 12, 32.2, 5.3%; 13, 34.2, 3.1%; 14, 48.1, 0.7%; 15, 51.1, 1.1%; and 16, 52.4, 1.8%.

3-Hydroxybicyclo[2.2.2]octan-2-one (12).—One gram (6.4 mmol) of 3-chlorobicyclo[2.2.2]octan-2-one (**8**) was added to a solution of 7.2 g of potassium carbonate and 60 ml of water. The reaction mixture was heated to a gentle reflux for 3 hr under a nitrogen atmosphere. The α-chloro ketone gradually collected on the condenser and was washed back into the basic medium with a small amount of water. Upon termination of the reaction, 0.26 g of unreacted **8** was removed from the condenser. Ether extraction of the reaction mixture followed by distillation of the ether afforded 0.62 g of a 81:19 mixture of **12** and **8**, respectively, as analyzed by glpc. The yield of **12** was 93% based on converted **8**. Although the unreacted **8** could be removed by fractional sublimation at a bath temperature of 50° (100 mm), by crystallization from ether–hexane, and by glpc, the resulting α-hydroxy ketone, **12**, always contained varying amounts of another substance, apparently its dimer, as shown by the attenuated carbonyl absorption in the infrared spectrum and a change in the pattern of the nmr spectrum. Complete reversal of the dimerization process could be induced by heating a sample dissolved in chloroform to 60° as detected by nmr spectroscopy. The infrared spectrum (KBr) of **12** contained characteristic absorptions at 3.02 (OH), 5.82 (CO), 9.12, and 9.42 μ. The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 6.03 ("d of d," 1, J = 3 and 1 Hz), 6.41 (OH, washed out with D_2O, 1), and 7.5–8.9 (m, 10).

Treatment of 0.79 g (5.0 mmol) of **8** with 10.0 g of potassium carbonate and 30 ml of water under reflux for 3 days gave 0.62 g (89%) of **12**. The α-hydroxy ketone was allowed to stand at room temperature for a number of days before work-up and the product was isolated mostly in the dimerized form.

3-Acetoxybicyclo[2.2.2]octan-2-one (11).—To a solution of 2 ml of pyridine and 1.2 ml of acetic anhydride was added 160 mg (1.14 mmol) of 3-hydroxybicyclo[2.2.2]octan-2-one. After standing for 8 hr at 0°, the reaction mixture was decanted onto a small amount of ice and extracted with three 10-ml portions of ether. The ether extracts were washed with 5% hydrochloric acid, aqueous sodium bicarbonate (saturated), and water. After drying over magnesium sulfate, the ether was removed by rotatory evaporation, leaving 190 mg of crude product consisting of a 12.9:87.1 mixture of **12** and **11** as analyzed by glpc. The yield of **11** was 94.4% based on converted **12**. Glpc collection, recrystallization from ether, and sublimation at a bath temperature of 60° (10 mm) afforded a pure sample of the acetate as a white, crystalline solid, mp 72–73°. The infrared spectrum (KBr) had characteristic absorptions at 5.80 (CO) and 8.08 μ (OAc). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 4.91 (m, 1) and 7.58–8.67 [m (7.90 for methyl singlet), 10].

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.21; H, 7.91.

Hydrochlorination of 2-Chlorobicyclo[2.2.2]oct-2-ene Oxide.—Anhydrous hydrogen chloride was bubbled into 100 ml of dry ether (distilled from calcium hydride) for 15 min. A solution of 1.0 g of **4** in 10 ml of ether was added dropwise. After stirring for 9 days at room temperature the ether was removed under reduced pressure in a short-path distillation, leaving *ca.* 1.1 g of a white solid. Analysis of the nmr spectrum ($CDCl_3$, internal TMS) indicated a mixture of 3,3-dichlorobicyclo[2.2.2]octan-2-ol (**10**) and 3-chlorobicyclo[2.2.2]octan-2-one (**8**) in the approximate ratio of 2:1 with absorptions at τ 5.87 (C_2 H and C_3 H of the two respective compounds overlapping), 7.14 (s, OH of **10**), and 7.4–8.8 (br). Analysis by glpc showed two peaks in the ratio of 64.8:35.2. The first peak was identified as **8**, while the second peak was assigned the structure of **10**. Reinjection of **10** showed that this compound partially decomposed to **8**. However, the infrared and nmr spectra of the **10** indicated the absence of α-chloro ketone **8**. The infrared spectrum (KBr) had characteristic absorptions at 3.1 (OH) and 11.9 μ. The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 5.84 (m, C_2 H, 1), 7.25 (m, OH, 1), and 7.5–9.0 (m, 10).

Attempted separation of the two compounds by recrystallization from pentane or by sublimation failed. Column chromatography of 100 mg of the mixture on 5 g of acid-washed, activity III alumina gave *ca.* 20 mg of slightly impure **10** still containing a small amount of **8**. Rechromatography of the 20-mg sample did not improve the purity.

To 2 ml of stock dichromate solution (prepared from 117.5 g of potassium dichromate, 54.5 ml of 96% sulfuric acid, and 600 ml of water) and 1 ml of acetone was added 200 mg of the hydrochlorination mixture. The temperature rose to 31° and the color darkened. After stirring for 1 hr the reaction mixture was extracted several times with ether. The combined extracts were washed and dried over magnesium sulfate. The ether was removed under reduced pressure in a short-path distillation, leaving *ca.* 200 mg of white solid. Analysis by glpc showed two components in the ratio of 69.3:30.7, which, after collection, were identified as **8** and 3,3-dichlorobicyclo[2.2.2]octan-one (**9**), respectively, by comparison of their infrared and nmr spectra with those of authentic samples.

(15) E. R. H. Jones, K. Bowden, I. M. Heilbron, and B. C. Weedon, *J. Chem. Soc.*, 39 (1946); E. R. H. Jones, A. Bowers, T. G. Halsall, and A. T. Lemin, *ibid.*, 2548 (1953).

Registry No.—**4**, 23804-45-7; **6**, 23804-46-8; **7**, 23804-47-9; **8**, 23804-48-0; **9**, 23804-49-1; **11**, 23804-50-4.

Acknowledgment.—The authors are indebted to the National Science Foundation (GP-7818) for support of this research.

Conformational Analysis. LXVI. Some Studies Involving the 3-*t*-Butylcyclooctyl Ring System[1]

Norman L. Allinger,[2] Irving Lillien, Calvin L. Neumann, Hiroshi Sugiyama, and Nicholas A. Pamphilis

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received January 28, 1969

3-*t*-Butylcyclooctyl tosylate (one stereoisomer) was prepared and solvolyzed in acetic acid and in 80% ethanol, and the solvolysis rates of this compound and related compounds were measured. Very little transannular hydride transfer was observed. Of the olefins obtained, 3-*t*-butylcyclooctene predominated strongly over the 4 isomer, and this predominance appears to result from a subtle steric effect. The other stereoisomer of 3-*t*-butylcyclooctanol could not be obtained in spite of many attempts. Reaction of the tosylate with tetramethylammonium acetate under conditions known to give mainly inversion of configuration with other compounds (including other cyclooctyl compounds) here appeared to give largely retention of configuration (plus much elimination) presumably *via* an Sn mechanism.

The relatively unusual physical and chemical properties of the eight-membered ring have long been known, and are considered to be largely due to conformational effects.[3] Actual definitive evidence concerning the conformation of cyclooctane derivatives is scarce, however. From crystallographic studies, it is known that a boat–chair conformation is preferred in two particular cases.[4] The most detailed theoretical calculations carried out to date on the cyclooctane ring suggest that this conformation is either the one of lowest energy, or very close to it.[5] There are two other conformations which have calculated energies within 2 kcal of that of the boat–chair in the case of cyclooctane itself, and it seems likely that these conformations will be observed in due course in substituted molecules.

Cope and coworkers found many years ago[6] that cyclooctane rings undergo transannular reactions, in which hydride ions were observed to migrate 1,5 across the ring when an electron-deficient center was generated, and, in the case of acid-catalyzed ring openings of cyclooctane epoxides, both 1,5 and 1,3 hydride transfers were observed. Additional studies have shown that *cis*-5-*t*-butylcyclooctyl tosylate solvolyzes at a very much faster rate than does cyclooctyl tosylate itself, and, during the solvolysis, nearly 100% transfer of a hydride from C-5 to C-1 occurs.[7] Models show very clearly that it is quite easy for the hydrogen at C-5, which is *trans* to the leaving group, to move over and displace the leaving group in an inversion process. Models also show that it is quite difficult to obtain a reaction of this sort in a simply substituted cyclooctane ring from a hydride at C-3. Cope[8] determined the percentages of 1,5 *vs.* 1,3 hydride transfer in the ring opening of 5,6-d_2-*cis*-cyclooctene oxide, which were found to be 61 and 39%, respectively. However, the epoxides are highly deformed cyclooctanes, and their behavior is not necessarily that to be expected from simply substituted cyclooctanes.

That the hydride transfer observed with *cis*-5-*t*-butylcyclooctyl tosylate occurs from C-5 rather than from C-3 can be interpreted in terms of the stability of the carbonium ion formed after the hydride has migrated. If the migration occurs from C-5, the resulting carbonium ion is tertiary, whereas, if the hydride ion had migrated from C-3, the carbonium ion would have been secondary. That the hydride migrates exclusively from C-5, therefore, can be understood easily enough quite apart from the details of the conformational properties of the ring.

Since models suggest that a hydride transfer from C-3 is not sterically so feasible as it would be from C-5, one might ask what results would be expected from the solvolysis of 3-*t*-butylcyclooctyl tosylate. Carbonium ion stability indicates that hydride transfer from C-3 should occur, but the steric situation in the molecule suggests that this is not feasible, and, on that basis, participation would not be expected. The actual situation was investigated in the present work by means of a rate and product study.

Discussion

2-Cyclooctene-1-one[9] underwent conjugate addition of *t*-butylmagnesium chloride to furnish 3-*t*-butylcyclooctanone (I) in 74% yield. Lithium aluminum hydride reduced the ketone I to 3-*t*-butylcyclooctanol (II) in 84% yield. The latter, after distillation and recrystallization from pentane, showed a melting point of 43–44°.

When the *p*-nitrobenzoate of II was prepared, recrystallized, and then hydrolyzed to give back the

(1) This research was supported by Grant 2916 from the Petroleum Research Fund administered by the American Chemical Society. Part LXV: N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

(2) To whom correspondence should be addressed: Department of Chemistry, University of Georgia, Athens, Ga. 30601.

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1966, p 210.

(4) J. D. Dunitz and A. Mugnoli, *Chem. Commun.*, 166 (1966).

(5) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964); K. B. Wiberg, *ibid.*, **87**, 1070 (1965); N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *ibid.*, **90**, 1199 (1968).

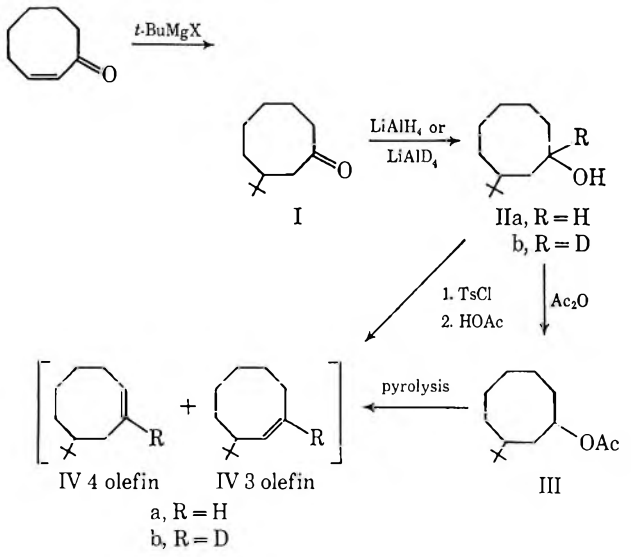
(6) For a review, see A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.* (London), **20**, 119 (1966).

(7) N. L. Allinger and S. Greenberg, *J. Amer. Chem. Soc.*, **84**, 2394 (1962); N. L. Allinger and W. Szkrybalo, *Tetrahedron*, **24**, 4699 (1968).

(8) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Amer. Chem. Soc.*, **82**, 6366 (1960).

(9) A. C. Cope, M. R. Kinter, and R. T. Keller, *ibid.*, **76**, 2757 (1954).

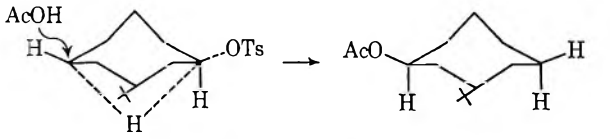
starting alcohol, material of the same melting point was obtained. The infrared spectrum of the alcohol recovered after purification through the nitrobenzoate was the same as prior to this treatment. The alcohol showed only one peak on vapor phase chromatography on a variety of columns under different conditions. It was therefore judged as most probable that the alcohol



obtained was a single stereoisomer. However, the possibility that the material is in reality an inseparable mixture of stereoisomers had to also be considered. With the 5-*t*-butylcyclooctanols, one isomer was easily obtained by methods similar to those above, and the other isomer was most easily obtained by converting the first isomer into the tosylate and then displacing the tosyl group with tetramethylammonium acetate, which gave an inverted configuration in good yield. When a similar reaction sequence was tried with the 3-*t*-butylcyclooctyl tosylate, the acetate obtained (in only 20% yield) was identical with that prepared by acetylation of the starting alcohol. Furthermore, saponification and esterification of the resulting alcohol with *p*-nitrobenzoyl chloride gave the *p*-nitrobenzoate of the starting alcohol (by melting point and mixture melting point). Thus it would seem that an SN1 reaction had occurred with essentially complete retention of configuration. This is quite an unusual circumstance, but it is known to happen in at least a few other cases.[10]

We were never able to isolate the other stereoisomer of 3-*t*-butylcyclooctanol, nor were we able to establish with certainty which stereoisomer we had in hand. We are reasonably certain that it was, however, a single pure (racemic) stereoisomer, on the basis of several experiments to be described below, and because persistent efforts to separate it into two compounds always resulted in failure.

In an attempt to convert the 3-*t*-butylcyclooctanol into its epimer, the compound was treated with aluminum isopropoxide under conditions which bring about the epimerization of 5-*t*-butylcyclooctanol. No change in the compound appeared to occur, judging by the fact that the infrared spectrum and the vapor phase chromatogram of the compound were not changed. Thus it appeared that the solvolysis had gone with *retention* of configuration. Since it is most unusual for an SN1 (or an SN2) reaction to go with *retention* of configuration, the following possibility was considered. If the attack by acetate were at the 5



position, and a simultaneous hydride transfer occurred as the tosylate ion departed (in analogy to the predominant reaction of the 5-*t*-butyl isomer), it would be conceivable that the apparent retention of configuration would be in fact due to a double inversion. This possibility was eliminated by preparing the 1-deutero-3-*t*-butylcyclooctyl tosylate and treating it under these circumstances. If a 1,5 hydride shift had occurred, the product would be the acetate of 3-*t*-butyl-5-deuteriocyclooctanol. The infrared spectrum of the product was identical with that of 1-deuterio-3-*t*-butylcyclooctyl acetate, however.

By the usual criteria, the 3-*t*-butylcyclooctanol is a single pure diastereomer. However, it has been noted previously that the *cis–trans* isomers of cyclooctane derivatives differ very little in energy.[4,11] It is therefore unclear why we are not able to isolate a second diastereomer, and the possibility that the isolated compound is a mixture of diastereomers needs careful consideration. If it is, the mixture apparently contains close to equilibrium amounts of the two diastereomers, and is nicely crystalline both as the alcohols and as the *p*-nitrobenzoates.

Results

Our previous solvolysis work on related compounds, and also the preparative work, has been done in glacial acetic acid with acetate buffer. Rough values for rate constants were obtained in acetic acid, but it was found for instrumental reasons that the rates could be more easily determined in alcohol. The relative rates are qualitatively similar in either solvent. For quantitative rate constants, the solvolysis rates of a number of cyclooctyl tosylates were determined in 80% ethanol, and the results are summarized in Table I.

TABLE I

Compd	Rate constant, sec^{-1}	Relative rate
2-Pentyl tosylate	3.2×10^{-6}	1
cis-5-*t*-Butylcyclooctyl tosylate	9.97×10^{-4}	312
trans-5-*t*-Butylcyclooctyl tosylate	2.92×10^{-5}	9.1
Cyclooctyl tosylate	1.26×10^{-4}	39
3-*t*-Butylcyclooctyl tosylate	5.46×10^{-4}	171

A comparison of the numbers of Table I shows that, relative to a simple open-chain tosylate, cyclooctyl tosylate solvolyzes quite rapidly. This is one of the classical manifestations of I strain,[12] the unfavorable torsional situation being relieved to some extent as the cyclooctyl derivative is converted into a transition state

(10) D. J. Cram and F. L. Harris, Jr., *J. Amer. Chem. Soc.*, **89**, 4642 (1967); P. von R. Schleyer, R. C. Fort, Jr., W. E. Watts, M. B. Comisarow, and G. A. Olah, *ibid.*, **86**, 4197 (1964); E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, **77**, (1965), and references cited therein.

(11) N. L. Allinger and S. Hu, *J. Amer. Chem. Soc.*, **83**, 1664 (1961).

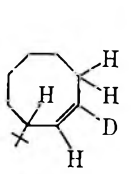
(12) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *ibid.*, **73**, 212 (1951); H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

with a carbonium ion type of geometry. *trans*-5-*t*-Butylcyclooctyl tosylate solvolyzes about one-fourth as rapidly as cyclooctyl tosylate itself, and this would seem to be due to a small unfavorable steric effect. It is known[7] that very little rearrangement accompanies this solvolysis. The *cis* isomer of 5-*t*-butylcyclooctyl tosylate, on the other hand, solvolyzes about eight times faster than cyclooctyl tosylate, and is almost completely rearranged by a 1,5 hydride transfer. It seems likely that neighboring-group participation is being observed in this case, although the rate difference is not sufficient to unequivocally rule out a steric effect.

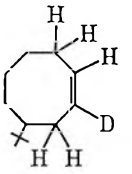
In the present work, we found that 3-*t*-butylcyclooctyl tosylate solvolyzes about four times faster than cyclooctyl tosylate, or a little over one-half as fast as *cis*-5-*t*-butylcyclooctyl tosylate. However, the olefin mixture obtained from 3-*t*-butylcyclooctyl tosylate shows that only about 1% of a 1,3-hydride transfer has occurred. Thus the fast rate is best not attributed to neighboring-group participation, but must be a result of steric effects in the ring system.

There are two olefins that would be expected to be formed from a simple elimination reaction by 3-*t*-butylcyclooctyl derivatives: 3-*t*-butyl- and 4-*t*-butylcyclooctene. These compounds are not independently known, but a mixture of them was prepared by pyrolysis of 3-*t*-butylcyclooctyl acetate. From that reaction, two compounds were obtained which appeared to be *t*-butylcyclooctenes, and upon hydrogenation they gave material which appeared to be *t*-butylcyclooctane, from the retention time on vpc. The two *t*-butylcyclooctenes obtained from this pyrolysis were different from 1-*t*-butylcyclooctene and from 5-*t*-butylcyclooctene, both of which were known from previous work. They were characterized by their nmr spectra, and each showed a *t*-butyl group with nine equivalent protons and two vinyl hydrogens. The question as to which was 3-*t*-butyl- and which was 4-*t*-butylcyclooctene was more difficult, as indicated below.

When the solvolysis of 3-*t*-butylcyclooctyl tosylate was carried out in acetic acid, and the product then subjected to vpc, there was observed about 1% 1-*t*-butylcyclooctene, about 1% an unidentified compound, 66% the acetate of 3-*t*-butylcyclooctanol, 31% 4-*t*-butylcyclooctene, and 1% 3-*t*-butylcyclooctene. In different runs the ratio varied somewhat, but it was noteworthy that the 4-*t*-butylcyclooctene always *strongly* predominated over the 3 isomer. We were unable to deduce from a study of models which isomer would be preferentially formed, and, while this preference must be the result of a conformational effect, it does not appear to us to be any simple, obvious one. It was therefore felt desirable to establish experimentally which of the olefins was 3-*t*-butyl- and which was 4-*t*-butylcyclooctene. In order to do this, 1-deuterio-3-*t*-butylcyclooctanol was prepared by reduction of 3-*t*-butylcyclooctanone with lithium aluminum deuteride. This alcohol was converted into the tosylate and the latter was solvolyzed as previously. Two olefins [IV-3(b) and IV-4(b)] were isolated as before, and they were clearly of the structures indicated; the problem was to determine which was which. This was done by examining their nmr spectra, and particularly by considering the vinyl hydrogens. It can be seen that IV-3(b) has only one proton vicinal to the vinyl hydrogen, while IV-4(b)



IV-3 (b)



IV-4 (b)

has two. The former should, therefore, to the first-order approximation, show a doublet in the vinyl region, while the latter should show a quartet (or a triplet if the coupling constants are accidentally the same), and the coupling constants should be in the range of 4–10 cps. Such an interpretation is not expected to be completely adequate, however, because allyl coupling of the type $H_a—C—C=C—H_b$ generally has J_{ab} in the range of 0–3 cps.[13] Several other long-range couplings of the order of 0–1 cps are also to be expected.

The nmr spectra of these compounds showed them both to be *t*-butylcyclooctenes, since they each showed a sharp singlet at δ 0.88 (*A* 9), a broad complex methylene resonance at δ 1.06–2.44 (*A* 11), and a complex vinyl resonance at *ca.* δ 5.45 (*A* 1).

The nmr spectrum of the compound assigned structure IV-4(b) showed the vinyl proton as a multiplet, which appeared as a large central peak flanked on each side by two peaks, similar in height and half as high as the central peak. Additional fine structure was also present. The interpretation given is a triplet (J = 6.9 cps) further split into doublets (J = 3.0 cps). This interpretation is not completely convincing, but it appears to be the best available.

The compound assigned the IV-3(b) structure showed the vinyl proton as a doublet of triplets, with the spacing between the components of the doublet 10.0 cps, and the spacings between the components of the triplets 1.2 cps. In addition, five sharp peaks were scattered across the vinyl region, and accounted for about 10% of the total area. Since this compound was only obtained in very small yield, we suspect that these extra peaks are impurities. The nmr spectra are unfortunately rather complex, and we do not regard our structural assignments as completely unequivocal.

Even accepting that 4-*t*-butylcyclooctene predominated very largely over the 3 isomer in the solvolysis products of 5-*t*-butylcyclooctyl tosylate, a study of models still led to no conclusive results regarding the conformation of the ring and/or the substituents during the solvolysis reaction. It may well be that what we are observing here is a thermodynamic effect, rather than something characteristic of the reaction. 3,3-Dimethylcyclohexene is known to be more stable than the 4 isomer by about 1 kcal,[14] and a related sort of effect may be present with the olefins being studied here.

This work has raised some questions which we are unable to answer. It is disappointing to be unable to explain the apparent preponderance of one diastereomer

(13) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 145.

(14) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

of 3-*t*-butylcyclooctanol over the other, which seems to result from both thermodynamic and kinetic control. The conformations of the ring which are possible, their relative energies, and the conformational energies of attached substituents[15] are believed to be fairly well understood, but do not suffice to explain the observed facts. The strong predominance of 4-*t*-butylcyclooctene over the 3 isomer in the solvolysis reactions also remains poorly understood.

We are, however, able to draw some definite conclusions. Hydride migration from the 3 position of cyclooctyl tosylate does not occur to any appreciable extent during solvolysis,[16] and placing a *t*-butyl group at C-3 so that the carbonium ion generated by the hydride migration is tertiary, rather than secondary, does not substantially alter the situation. The rate of reaction here, where neighboring-group participation appears to be insignificant, is only a factor of two less than in *cis*-5-*t*-butylcyclooctyl tosylate solvolysis, which indicates that the fast rate of the latter does not have to result from participation, but may be a result of a simple steric effect of the *t*-butyl group.

Experimental Section

All infrared spectra were determined on liquid films, and nmr spectra in $CDCl_3$ solvent with TMS standard.

2-Cycloocten-1-one.[17]—This compound was prepared in 50–55% yield *via* Oppenauer oxidation of 2-cycloocten-1-ol. It was freed from residual traces of alcohol by chromatographing on Merck acid-washed alumina and eluting with pentane, bp 52–56° (0.5 mm), $n^{26}D$ 1.4960 (lit.[15] $n^{25}D$ 1.4953).

3-*t*-Butylcyclooctanone (I).—A 29-g sample of 2-cyclooctan-1-one in 50 ml of ether was added dropwise with good stirring to the Grignard reagent prepared from 55.2 g of *t*-butyl chloride and 16 g of magnesium in 500 ml of ether, maintained at −20 to −30°. Stirring was then continued overnight while the reaction mixture was allowed to come to room temperature. The mixture was hydrolyzed with a saturated ammonium chloride solution, and the ether layer was removed, washed, and dried. Evaporation of the ether left an oil, which after two passes through a column of Merck acid-washed alumina in pentane solution showed only a little OH absorption in the infrared. The oil was distilled through a small column. After a small forerun, the major fraction was collected at 62–63° (0.5 mm). The product was free of OH and conjugated ketone absorption in the infrared: yield 31.5 g (73.9%); $n^{22}D$ 1.4760; λ_{max} 5.87 (CO) and 7.30 μ (*t*-butyl).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.12; H, 12.09. Found: C, 79.25; H, 12.08.

The *p*-nitrophenylhydrazone of 3-*t*-butylcyclooctanone, recrystallized from ethyl acetate–petroleum ether, had a melting point of 165–166°.

Anal. Calcd for $C_{18}H_{27}N_3O_2$: C, 68.14; H, 8.52. Found: C, 68.10; H, 8.62.

3-*t*-Butylcyclooctanol (II).—To a stirred slurry of 1.52 g of lithium aluminum hydride in 200 ml of ether was added 4 g of 3-*t*-butylcyclooctanone in 100 ml of ether at a rate sufficient to maintain gentle reflux. The mixture was stirred for 1 hr, after which time the excess lithium aluminum hydride was decomposed by ethyl acetate followed by water, the solution was dried, and the solvent was evaporated, leaving a viscous oil which resisted attempts at crystallization. It was distilled at reduced pressure: yield 3.4 g (84%); bp 92–94° (1.5 mm); $n^{21}D$ 1.4834; ir 3.1 (OH), 7.32 (*t*-butyl), and 9.51 μ (CO). This material was purified through the *p*-nitrobenzoate (see below). It was later found that the distillate could be induced to solidify by seeding. The solid was contaminated with a small amount of oil at room temperature, and could be purified by crystallizing from pentane. Either way, the alcohol had a melting point of 45–46°.

Attempted Equilibration of the *cis* and *trans* Isomers of II.—A solution of 500 mg of crystalline II, 250 mg of aluminum isopropoxide, and 1 drop of acetone were dissolved in 25 ml of isopropyl alcohol, and the solution was heated under reflux for 45 hr. The solvent was evaporated, the residue was poured into 100 ml of water, and the solution was extracted with ether. The ether layer was separated, washed with water, and dried over sodium sulfate. After evaporation of the solvent, the residual oil crystallized, yield 470 mg, mp 45–46°. The infrared spectrum and the vpc showed the product to be indistinguishable from II. Under the same conditions *cis*-5-*t*-butylcyclooctanol was converted into a mixture of the *cis* and *trans* epimers.

Attempted Epimerization of 3-*t*-Butylcyclooctanol.—A solution of 0.9 g of the pure crystalline tosylate of II (see below) and 5 g of tetraethylammonium acetate monohydrate in 100 ml of dry acetone was stirred for 7 days at room temperature, and then the mixture was heated under reflux for 1 hr. The solution was reduced in volume, and the mixture was poured into water and extracted with ether. The ether extracts were separated, washed, and dried over sodium sulfate, and the ether was evaporated under reduced pressure, leaving 5 g of residual oil. Analysis of this oil was carried out on an 8-ft, 10% Carbowax column at 180°. There were three major peaks, two olefins and the acetate, with retention times of 1.5, 2.0, and 12.0 min. The peak areas of total olefin to acetate were in the ratio 5.3:1.

A solution of 0.5 g of potassium hydroxide in 8 ml of ethanol was added to the oil, and the solution was refluxed for 1 hr and allowed to stand overnight. A 100-ml portion of water was added to the solution, which was extracted with ether. The ether layer was separated, washed, and dried and the ether was evaporated, leaving 0.4 g of an oil. The oil was taken up in 2.5 ml of dry pyridine, and 0.4 g of *p*-nitrobenzoyl chloride was added. The solution was allowed to stand overnight and then diluted with 50 ml of water, and the precipitated oil was extracted with benzene. The benzene layer was washed with dilute hydrochloric acid and then with water, and the benzene was evaporated under reduced pressure. The residual oil was then crystallized from ethanol and recrystallized from ethyl acetate, yield 122 mg, mp 94–94.5°. The infrared spectrum was identical with that of an authentic sample of the *p*-nitrobenzoate of II, and they showed no mixture melting point depression.

Under the same reaction conditions, *cis*-5-*t*-butylcyclooctanol was converted into the *trans* isomer in good yield.

3-*t*-Butylcyclooctyl Acetate (III).—Alcohol II, 1.7 g, was heated under reflux with 1.1 g of acetic anhydride in 5 ml of pyridine for 12 hr. The solution was cooled and treated with 10% hydrochloric acid until no pyridine odor remained. The solution was then extracted with ether, and the ether extracts were washed with water, sodium bicarbonate, and water and dried. The residual oil showed a weak OH bond in the infrared, and was therefore dissolved in pentane, and the solution was passed through a calcium chloride column twice. The residual oil was distilled: bp 110–111° (3 mm); $n^{25}D$ 1.4566; ir 5.75 (CO), 7.28 (*t*-butyl), and 8.0 μ (acetate).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.34; H, 11.59. Found: C, 74.65; H, 11.51.

Pyrolysis of Acetate III.—3-*t*-Butylcyclooctyl acetate was pyrolyzed by dripping the neat liquid under a positive pressure of nitrogen onto a 7 × 0.5 in. column packed with glass helices heated at 511°. The effluent vapor was condensed in a Dry Ice trap. The condensate was taken up in ether, which was washed with sodium carbonate and water and dried. After evaporation of the solvent, the residual oil was distilled twice. The final fraction was collected at 68–80° (6 mm). The infrared spectrum was free of OH or CO absorption. Vpc analysis is discussed below.

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.38; H, 13.11.

A mixture of 3- and 4-*t*-butylcyclooctene was prepared by an unambiguous route: pyrolysis of 3-*t*-butylcyclooctyl acetate. Hydrogenation of this mixture gave *t*-butylcyclooctane, which was identified by comparison with authentic sample on vpc.

Vapor Phase Chromatography of the Acetate Pyrolysis Product.—A 7-ft column packed with 25% of the tricyanoethylation product of glycerol on firebrick at 100° was used. The product from the acetate pyrolysis was resolved into three major peaks, with retention times of 4.55, 10.20, and 16.15 min. The first peak is believed to be an acyclic diene, analogous to that found earlier by Bloomquist from the pyrolysis of cyclooctyl acetate.[18]

(15) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7043 (1967).
(16) A. C. Cope and D. M. Gale, *ibid.*, **85**, 3747 (1963).
(17) A. C. Cope, M. R. Kinter, and R. T. Keller, *ibid.*, **76**, 2757 (1954).
(18) A. T. Blomquist and P. R. Taussig, *ibid.*, **77**, 6399 (1955).

The peaks at 10.2 and 16.15 min are assigned the 4- and 3-*t*-butylcyclooctene structures, respectively.

3-*t*-Butylcyclooctyl *p*-Nitrobenzoate.—The oily product from the lithium aluminum hydride reduction of 1.0 g of 3-*t*-butylcyclooctanone was dissolved in 60 ml of dry pyridine, and 10.6 g of *p*-nitrobenzoyl chloride was added with shaking. After standing for 6 hr, the solution was poured into water and the precipitate was collected and carefully recrystallized from ethanol and then from pentane, mp 94–95°. Further recrystallization did not raise the melting point.

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16. Found: C, 68.29; H, 8.43.

3-*t*-Butylcyclooctanol.—A 3-g sample of the above *p*-nitrobenzoate was refluxed with a solution of 5 g of potassium hydroxide in 100 ml of 95% ethanol for 2 hr. The mixture was poured into water, and the solution was extracted with ether. The ether extracts were washed and dried, and the ether was evaporated. The residual oil was triturated with a small amount of pentane, whereupon it crystallized. The material was twice recrystallized from pentane, yield 1.5 g, mp 45–46°.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.13. Found: C, 78.21; H, 13.00.

Preparation and Solvolysis of 3-*t*-Butylcyclooctyl Tosylate.—A solution of 0.5 g of 3-*t*-butylcyclooctanol (crystalline) in 20 ml of dry pyridine was cooled to 0° and 1 g of tosyl chloride was added. After standing at 5° for 16 hr, the solution was poured into ice–water and the white crystals were collected on a filter, washed with water, and dried under vacuum at room temperature. The crystalline tosylate melted sharply at 68.5–69°.

The freshly prepared tosylate (0.8 g) was added to a solution prepared from 5 ml of glacial acetic acid and 0.2 g of sodium acetate (anhydrous). The solution was heated under reflux for 16 hr, and was then poured into water. The mixture was extracted with pentane, the pentane extracts were washed and dried, and the solvent was evaporated. The residue was subjected to vpc analysis.

The vpc conditions were as follows: column, 20 ft, containing 30% SE-30 on Chromosorb W at 175°, followed by 200°. The results are given in Table II.

TABLE II

VPC ANALYSIS OF SOLVOLYSIS PRODUCTS FROM 3-*t*-BUTYLCYCLOOCTYL TOSYLATE

Fraction	Assigned structure (-cyclooctene)	Temp, °C	Retention time, min	Peak areas	Olefin fraction, %
1	?	175	29.1	1.05	3.10
2	3-*t*-Butyl	175	31.1	0.42	1.24
3	1-*t*-Butyl	175	33.2	1.44	4.25
4	4-*t*-Butyl	175	35.7	30.98	91.41
5	Acetate	200	123.	66.11	...

General Procedure for Kinetic Experiments.—The methods previously employed[7] were used with some exceptions. Preparation of 80% ethanol was carried out by dilution of 95% ethanol with distilled water sufficient to make the solvent 80% ethanol by volume. Kinetic runs in acetic acid were carried out manually as previously described.[7] These tended to be laborious and somewhat inaccurate. Since there was available a Sargeant pH-Stat, it was decided to repeat all the kinetic runs in 80% ethanol with the aid of this device. In all but the slowest runs, the solvolysis was allowed to proceed for at least two half-lives. In cases where the half-lives of the reaction were more than 3 days, the rates were followed for a single half-life.

The data were obtained as a plot of milliliters of titrant *vs.* time. The plots were smoothed with a French curve, and points were taken from the smoothed graph. Between 10, and 75 points were taken in each case. The logarithm of the concentration was then plotted *vs.* time, and the rate constants were determined graphically in the usual way.

It was found that for highest precision, some modification in the use of the equipment was necessary. An external voltage regulator was used to alleviate pen drift owing to variance in the line voltage. It was also necessary to construct a cover to more tightly seal the reaction vessel from the atmosphere, otherwise the absorption of carbon dioxide was troublesome. In addition, a grid was placed around the reaction vessel to eliminate errors owing to changes in atmospheric capacitants. With these precautions, the relative rate constants obtained are believed accurate to about 1%.

3-*t*-Butylcyclooctanol-1-*d*.—The deuterated alcohol was prepared as described for its hydrogen analog, and was obtained as a viscous liquid, which solidified after seeding and trituration with pentane. The pentane was evaporated and left a crystalline mass, which at room temperature was contaminated with a small amount of liquid. The infrared spectrum showed the expected hydroxyl band at 3325 cm^{-1} and a sharp C–D stretching band at 2120 cm^{-1}. The acetate was prepared as described for the nondeuterated analog, and its ir showed strong absorption at 2160, 1730, and 1250 cm^{-1}.

Preparation and Solvolysis of 3-*t*-Butylcyclooctyl-1-*d* Tosylate.—The tosylate was prepared as previously described for the hydrogen analog and the crystals were collected, dried, and treated with refluxing acetic acid containing sodium acetate as previously. A similar work-up gave a residual oil, which upon vpc gave fractions of the same retention times as previously, although the ratios were somewhat different. Fractions 1–5 in Table II in this case gave the following peak areas: 2.29, 16.02, 4.21, 40.65, and 36.83. Fractions 2, 4, and 5 were collected by vpc.

Fraction 2 gave the following data: ir 3020, 2240, 1650, 1398, and 1370 cm^{-1}; nmr a multiplet at δ 5.30–5.75 (1 H) with a doublet of triplets at δ 5.45 predominating, a broad region at δ 1.06–2.44 (11 H), and a sharp singlet at δ 0.88 (9 H). It was assigned the structure of 3-*t*-butylcyclooctane. The relatively large amount of this fraction may be noted. In all other solvolyses (with nondeuterated material) this fraction accounted for only about 1% of the total olefins. Whether the discrepancy is due to deuteration or to some unrecognized experimental factor is not known.

Fraction 4 gave the following data: ir 3030, 2260, 1655, 1400, and 1370 cm^{-1}; nmr a triplet of triplets at δ 5.45 (1 H), a broad region at δ 1.00–2.50 (11 H), and a sharp singlet at δ 0.88 (9 H). It was assigned the structure of 4-*t*-butylcyclooctene.

Fraction 5 gave the following data: ir 2160, 1730, and 1250 cm^{-1}; nmr a sharp singlet at δ 2.0 (3 H), a broad methylene region at δ 1.00–1.94 (13 H), and a sharp singlet at δ 0.87 (9 H). It was assigned the structure of 3-*t*-butylcyclooctyl acetate.

Registry No.—I, 23804-51-5; I *p*-nitrophenylhydrazone, 23804-52-6; II, 23809-66-7; III, 23809-67-8; 4-*t*-butylcyclooctene, 23796-85-2; 3-*t*-butylcyclooctene, 23809-68-9; 3-*t*-butylcyclooctyl *p*-nitrobenzoate, 23809-69-0; 3-*t*-butylcyclooctyl tosylate, 23809-70-3.

The Reaction of 1-Tetralones with Potassium Hydroxide–Sodium Hydroxide[1a]

J. M. SPRINGER,[1b-d] C. W. HINMAN,[1e,f] AND E. J. EISENBRAUN[1g]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

P. W. K. FLANAGAN AND M. C. HAMMING

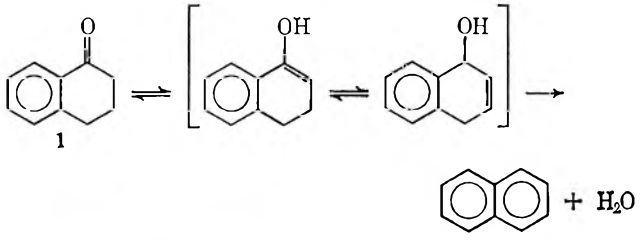
Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

Received November 17, 1969

The course of the alkali fusion of several methyl-substituted 1-tetralones has been found to be stereochemically controlled. The products include naphthalenes, naphthols, tetralols, and dimer acids. The analogous reaction with 2-tetralone gives a dimer acid in 45% yield. Some reactions of the latter are described.

It has been reported[2] that the fusion of 3,4-dihydro-1(2H)-naphthalenone, hereafter referred to as 1-tetralone (**1**), with a 1:1 mixture of KOH–NaOH at 220° yields naphthalene (58%); no mention was made of additional products. The proposed mechanism involved dehydration of an isomer of the enol of **1** (Scheme I).

SCHEME I

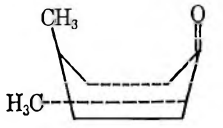


Data resulting from extension of this reaction to several methyl-substituted 1-tetralones are summarized in Table I. The steam-volatile fraction contained the unreacted tetralone (from **2**, **3**, and **8–13**), the corresponding naphthalene (from **1** and **3–7**), and the corresponding tetralol (from **2** and **3**); the base-soluble and/or nonsteam-volatile material included the corresponding naphthol (from **2** and **3**), dimer acid (from **1**, **4**, **5**, and **7**), and unknown components (from **6** and **8–13**). These data show that the less reactive 1-tetralones (0–5% yield of the naphthalene) possess one or more of three features: a *peri*-methyl group, 4- and 5-methyl groups, and a 2-methyl group.

The influence of the *peri*-methyl group can be seen by comparison of the naphthalene yields from **6–8**. The unreactivity of **8** is not unexpected, since the steric bulk of the methyl group at position 8 is sufficient to twist the carbonyl out of the plane of the aromatic ring.[3] 3,3,6,8-Tetramethyl-1-tetralone is unreactive and was recovered unchanged from the reaction mixture.

It has been shown[3b] that the 4,5-dimethyl interaction in 1-tetralones causes departure from the normal chair conformation and assumption of the boat conformation with the 4-methyl group in the axial position. The inhibiting effect of the boat conformation is evidenced by contrasting the 63% yield of 1,3-dimethylnaphthalene from **7** with the negligible yield of 1,3,8-trimethylnaphthalene from **9**.

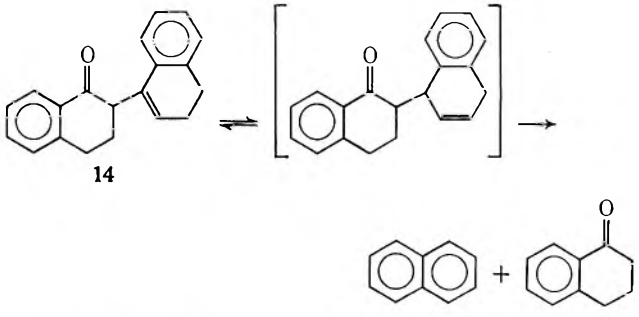
7



9

The explanation of the course of the difference in the reactions of **2** and **3** (Table I) is not so clear-cut. If the mechanism proposed by Birch is correct, there can be no argument on such steric grounds as used above; *i.e.*, the most stable ground-state conformation for **2** is that in which the alicyclic ring is a chair with the methyl group in the equatorial position[3b] and the methyl group appears to have little steric effect either in inhibiting the conjugation of the carbonyl group with the benzene ring[4] or in hindering the approach of reacting species.[3b,5] If, however, dimerization is prerequisite to naphthalene formation, then the steric hindrance owing to the 2-methyl (and possibly 3-methyl) group would be important. This is made more probable by the fact that the alkali fusion of the 1-tetralone dimer **14** affords 60% naphthalene (Scheme II). The formation of both

SCHEME II



2-methyl-1-tetralol (**15**) and 2-methyl-1-naphthol (**16**) suggests a hydride transfer reminiscent of the Cannizzaro reaction, as depicted in Scheme III. The reaction of **3**, which yields the corresponding naphthalene, naphthol, and tetralol, would be intermediate between the two extremes, *i.e.*, naphthalene (Schemes I and II) *vs.* naphthol and tetralol formation (Scheme III).

Data on the isolated crystalline dimer acids (Tables II and III) support the fully aromatic structures, **17–20**.

(1) (a) E. J. Eisenbraun, J. M. Springer, C. W. Hinman, P. W. K. Flanagan, and M. C. Hamming, *Amer. Chem. Soc., Div. Petrol Chem., Preprints Gen. Papers*, **14** (3), A49 (1969); (b) American Petroleum Institute Graduate Research Assistant, 1965–1967; (c) National Science Foundation Graduate Trainee, 1967–1968; (d) American Chemical Society Petroleum Research Fund Fellow (Grant GF 395), 1968–1969; (e) American Petroleum Institute Graduate Research Assistant, 1962–1965; (f) deceased; (g) to whom correspondence should be addressed.

(2) A. J. Birch and D. A. White, *J. Chem. Soc.*, 4086 (1964).

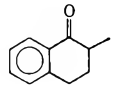
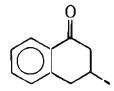
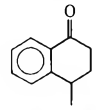
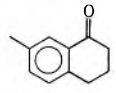
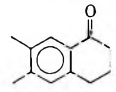
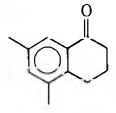
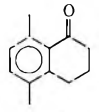
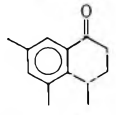
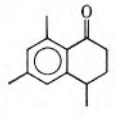
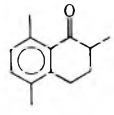
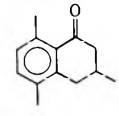
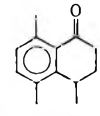
(3) (a) E. A. Braude, "Progress in Stereochemisty," Vol. I, W. Klyne, Ed., Academic Press Inc., New York, N. Y., 1954, pp 144–148; (b) G. D. Johnson, S. Searles, and W. C. Lin, *J. Org. Chem.*, **27**, 4031 (1962).

(4) G. Baddeley, J. W. Rasburn, and R. Rose, *J. Chem. Soc.*, 3168 (1958).

(5) K. Hanaya, *Nippon Kagaku Zasshi*, **87**, 991 (1966); *Chem. Abstr.*, **65**, 18474*a* (1966).

TABLE I

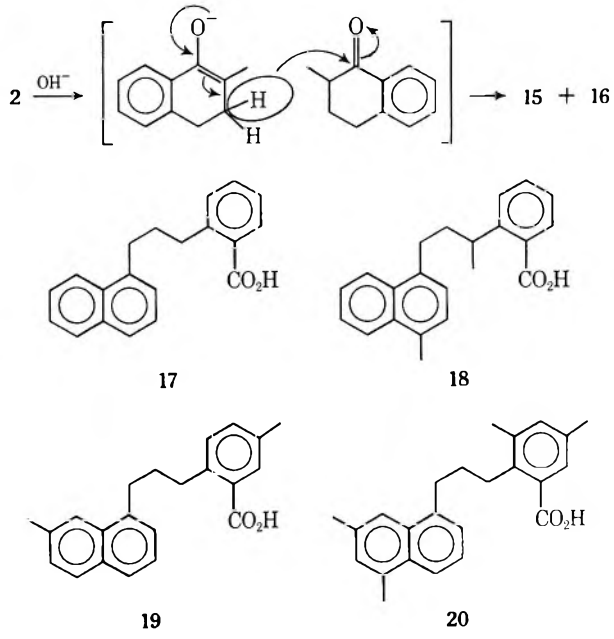
REACTION OF 1-TETRALONES WITH KOH–NaOH

Compd. no.	Tetralone structure	Yield, % Naphthalene[a]	Yield, % Dimeric or phenolic products[b]
1		75	23[c]
2		0[d]	47[e]
3		22[f]	47[e]
4		51	43[c]
5		65	22[c]
6		62	30[g]
7		63	26[c]
8		5	39[h]
9		5	89[g]
10		5	41[h]
11		0	6[g]
12		0	26[g]
13		0	32[h]

[a] Yield determined by glpc. [b] Yield determined gravimetrically and based on 5 g of tetralone. [c] Dimer acid. [d] Steam-volatile fraction contains 2-methyl-1-tetralol. [e] Corresponding naphthol. [f] Steam-volatile fraction contains 3-methyl-1-tetralol. [g] Unknown crystalline solid. [h] No useful product isolated from residue.

The probable intermediates are the α,β-unsaturated ketones, such as **14**. In addition to naphthalene (Scheme II), the alkali fusion of **14** gives **17** in 26% yield.

SCHEME III



The alkali fusion of 3,4-dihydro-2(1H)-naphthalenone (2-tetralone, **21**) was found to give the crystalline dimer acid **22b** in 45% yield. The proposed rationalization in Scheme IV is analogous to that suggested by Cairns, *et al.*,[6] to explain the formation of dimer acid in the reaction of cyclohexanone with fused alkali. Hydrogenation and dehydrogenation yielded **23** and **24**, respectively. Structure **22a** was eliminated as a possibility through the isolation of **25** and the absence of **21** in the indicated sequence[7a,b] of Scheme V.

Separate but identical alkali fusions of **1** and **2** were found by mass spectrometric analysis to produce hydrogen.[7c] Peak height comparisons of the mass spectra of the off-gases from these reactions showed the ratio 5.3:2.4 (1 to 2) for hydrogen. The yield of hydrogen probably did not exceed 0.03 mol/mol of tetralone.

Experimental Section[8]

The ketones used in this study were purchased (**1**, **4**, **6**, and **7**) or were prepared by one of the following three methods.

Friedel–Crafts condensation of *m*-xylene or *p*-xylene with γ-valerolactone in the presence of $AlCl_3$ was used to give a 4-arylpentanoic acid.[9] These acids then were cyclized to **9**, **10**, and **13** by reaction with hot PPA.[10] Where necessary, the ketones were purified by preparative glpc (**9** and **10**).

Friedel–Crafts condensation of succinic anhydride[11] or methylsuccinic anhydride[12] with benzene or *p*-xylene in the presence of

(6) T. L. Cairns, R. M. Joyce, and R. S. Schreiber, *J. Amer. Chem. Soc.*, **70**, 1689 (1948).

(7) (a) R. E. Ireland and J. Newbold, *J. Org. Chem.*, **28**, 23 (1963); (b) J. S. Baran, *ibid.*, **25**, 257 (1960); (c) F. X. Werber, J. E. Jansen, and T. L. Gresham, *J. Amer. Chem. Soc.*, **74**, 532 (1952).

(8) Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined on Varian HR-60 and A-60 spectrometers. Mass spectrometric data were compiled using a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. Ir and uv spectra were obtained on Beckman IR-5A and Cary 14 spectrophotometers, respectively. Melting points are corrected. Glpc analyses and preparative separations were made with Hewlett–Packard Model 5750 and F & M Model 700 equipment.

(9) W. L. Mosby, *ibid.*, **74**, 2564 (1952).

(10) H. R. Snyder and F. X. Werber, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, pp 798–800.

(11) E. de Barry Barnett and F. G. Sanders, *J. Chem. Soc.*, 434 (1933).

(12) F. Mayer and G. Stamm, *Chem. Ber.*, **56**, 1424 (1923).

TABLE II
COMPARISON OF GLPC AND NMR DATA FROM DIMER ACIDS

Precursor ketone	Dimer acid	Retention time,[a] min	Proton absorptions[b] CH_3	$>CH_2$, $>CH$	ArH	Miscellaneous
21	22b	10.5		2.0–3.2 (m, 8)	6.77–7.3 (m, 8)	3.55 (s, 2)[c,d] 6.07 (s, 1)[e]
21	23	9.5		1.6–3.1 (m, 13)	7.0–7.25 (m, 8)	
21	24	11.5		2.26–3.17 (m, 4)	7.07–7.87 (m, 11)	4.16 (s, 2)[f]
1	17	12		1.8–2.4 (m, 2)	7.05–8.18 (m, 11)	3.0–3.4 (m, 4)[c]
4	18	15	1.38 (d, 3) 2.60 (s, 3)	1.7–2.3 (m, 2)	7.12–8.12 (m, 10)	2.82–3.20 (m, 2)[c] 3.8–4.23 (q, 1)[g]
5	19	15	2.37 (s, 3) 2.48 (s, 3)	1.8–2.26 (m, 2)	7.12–7.93 (m, 9)	2.92–3.33 (m, 4)[c]
7	20	26.5	2.22 (s, 3) 2.28 (s, 3) 2.42 (s, 3) 2.61 (s, 3)	1.77–2.18 (m, 2)	7.04–7.92 (m, 7)	2.90–3.38 (m, 4)[c]

[a] As methyl ester using a 6 ft × 0.25 in. column of 5% silicone rubber on acid-washed, DMCS-treated Chromosorb W at 275°. [b] $CDCl_3$ solvent with δ in parts per million from TMS. [c] $ArCH_2$. [d] $-\overset{|}{C}=\overset{|}{C}CH_2$. [e] $-\overset{|}{C}=\overset{|}{C}H$. [f] Ar_2CH_2. [g] ArCH.

$AlCl_3$ using excess hydrocarbon or nitroethane solvent was used to prepare ketones **2**, **3**, **8**, **11**, and **12**. In the case of methylsuccinic anhydride, a mixture of β-aroylpropionic acids having a methyl group at either an α or a β position was obtained. These γ-oxo acids were separated by a combination of crystallization and distillation. The γ-oxo acids were reduced (Clemmensen reduction or catalytic hydrogenolysis) to the corresponding γ-arylbutyric acids, which were cyclized with hot PPA[10] to the expected ketone.

7-Methyl-1-tetralone (**5**) was prepared by air oxidation of uv-irradiated 1,2,3,4-tetrahydro-6-methylnaphthalene to a mixture of hydroperoxides.[13] These hydroperoxides were decomposed with alkali to a mixture of tetralols and tetralones that in turn was oxidized with chromic acid[14] to a 45:55 mixture of 6-methyl-1-tetralone and **5**. The latter was isolated from this mixture by preparative glpc and crystallized from petroleum ether.

Naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, 2,3-dimethylnaphthalene, and 1,4-dimethylnaphthalene were commercially available. The other naphthalenes necessary for the preparation of standard solutions for glpc analyses were obtained by one of the following three routes.

Clemmensen reduction of the corresponding tetralone and subsequent dehydrogenation (Pd–C) of the tetralin gave 1,4,5- and 1,4,6-trimethylnaphthalene.

Catalytic hydrogenation of the appropriate tetralone followed by dehydrogenation (Pd–C) of the tetralin gave 1,3,5- and 1,3,8-trimethylnaphthalene.

Dehydrogenation (Pd–C) of 5,7-dimethyl-1-tetralone gave 1,3-dimethylnaphthalene.

General Reaction of 1-Tetralones with KOH–NaOH. Apparatus.—The reaction vessel is a 25-ml, one-necked, flat-bottomed, stainless steel flask surmounted by a water-cooled, straight-bore glass condenser. One end of the condenser is a ball joint fitted with a Teflon O ring which provides a seal with the flask. The other end is threaded and fitted with a screw cap containing a 0.25-in.-o.d., thin-walled, stainless steel tube which extends *ca.* one-third the distance into the flask. The tube, which provides a helium inlet, is sealed to the screw with silicone rubber. An extra side arm of the condenser located above the water jacket acts as the helium outlet. The inlet and the outlet are fitted with Tygon tubing. The end of the latter tube is immersed in water so that gas flow may be observed. Heating is accomplished with a Wood's metal bath held at 220° (measured with a thermocouple probe and pyrometer).

Procedure.—A 5-g sample (in most cases) of the tetralone, 0.8 g of KOH pellets, and 0.8 g of NaOH pellets are added to the flask and the assembled system is purged for several minutes with a fast stream of helium. The flow is lessened to maintain a slight positive pressure and the flask is lowered into the preheated (220°) metal bath. After 3 hr of heating, the reaction mixture is allowed to cool under a helium atmosphere. The reaction mixture, after steam distillation for a few hours, is acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extract is washed with water and saturated sodium chloride solution, dried ($MgSO_4$), filtered, and concentrated to give a tarlike residue. This residue is triturated with hot petroleum ether (bp 60–68°), and the liquid is decanted and refrigerated; any resulting crystals are naphthols or dimer acids. If the former is the case, purification is accomplished by recrystallization from petroleum ether or by sublimation; if the latter is the case, only recrystallization from chloroform–petroleum ether is employed, since decomposition occurs on attempted sublimation.

The steam distillate (above) is extracted with ether and the extract is washed with saturated sodium chloride solution, dried ($MgSO_4$), and filtered. The filtrate is concentrated to *ca.* 15 ml by distillation at atmospheric pressure. The concentrate is added to a 25- or 50-ml volumetric flask and diluted with ether. A 25- or 50-ml standard solution (in ether) of the naphthalenic product is prepared using a weight close to that of the expected yield. Identical aliquots (10–20 μl) of the unknown and the standard are injected under identical conditions on a suitable glpc column[15] and the percentage yield of the unknown is calcu-

TABLE III
INSTRUMENTAL DATA FOR DIMER ACIDS

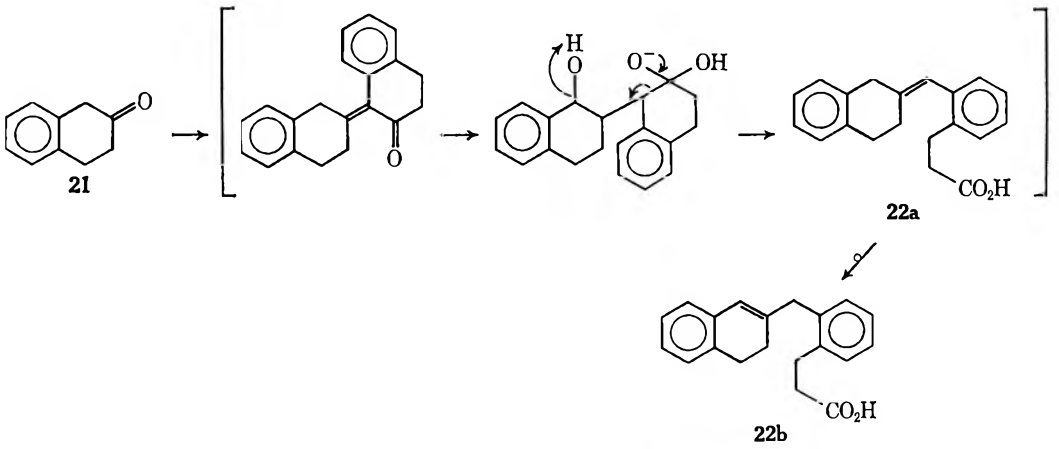
Precursor ketone	Dimer acid	Mp, °C	Uv,[a,b] mμ (log ε)	Ir,[c] cm^{-1}	Mass spectra (parent ion)
1	17	113.5–115	225 (4.90) 283 (3.97)	1672	290 304[d]
4	18[e]	145–147	228 (4.71) 288 (3.97)	1692	*f*
5	19	145–146	228, 284	1686	*f*
7	20	186–187.5	232, 290	1686	*f*

[a] These spectra were determined in 95% ethanol. [b] ϵ values for **19** and **20** are omitted, since the purity of these acids was questionable. The ratio of their ϵ values is *ca.* 10:1, the hypsochromic value predominating. [c] In $CHCl_3$. [d] The parent ion of the methyl ester. [e] *Anal.* Calcd for $C_{22}H_{22}O_2$: C, 82.98; H, 6.96. Found: C, 82.83; H, 7.04. [f] The parent ion was not observed.

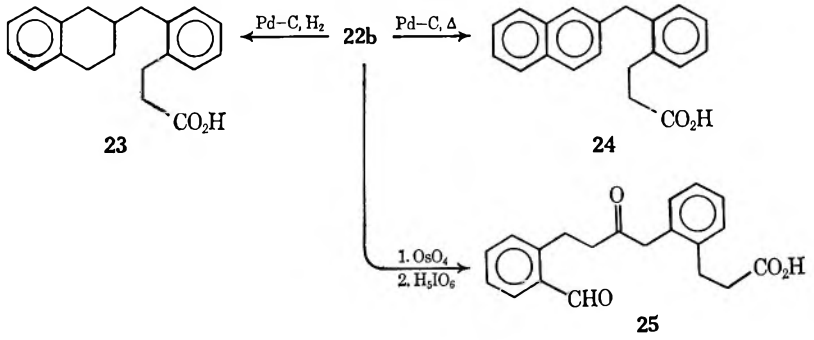
(13) R. B. Thompson, *Org. Syn.*, **20**, 94 (1940).
(14) E. J. Eisenbraun, *ibid.*, **45**, 28 (1965).

(15) Analysis of reaction mixtures can be carried out on any of three columns: 11 ft × 0.25 in. 10% SE-31 on DMCS-treated, acid-washed Chromosorb G; 10 ft × 0.25 in. 25% Carbowax 20M on acid-washed Chromosorb W; 6 ft × 0.25 in. 5% silicone rubber on acid-washed, DMCS-treated Chromosorb W. Appropriate temperatures are 160–242°, depending on alkyl substitution. For the separation of 4,5,8-trimethyl-1-tetralone and 1,4,5-trimethylnaphthalene, a 10 ft × 0.25 in. column of 5% phenyldiethanolamine succinate on acid-washed Chromosorb P should be used.

SCHEME IV



SCHEME V



lated from the ratio of the peak areas. The chart speed, injected volume, column temperature, and attenuation are so chosen that a peak of sufficient height and width at half-height for reliable measurement is obtained.

Employment of the above procedure gave yields of 72, 74, and 75% for three separate reactions of **1** with KOH–NaOH.

Identification of Tetralols in the KOH–NaOH Reactions of 2 and 3.—The ir spectra of the steam-volatile materials obtained from **2** and **3** showed absorptions which were due to the presence of hydroxyl (3390 cm^{-1}) and carbonyl (1680 cm^{-1}) functions. Analysis (glpc) revealed peaks which did not correspond to the appropriate tetralones, tetralins, naphthalenes, or naphthols. Oxidation with chromic acid[14] gave products showing neither the unknown peaks in the gas chromatograms nor hydroxyl absorption in the ir spectra. The retention times of the unknown peaks were the same as those of authentic samples of the tetralols prepared by reduction of **2** and **3** with diisobutylaluminum hydride.

Dimerization[15] of 1-Tetralone (1) to 14.—To a 250-ml, three-necked flask equipped with a gas-inlet tube and reflux condenser was added 168 g (1.15 mol) of distilled **1**. Anhydrous hydrogen chloride was bubbled into **1** at a moderate rate for 15 min. The reaction mixture then was heated at 80–90° for 96 hr, being recharged each 24 hr with hydrogen chloride gas. The dark orange-brown, viscous reaction product was diluted to *ca.* 500 ml with ether, which precipitated 40 g of a tan solid. The latter was isolated by filtration and a portion was triturated with acetone, filtered, and recrystallized from acetone to give **14** as white crystals: mp 132–135° (lit.[16] mp 132.5–134.2°); mass spectrum (70 eV) *m/e* (rel intensity) 274 (77), 146 (75), 129 (100), 43 (97), and 29 (91); nmr ($CDCl_3$) δ 8.24 (m, 1, ArH), 7.63–7.24 (m, 7, ArH), 5.88 (t, 1, C=CH), 3.89 (t, 1, C=CCH and adjacent to >C=O), 3.21–2.02 (m, 8, $>CH_2$); uv max (95% C_2H_5OH) 2.08 mμ (log ε 4.65) and 253 (4.36) [lit.[16] 208 mμ (log ε 4.45) and 253 (log ε 4.3)]; ir ($CHCl_3$) 3.23, 3.26, 3.42, 3.46, and 3.53 μ[17] [lit.[16] 3.31, 3.40, and 3.47 μ]. A portion of these crystals was converted into the orange 2,4-dinitrophenylhydrazone, recrystallized from 95% ethanol and melting at 245–248° dec (lit.[16] mp 247–248° dec).

The ethereal mother liquor was washed with 10% NaOH solution and water, dried ($MgSO_4$), filtered, and concentrated. Fractional distillation *in vacuo* of the resulting dark brown oil afforded 96 g of unreacted **1** and 17 g of a viscous, yellow oil which crystallized from acetone as white crystals. The total amount of crude dimer isolated was 57 g; the total amount of dimer after one recrystallization from acetone was 39 g (59% yield based on consumed **1** or 25% actual yield). The gas chromatograms (10% UC-W98 on 80/100s Chromosorb W, DMCS treated) at 290° of all fractions showed the same peak as for **14**.

Reaction of 14 with KOH–NaOH.—A 3.66-g (0.013 mol) sample of **14** was heated for 3 hr with 1 g of KOH pellets and 1 g of NaOH pellets using the same apparatus and procedure as described for the general reaction of 1-tetralones with KOH–NaOH. After the reaction product was steam distilled, the alkaline pot residue was extracted with ether, acidified with concentrated hydrochloric acid, and extracted with ether. The latter ethereal extract was washed with water, dried ($MgSO_4$), filtered, and concentrated to give 1 g (26% yield) of crude **17**. Three recrystallizations from chloroform–petroleum ether gave 0.31 g of pale gray, fibrous solid, mp 114.5–115.5°.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.59; H, 6.34.

The steam distillate was worked up and analyzed as described for the general reaction of 1-tetralones. The yield of naphthalene was 2.05 g (60%).

Formation of 22b from 2-Tetralone (21).—A 4.98-g (0.034 mol) sample of **21**, 0.82 g of KOH pellets, and 0.85 g of NaOH pellets were heated at 220° for 2 hr as described for 1-tetralones. The cooled reaction mixture was steam distilled and the residue was extracted with ether (the frequently occurring emulsions were broken up with saturated sodium chloride solution). The alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), filtered, and concentrated to give 2.00 g of yellow-brown solid (40% crude yield, other runs gave yields of 45 and 48%). Recrystallization from isopropyl alcohol afforded **22b** as a cream-colored powder

(16) M. Orchin, L. Reggel, and R. A. Friedel, *J. Amer. Chem. Soc.*, **71**, 2743 (1949); this repetition of the reported preparation of tetralylidenetetralone afforded **14** instead, as shown by nmr analyses. The agreement of the uv and ir spectrum and melting point of **14** and the melting point of the 2,4-dinitrophenylhydrazone of **14** with the literature values show that the previously reported ketone is probably **14** rather than tetralylidene-1-tetralone.

(17) We thank Dr. M. Evens, Continental Oil Co., for this spectrum.

which was sublimed *in vacuo* to deposit white crystals: mp 118–120°; mass spectrum (70 eV) *m/e* (rel intensity) 189 (92), 133 (100), 40 (84), 18 (82), and 15 (100); for nmr, see Table II.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.98. Found: C, 81.84; H, 6.66.

The methyl ester of **22b** was prepared with diazomethane and evaporatively distilled *in vacuo* as a white solid: mp 46–50°; mass spectrum (70 eV) *m/e* (rel intensity) 129 (100), 128 (67), 117 (27), 115 (28), and 91 (31).

Dehydrogenation (Pd–C) of 22b.—A 0.31-g (0.0011 mol) sample of **22b**, 0.1 g of 10% Pd–C, and 8 ml of distilled 1-methylnaphthalene were added to a 15-ml, one-necked flask equipped in the same manner as for the KOH–NaOH reactions. The reaction mixture was refluxed vigorously (245°) for 6.5 hr under a helium atmosphere, cooled, dissolved in ether, filtered through Dicalite, and extracted with 10% NaOH solution. The cloudy, alkaline solution was filtered first through Whatman No. 31 filter paper, and then through Dicalite to remove an unknown white solid. The clear solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was dried ($MgSO_4$), filtered, concentrated, and dried *in vacuo* to give 0.17 g (55% crude yield) of cream-colored solid. Sublimation *in vacuo* afforded **24** as a white powder: mp 126–127.5°; mass spectrum (70 eV) *m/e* (rel intensity) 290 (69), 217 (100), 105 (96), 43 (58), and 41 (59); for nmr, see Table II.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.49; H, 6.31.

Hydrogenation (Pd–C) of 22b.—To a 100-ml, one-necked flask were added 0.25 g (0.001 mol) of **22b**, 0.012 g of 10% Pd–C, and 50 ml of ethanol. The stirred solution was hydrogenated at room temperature for 17 hr. The reaction mixture was filtered through Dicalite, concentrated, and dried *in vacuo* to give 0.22 g (crude yield 86%) of white solid. Sublimation *in vacuo* afforded **23** as white crystals: mp 131–133°; mass spectrum (70 eV) *m/e* (rel intensity) 131 (100), 130 (28), 115 (28), 91 (27), 41 and (28); for nmr, see Table II.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.31; H, 7.58.

The methyl ester was prepared with diazomethane and evaporatively distilled *in vacuo:* mass spectrum (70 eV) *m/e* (rel intensity) 131 (100), 130 (32), 129 (32), 91 (34), and 28 (68).

Degradation of 22b.—To a three-necked, 100-ml flask were added in order 1.25 g (4.94 mmol) of OsO_4, 30 ml of anhydrous pyridine (dried with KOH), and 1.33 g (4.55 mmol) of **22b**. The yellow solution of OsO_4 in pyridine turned black immediately on addition of **22b**. The solution was stirred magnetically for 25 hr. The osmic ester was decomposed by addition of a solution consisting of 45 ml of H_2O, 22.5 ml of anhydrous pyridine, and 3 g of $NaHSO_3$. The reaction mixture was stirred for 12 hr and the liquid was decanted from the precipitate. The resulting red solution was extracted with five 40-ml portions of $CHCl_3$ and the extract was dried ($MgSO_4$), decanted, and concentrated to give the crude, oily diol. The crude product was dissolved in 50 ml of ether and transferred to a 250-ml erlenmeyer flask. To this solution was added 75 ml of anhydrous ether containing 1.13 g (4.96 mmol) of H_5IO_6. The reaction mixture was stirred for 4 hr. The ethereal solution was decanted from the white precipitate (HIO_3), washed with water, dried (Na_2SO_4), decanted, and evaporated to dryness under reduced pressure to give 1.09 g (74% yield) of a yellow solid. Recrystallization from a $CHCl_3$–petroleum ether mixture gave 0.42 g of **25** as a white solid: mp 89.5–91.5°; mass spectrum (70 eV) *m/e* (rel intensity) 306 (5), 288 (16), 246 (5), 160 (4), 143 (100), and 115 (29); nmr ($CDCl_3$) δ 10.18 (s, 1, CHO), 9.3 (broad absorption, 1, COOH), 7.7 (s, 1, ArH *ortho* to CHO), 7.5–7.0 (m, 7, ArH), 3.75 (s, 2, $ArCH_2$ adjacent to >C=O), 3.28 (t, 2, $ArCH_2$ *ortho* to CHO), and 2.96–2.46 (m, 6, $>CH_2$ and $ArCH_2$).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.86; H, 6.65.

In a separate experiment, the products of the periodic acid cleavage were steam distilled and **21** could not be detected nor were there any uv-active, steam-volatile products.

Mass Spectrometric Analysis of Reaction Gases.—Normal alkali fusions of **1** and **2** were carried out in a closed system and the off-gases were trapped in two evacuated steel bombs. Mass spectrometric analysis at 70 eV showed *m/e* of 2 in excess of the fragmentation peak in the helium carrier gas. The ratio of hydrogen in equal samples was 5.3:2.4 (1 to 2).[18]

Registry No.—**14**, 23804-16-2; 2,4-dinitrophenylhydrazone of **14**, 23796-79-4; **17**, 23804-17-3; **18**, 23804-18-4; **19**, 23804-19-5; **20**, 23804-20-8; **22b**, 23796-80-7; methyl ester of **22b**, 23796-81-8; **23**, 23804-21-9; methyl ester of **23**, 23804-22-0; **24**, 23804-23-1; **25**, 23804-24-2; potassium hydroxide, 1310-58-3; sodium hydroxide, 1310-73-2.

Acknowledgment.—We thank the American Petroleum Institute for support of this work through API Research Project 58A, and the Research Foundation of Oklahoma State University for their assistance. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research. We thank Dr. O. C. Dermer for having read the manuscript.

(18) We thank Mr. H. M. Curtis, Continental Oil Co., for these determinations.

Metal–Amine Reactions.[1] The Reductive Amination of Aromatic Hydrocarbons[2]

E. J. EISENBRAUN, R. C. BANSAL,[3a,b] D. V. HERTZLER,[3c,d] AND W. P. DUNCAN[4]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

P. W. K. FLANAGAN AND M. C. HAMMING

Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

Received September 22, 1969

The reductive amination of polynuclear aromatic hydrocarbons provides a new synthesis of novel secondary and tertiary amines. The conditions affecting this reaction of aromatic hydrocarbons with alkali metals and amines were studied. Reductive amination takes place concurrently with, and at times in preference to, metal–amine reduction when an aromatic hydrocarbon is treated with sodium and a secondary or primary amine. This side reaction to the Birch-type reduction takes place readily with naphthalene and alkylated naphthalenes and generally at the β position of the less substituted ring, provided that there is no alkyl group at either vicinal position. Steric effects in both the aromatic hydrocarbon and in the amine influence the competition of reductive amination and Birch-type reduction.

The reduction of naphthalene to 1,2,3,4-tetrahydronaphthalene (**1**) by sodium in liquid ammonia was first studied in 1914.[5] Later it was shown that four atoms of sodium were involved, though a large excess was present.[6] In 1939, naphthalene was shown to react with two atomic proportions of sodium in liquid ammonia at −75 to −65° to form a red complex which, on decomposition with methanol, gave 1,4-dihydronaphthalene (**2**).[7a] The complex was found to be stable at low temperatures but ammonolyzed above −50° to form **2**, which was isomerized to 1,2-dihydronaphthalene (**3**). The latter isomer then reduced at this temperature to **1**. It was therefore concluded that the reduction of naphthalene to **3** is a stepwise process, involving successive formation of a disodium adduct, protonolysis of the adduct to **2** and sodium amide, base-induced rearrangement of **2** to **3**, and, finally, reduction to **1**. Similar results were obtained with calcium.[7a] It was inferred that the organometallic intermediates in these reactions are salts, and that the reduction is initiated by the addition of electrons to the naphthalene nucleus to form a radical anion and dianion. Other contributions to our understanding of dissolving metal reactions have been made[7b–f] and general discussions are available.[7g–i]

Birch, in the early 1940's, greatly extended Wooster's earlier observations,[6,8] and, as a result, the Birch reduction has been applied extensively in synthetic organic chemistry.[7g] The Birch reduction of polynuclear aromatic hydrocarbons and other aromatic systems has been thoroughly explored and reviewed.[9] Birch routinely included alcohols in his reaction mixtures. These were considered to be the source of protons for the reduction of aromatic systems.

Other authors have modified the original procedure utilized by Birch. Significant contributions regarding the relative merits of lithium and sodium resulted from the work of Wilds and Nelson[10] and, subsequently, from that of Dryden and coworkers[11a] and Harvey.[11b] The use of calcium hexammine in the selective reduction of aromatic hydrocarbons has been reported.[11c] Benkeser and coworkers pioneered the use of low molecular weight amines such as methylamine, ethylamine, and propylamine instead of liquid ammonia.[12] More extensive reduction results when these amines are used, since there is an increase in solubility of organic molecules and the reaction temperature may be higher. Reggel and coworkers showed that lithium in ethylenediamine appears to be the most powerful metal–amine system and can reduce aromatic hydrocarbons to saturated hydrocarbons.[13a–c] Slaugh and Raley[13d] reported reduction of benzene and alkyl-substituted benzenes with sodium–ammonia at 60–130°. Reduction of aromatic hydrocarbons has also been achieved by electrolysis in the presence of lithium chloride using a low molecular weight amine or ethylenediamine[14a] or hexamethylphosphoramide[14b] solvent.

(1) R. C. Bansal, E. J. Eisenbraun, and P. W. K. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966).

(2) (a) E. J. Eisenbraun, R. C. Bansal, P. W. K. Flanagan, and A. B. Carel, *Amer. Chem. Soc., Div. Petrol. Chem., Preprints Gen. Papers*, **11**, No. 3, 65 (1966); (b) E. J. Eisenbraun, D. V. Hertzler, W. P. Duncan, M. D. Raba, P. W. K. Flanagan, and R. D. Grigsby, *ibid.*, **13**, No. 1, 226 (1968).

(3) (a) R. C. Bansal, Ph.D. Thesis, Oklahoma State University, July 1966; (b) American Petroleum Institute Research Project 58A Graduate Research Assistant, 1962–1966; (c) American Petroleum Institute Research Project 58A Graduate Research Assistant, 1966–1968; (d) National Science Foundation Science Faculty Fellow, Grant 68098, June 1, 1968–March 31, 1969.

(4) National Science Foundation Research Participation Program for College Teachers, summer 1967, GY-2420.

(5) P. Lebeau and M. Picon, *Compt. Rend.*, **158**, 1514 (1914).

(6) C. B. Wooster and F. B. Smith, *J. Amer. Chem. Soc.*, **3**, 179 (1931).

(7) (a) W. Hückel and H. Bretschneider, *Justus Liebigs Ann. Chem.*, **540**, 157 (1939); (b) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959); (c) A. P. Krapcho and M. E. Nadel, *ibid.*, **86**, 1096 (1964); (d) J. J. Eisch and R. M. Thompson, *J. Org. Chem.*, **27**, 4171 (1962); (e) J. J. Eisch, *ibid.*, **28**, 707 (1963); (f) O. J. Jacobus and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 5799 (1965); (g) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 50–77; (h) W. Hückel, *Fortsch. Chem. Forsch.*, **6**, Part 2, 1 (1966); (i) J. J. Eisch, "The Chemistry of Organometallic Compounds," The Macmillan Co., Inc., New York, N. Y., 1967.

(8) C. B. Wooster and K. L. Godfrey, *J. Amer. Chem. Soc.*, **59**, 596 (1937).

(9) (a) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. I, Part 2, G. Jander, H. Spandau, and C. C. Addison, Ed., Interscience Publishers, New York, N. Y., 1963.

(10) (a) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953); (b) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953).

(11) (a) H. L. Dryden, G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961); (b) R. G. Harvey, *ibid.*, **32**, 238 (1967); (c) H. Boer and P. M. Duinker, *Rec. Trav. Chim. Pays-Bas*, **77**, 346 (1958).

(12) Part VIII: R. A. Benkeser, *et al.*, *J. Org. Chem.*, **29**, 1313 (1964).

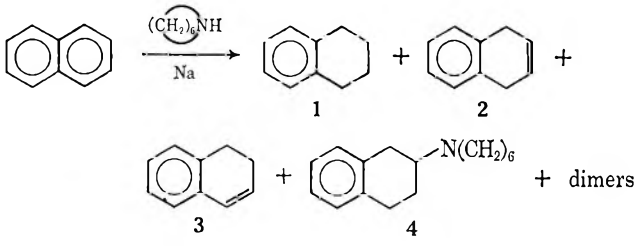
(13) (a) L. Reggel, R. A. Friedel, and I. Wender, *ibid.*, **22**, 891 (1957); (b) L. Reggel, S. Friedman, and I. Wender, *ibid.*, **23**, 1136 (1958); (c) J. D. Brooks, R. A. Durie, and H. Silberman, *Aust. J. Chem.*, **17**, No. 1, 55 (1964); (d) L. H. Slaugh and J. H. Raley, *J. Org. Chem.*, **32**, 369 (1967).

(14) (a) R. A. Benkeser, E. M. Kaiser, and R. F. Lambert, *J. Amer. Chem. Soc.*, **86**, 5272 (1964); (b) H. W. Sternberg, R. E. Markby, I. Wender, and D. M. Mohilner, *ibid.*, **89**, 186 (1967).

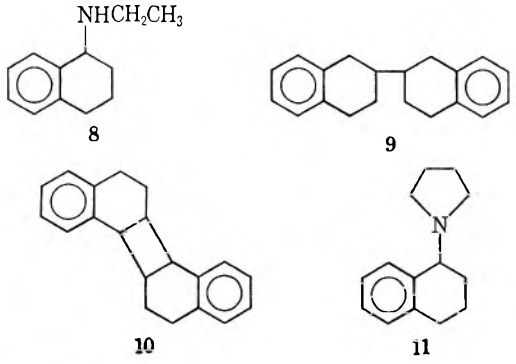
Results and Discussion

We previously demonstrated[1,2] that amines and sodium may be used in the reduction of naphthalene and alkylated naphthalenes to dihydronaphthalenes and tetrahydronaphthalenes. However, in some cases, the low yields of reduced hydrocarbons pointed to the formation of side reaction products. These were identified as hydrocarbon dimers[2b,15] and secondary or tertiary amines, of which N-(1,2,3,4-tetrahydro-2-naphthyl)hexamethylenimine (**4**) is typical. The hydrocarbon reduction products accompanying **4** are shown in Scheme I. In the case of naphthalene, **1** is the dominant volatile hydrocarbon product, and with certain amines, the presence of **2** can be detected[2b] in the early stages of the reaction. The tertiary amine **4** results from amination of **3**.[1]

SCHEME I



Various primary and secondary amines were used to test the generality of the reductive amination reaction. The results are summarized in Table I. Reductive amination products and hydrocarbon dimers (reductive dimerization) exceed the Birch-type reduction products when primary amines are used. For example, cyclohexylamine and *n*-hexylamine gave 33 and 28% yields of N-cyclohexyl-1,2,3,4-tetrahydro-2-naphthylamine (**5**) and N-*n*-hexyl-1,2,3,4-tetrahydro-2-naphthylamine (**6**), respectively, whereas N-ethyl-1,2,3,4-tetrahydro-2-naphthylamine (**7**) and N-ethyl-1,2,3,4-tetrahydro-1-naphthylamine (**8**) were obtained in 17% combined crude yield and the conventional Birch-type reduction products were essentially absent. The hydrocarbon dimers are a complex mixture, of which 1,2,3,4,1′,2′,3′,4′-octahydro-2,2′-binaphthyl (**9**)[16] and 5,6,6a,6b,11,12,12a,12b-octahydrodibenzo[*a*,*g*]biphenylene (**10**) generally predominate.[2b]

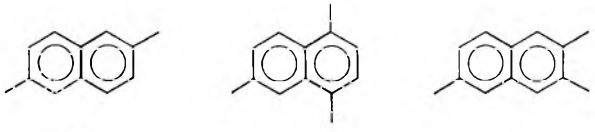


The dimer **9** has been reported to form in the reaction of naphthalene with sodium[16] and ethylamine or with either sodium[17a] or magnesium[17b] and ammonia.

The formation of a carbon–nitrogen bond during reductive amination generally takes place at the β position of the naphthalene nucleus. The observed major exceptions occur with ethylamine and pyrrolidine (Table I), which gave **8** and 1-pyrrolidino-1,2,3,4-tetrahydronaphthalene (**11**), respectively. In both cases, these are the minor products.

The yield of reductive amination product appears to be very susceptible to steric effects in the amine moiety. For example, 2-methylpyrrolidine and 2-methylpiperidine afforded small amounts (*ca.* 1–5%) of reductive amination products, whereas 2,5-dimethylpyrrolidine and 2,6-dimethylpiperidine failed to give more than trace amounts of such products. However, all of these amines cause reduction and reductive dimerization of naphthalene, as shown in Table I.

Several alkyl-substituted naphthalenes were subjected to reductive amination with sodium and hexamethylenimine. The results may be found in Table II. It is of interest that reductive amination for these examples takes place in the less alkyl-substituted ring of the naphthalene nucleus and at the 2 position. If the ring is substituted by alkyl groups in both rings, reductive amination may not take place.[1,2] For example, 2,6-dimethylnaphthalene (**25**), 1,4,6-trimethylnaphthalene (**26**), and 2,3,6-trimethylnaphthalene (**27**) failed to give reductive amination products; however, extensive Birch-type reduction or reductive dimerization of the individual hydrocarbons took place.



25 26 27

A definite assignment for the position of attachment of nitrogen for the reductive amination products from 1-methylnaphthalene, 2-methylnaphthalene, and 2-*t*-butylnaphthalene in Table II could not be made, since, for example, the nmr data did not permit distinction between **19a** and **19b**.

Consideration of the foregoing data and the probable mechanism[7a] for formation of **1**–**3** strongly suggests the overall sequence in Scheme II. This rationalization explains the formation of 1,2,3,4-tetrahydronaphthalenes as well as reductive amination products from 1,2-dihydronaphthalenes. We suggest that, for reduction and presumably for reductive amination, the necessary protons come from the amine solvent and not from the water used to quench the reaction. We also suggest that the amination step takes place by nucleophilic addition of the anion of hexamethylenimine to the conjugated double bond of **3** and subsequent abstraction of a proton from hexamethylenimine by anion **31**, as shown in Scheme II. It seems less likely that addition to **2** takes place, since **2** *is* readily isomerized to **3**. Under the same conditions, cyclohexene and cyclooctene gave no evidence of reaction.

(15) Presented before the Southwest Regional of the American Chemical Society, Albuquerque, N. M., Nov 30–Dec 2, 1966.

(16) L. Reggel, H. W. Sternberg, and I. Wender, *Nature*, **190**, 81 (1961).

(17) (a) W. Hückel and M. Wartini, *Justus Liebigs Ann. Chem.*, **686**, 40 (1965); (b) P. Markov, D. Lasarov, and C. Ivanov, *ibid.*, **704**, 126 (1967).

SCHEME II

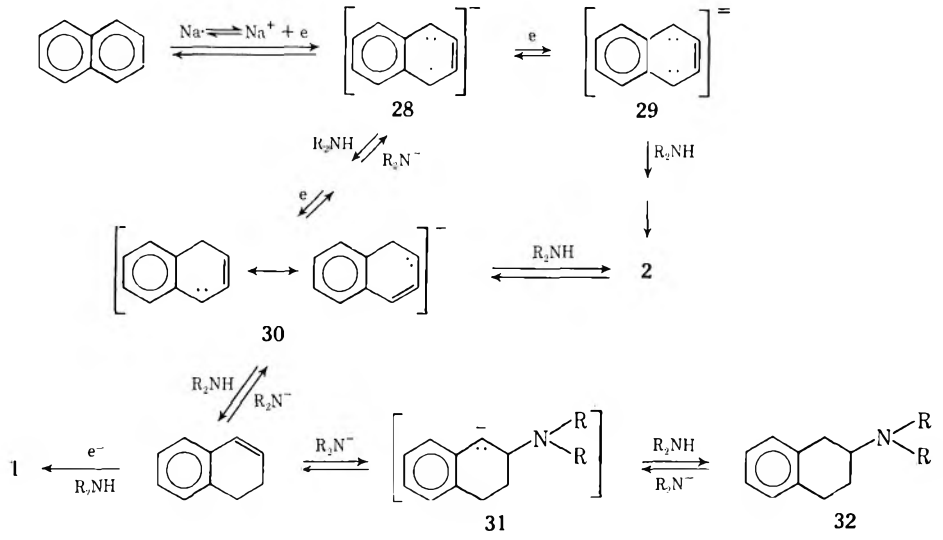
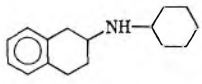
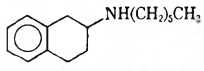
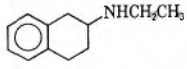
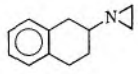
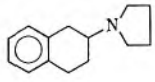
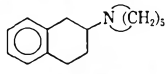
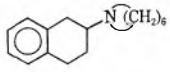
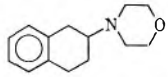
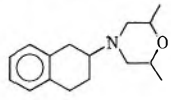
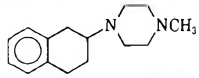
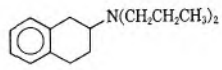


TABLE I

REDUCTIVE AMINATION OF NAPHTHALENE AT ROOM TEMPERATURE

Amine	Compd	Reductive amination products: Structure	Reductive amination products: %[a]	Hydrocarbons[a]: 1	Hydrocarbons[a]: 3	Dimers[b]
Cyclohexylamine	5		33	2	2	43
n-Hexylamine	6		28	0.3	0.8[c]	47
Ethylamine[d]	7		17[e]	...	1	80
Ethylenimine	12		*f*	*f*	*f*	*f*
Pyrrolidine	13		35[g]	20	...	36
Piperidine	14		46	4	0.7	11
Hexamethylenimine	4		28	8	0.4	35
Morpholine	15		33	32	...	8
2,6-Dimethylmorpholine	16		52	7	7	12
N-Methylpiperazine	17		64	6	0.8	5
Dipropylamine	18		6	4	9	55
2-Methylpyrrolidine			5	23	...	30
2,5-Dimethylpyrrolidine			...	25	...	36
2-Methylpiperidine			5	42	...	36
2,6-Dimethylpiperidine			...	5	4	85

[a] Yield based on consumed naphthalene. [b] Containing several dimers, of which **9** and **10** are major constituents. [c] This fraction contained *ca.* 25% **2**. [d] At 15°. [e] Nmr analysis showed this product to be a mixture of **7** and **8** (16:1). [f] The extreme sensitivity of **12** to acid does not allow the usual isolation procedure, and only sufficient quantities of **12** for identification and analysis were isolated. The hydrocarbons were not investigated in this case. [g] Gas chromatography analysis showed this product to be a mixture of **11** and **13** (1:11).

SCHEME III

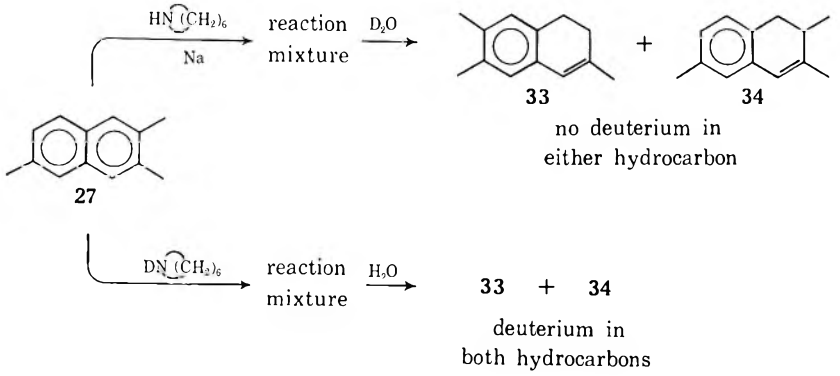
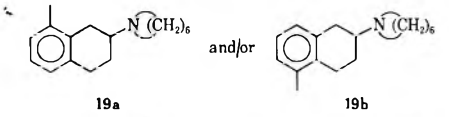
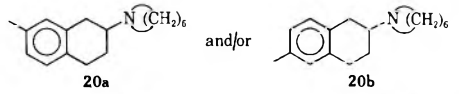
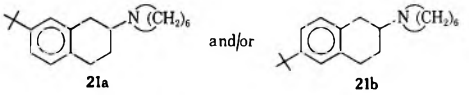
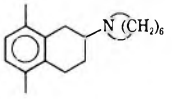
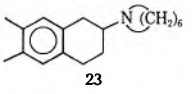
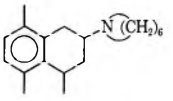


TABLE II

REDUCTIVE AMINATION OF ALKYLATED NAPHTHALENES WITH SODIUM AND HEXAMETHYLENIMINE AT 25°

Starting material	Yield of reductive amination product,[a] %	Structure of reductive amination products	Yield of hydrocarbon products, % Steam-volatile[b]	Yield of hydrocarbon products, % Non-volatile[b]
1-Methylnaphthalene	17	 19a and/or 19b	37	21
2-Methylnaphthalene	43	 20a and/or 20b	24	15
2-*t*-Butylnaphthalene	43	 21a and/or 21b	15	7
1,4-Dimethylnaphthalene	51	 22	17	8
2,3-Dimethylnaphthalene	69	 23	11	7
1,4,5-Trimethylnaphthalene	25	 24	37	8

[a] Yield calculations based on consumed aromatic hydrocarbon. [b] The compositions of these hydrocarbon products remain under study.

Evidence to support Scheme II was obtained by subjecting **27**, as shown in Scheme III, to conventional sodium and hexamethylenimine reaction conditions and subsequent hydrolysis of the reaction products with deuterium oxide to yield **33** and **34**, which were shown by nmr and mass spectrometric studies to be completely free of deuterium. However, when N-deuteriohexamethylenimine was substituted for hexamethylenimine in the reaction and hydrolysis was effected with water, substantial deuterium incorporation was observed in **33** and **34**. These studies gave **33** and **34** in a 5:1 ratio, which is in agreement with the data shown in Table II. The nmr studies showed that there was no positional selectivity in deuterium incorporation in **33** and **34**. However, a preference for deuterium exchange at benzylic positions was observed for recovered **27**.

That addition of amine anion to a conjugated olefin is reversible in the reductive amination reaction was demonstrated by the competitive study shown in Scheme IV. The formation of hydrocarbons **1** and **3** and the mixture of amines **11** and **13** was confirmed through instrumental studies and conclusively establishes that reductive amination is indeed a reversible process.

SCHEME IV

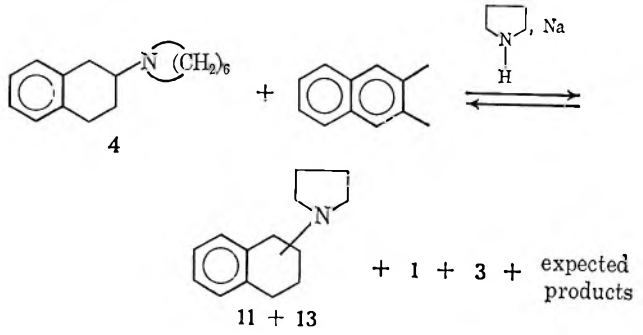
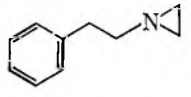


TABLE III
AMINATION OF 2 AND 3

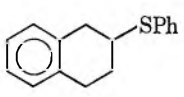
Hydrocarbon	Amine	Source of base	Yield of 4, %	Yield of hydrocarbons,[a] % 1	3	Dimers
2	HN(CH$_2$)$_6$	Na	66	24	6	4
3	HN(CH$_2$)$_6$	Na	58	30	7	5
3	HN(CH$_2$)$_6$	*n*-BuLi	64	...	35	1

[a] Yields determined by glpc analysis.

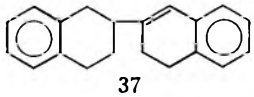
The addition of the anion derived from the reaction of *n*-butyllithium with hexamethylenimine to **2** and **3** (Table III) also substantiates Scheme II and is of interest because it takes place in a nonreducing system. Further, the addition of primary and secondary amines, in the presence of sodium to conjugated olefins is known.[18] For example, styrene stirred with sodium and ethylenimine at 45° gives an 89% yield of **35**.[18a] Other experiments designed to test nucleophilic addition to **3** showed that **36** could be formed from the anion derived from the reaction of *n*-butyllithium and thiophenol but that sodium hydride in dimethyl sulfoxide caused the formation[15] of the dimer **37** rather than the adduct comparable to **38** obtained from 1,1-diphenylethylene.[19] The formation of dimer **37** may also be caused by heating **2** with potassium *t*-butoxide in DMSO[20] or by heating **2** or **3** with KOH in DMSO. The latter gives a mixture of dimers containing varying proportions of **9**, **10**, and **37**.



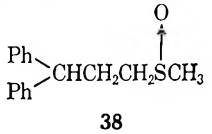
35



36



37



38

Experimental Section[21]

The amines used in this work were purchased from the usual sources except for gift samples[22a,b] and 2-methylpyrrolidine, which was prepared from 5-methyl-2-pyrrolidone by $LiAlH_4$ reduction. All amines were distilled from potassium hydroxide before use. The dispersed sodium was prepared by stirring freshly cut sodium pieces in hot xylene.

Structural Assignments.—The structures of the reductive amination products were assigned from nmr data summarized in Table IV and observation of the molecular ion peak in the individual mass spectrum (Table V). Acceptable elemental analyses (C, H, and N) were obtained for each amine and are presented in Table VI.[21]

Reductive Amination of Naphthalenes.—All reductive amination reactions were carried out under a nitrogen atmosphere in a 300-ml, three-necked flask equipped with air condenser and magnetic stirrer. The reductive amination with ethylamine was carried out at 15° under a Dry Ice condenser, but in all other cases the reactions were carried out at room temperature.

Reductive Amination of Naphthalene with Sodium and Hexamethylenimine.—To 6.4 g (0.05 mol) of naphthalene[22c] and 4.6 g (0.2 g-atom) of dispersed sodium contained in the reaction flask was added 100 ml of hexamethylenimine. A red color usually developed within 20 min. The mixture was stirred at 25° for 12 hr, and unreacted sodium which had agglomerated was removed. The reaction mixture was poured cautiously onto ice water and the red color disappeared. The product mixture was acidified with 10% aqueous hydrochloric acid. After the hydrocarbons had been removed by extraction with ether, the aqueous layer was made alkaline with dilute sodium hydroxide, and surplus hexamethylenimine was removed by steam distillation. The residue from steam distillation was extracted with ether. Drying (Na_2SO_4) gave 6.2 g (55% yield) of crude N-(1,2,3,4-tetrahydro-2-naphthyl)perhydroazepine (**4**); distillation gave a colorless oil (28% yield), bp 134–136° (0.8 mm).

The ether extract containing hydrocarbons was concentrated and then steam distilled to separate the volatile hydrocarbons from the C_{20} dimers. Extraction of the volatile fraction with ether, drying ($MgSO_4$), and concentrating afforded 0.55 g (8.4%) of a 20:1 (**1** to **3**) mixture. The ratio was determined by glpc on a Carbowax 20M column. Extraction of the residue of hydrocarbons from the steam distillation gave 2.3 g (35%) of a mixture of crude dimer hydrocarbon products, including **9** and **10**. A similar procedure was used for the reductive amination of naphthalene with other amines.

Isolation and Identification of 1,2,3,4,1′,2′,3′,4′-Octahydro-2,2′-binaphthyl (9) and 5,6,6a,6b,11,12,12a,12b-Octahydrodibenzo[*a*,*g*]biphenylene (10).—Dimer **9**, mp 80–83°, crystallized from an ether extract of the previously described steam distillation as white crystals and was recrystallized: mp 84–85°; nmr (CCl_4) δ 6.99 (s, 8, ArH), 2.73 (q, 8, ArCH), and 1.65 (m, 6, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 262 (42), 131 (100), 130 (39), 129 (32), 104 (40), and 91 (29).

Dimer **10** crystallized from an ether solution of the nonvolatile hydrocarbon residue in the reaction of naphthalene with ethylenediamine. It was purified by crystallization from ether–petroleum ether as colorless crystals: mp 179–180°; nmr (CCl_4) δ 6.99 (s, 8, ArH), 2.76–3.46 (m, 6, ArCH), and 1.20–2.07 (m, 6, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 260 (41), 131 (38), 130 (40), 129 (100), 128 (63), and 115 (21).

Reductive Amination of Naphthalene with Sodium and Ethylenimine.—To 6.4 g (0.05 mol) of naphthalene and 4.6 g (0.2 g-atom) of dispersed sodium contained in the reaction flask, 100 ml of ethylenimine was added. After the mixture had been stirred at 25° for 12 hr, unreacted sodium was removed and the surplus ethylenimine was distilled under vacuum (water aspirator). The residue in the flask was diluted with water and shaken with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and filtered. Distillation of ether gave 7.0 g of dark oil. Gas chromatographic analysis of this oil on a 10 ft × 0.375 in. column of base-washed Chromosorb W coated with 25% Carbowax 20M showed 28% tertiary amine **12**. Since **12** is very sensitive to acid, it was purified directly from the mixture by preparative gas chromatography using the above column.

Reduction of 2,3,6-Trimethylnaphthalene (27) with Sodium

(18) (a) H. Bestian, *Justus Liebigs Ann. Chem.*, **566**, 210 (1950). (b) A. P. Stuart and C. E. Scott, U. S. Patent 3,118,938 (1964); *Chem. Abstr.*, **60**, 9167 (1964).

(19) C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964).

(20) Private communication from M. Baum. We acknowledge his prior preparation of **37**, which proved to be identical with **37**, from our reactions.

(21) Nmr spectra were obtained with a Varian HR-60 spectrometer. Peak positions are reported in terms of parts per million downfield from internal TMS standard in CCl_4 solvent. Mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-103 C mass spectrometer. Glpc analyses for the hydrocarbons were obtained with a Hewlett–Packard Model 5750 gas chromatography apparatus fitted with thermal conductivity and hydrogen-flame detectors using helium as a carrier gas. The financial assistance from the Research Foundation, Oklahoma State University, PHS Grant 5-505-FR077-04, which made this instrument available is gratefully acknowledged. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(22) (a) We are grateful to the Union Carbide Co. for supplying amines used in the preparation of **6** and **15–18**. (b) The ethylenimine used to prepare **12** was supplied by Dow Chemical Co. (c) We thank the Sun Oil Co. for the high-purity naphthalene used in these studies.

TABLE IV

NMR DATA FOR REDUCTIVE AMINATION PRODUCTS

Compd	Aromatic protons absorption, δ ppm	Other proton absorptions, δ (ppm)
4	6.93 (4 H, s)	1.60 (8 H, s),[a] 1.14–2.25 (2 H, m),[b] 2.74 (9 H, m)[c]
5	6.89 (4 H, s)	0.61 (1 H, NH, s), 1.25–1.85 (12 H, m),[b] 2.71 (6 H, m)[c]
6	6.94 (4 H, s)	0.75 (1 H, NH, s), 0.88 (3 H, methyl, s), 1.31 (8 H, s),[a] 1.92 (2 H, m),[b] 2.70 (7 H, m)[c]
7 and 8	6.96 (4 H, s)	0.96 (1 H, NH, s), 1.08 (3 H, methyl, t), 1.72 (2 H, m),[b] 2.76 (7 H, m),[c] 3.82 (0.06 H, m)[d]
12	6.97 (4 H, s)	0.95 (2 H, t),[e] 1.20 (1 H, m),[f] 1.60–2.50 (2 H, m),[g] 1.56 (2 H, t),[h] 2.72 (4 H, benzylic, t)
11 and 13	6.92 (4 H, s)	1.67 (4 H, s),[a] 1.31–2.23 (2 H, m),[b] 2.61 (9 H, m),[c] 3.68 (0.43 H, m)[i]
14	6.91 (4 H, s)	1.47 (6 H, s),[a] 1,50–2.20 (2 H, m),[b] 2.46–2.69 (9 H, m)[c]
15	6.91 (4 H, s)	1.66 (2 H, m),[b] 2.55 (9 H, m),[c] 3.54 (4 H, q)[j]
16	6.93 (4 H, s)	1.15 (6 H, 2 methyl, d), 1.80–2.90 (11 H, m),[b,c] 3.25–4.00 (2 H, m)[j]
17	6.95 (4 H, s)	1.65 (2 H, m),[b] 2.20 (3 H, methyl, s), 2.26-2.90 (13 H, m)[c]
18	6.94 (4 H, s)	0.90 (6 H, methyl, t), 1.52 (4 H, m),[a] 1.90 (2 H, m),[f] 2.50 (4 H, t),[k] 2.77 (5 H, q)[l]
19a or 19b	6.81 (3 H, s)	1.22–1.93 (2 H, m),[f] 1.59 (8 H, s),[a] 2.13 (3 H, methyl, d), 2.68 (9 H, m)[c]
20a or 20b	6.76 (3 H, s)	1.26–1.89 (2 H, m),[f] 1.58 (8 H, s),[a] 2.21 (3 H, methyl, s), 2.69 (9 H, s)[c]
21a or 21b	6.95 (3 H, s)	1.28 (9 H, methyl, s), 1.59 (8 H, s),[a] 1.95 (2 H, m),[f] 2.72 (9 H, m)[c]
22	6.71 (2 H, s)	1.63 (10 H, s),[a] 2.14 (6 H, methyl, s), 2.66 (9 H, m)[c]
23	6.96 (2 H, s)	1.32–1.91 (2 H, m),[b] 1.58 (8 H, m),[a] 2.11 (6 H, methyl, s), 2.64 (9 H, m)[c]
24	6.72 (2 H, s)	1.11 and 1.23 (3 H, methyl, d, J = 7 cps), 1.60 (8 H, s),[a] 1.80–2.49 (2 H, m),[b] 2.14 and 2.23 (6 H, methyl), 2.68–3.30 (8 H, m)[c]

[a] Methylene protons not adjacent to nitrogen. [b] Methylene protons not adjacent to nitrogen or aromatic ring. [c] Methylene protons adjacent to nitrogen or aromatic ring. [d] Protons adjacent to aromatic ring and nitrogen indicating 6% **8**. [e] Methylene protons on one side of aziridine ring. [f] Methylene proton at C_3. [g] One methylene proton at C_2 and one at C_3. [h] Methylene protons on other side of aziridine ring. [i] Protons adjacent to aromatic ring and nitrogen indicating 43% **11**. [j] Protons adjacent to oxygen. [k] Methylene protons adjacent to nitrogen. [l] Protons at C_1, C_2, and C_4.

and N-Deuteriohexamethylenimine.—A mixture of 3.29 g (0.02 mol) of **26**, 3.0 g (0.13 g-atom) of sodium, and 100 ml of N-deuteriohexamethylenimine (65% D) was stirred at room temperature under a nitrogen atmosphere for 50 hr. The amine solution was decanted from the unreacted sodium and poured over crushed ice. The aqueous mixture was acidified with concentrated HCl and extracted twice with ether. The ether layer was washed twice with water and dried over anhydrous sodium sulfate, and the ether was distilled, leaving 2.8 g of oil. Unreacted starting material and compounds **33** and **34** were isolated by preparative gas chromatography. Mass spectrometric analysis of **33** showed the following incorporation (d_n, %) of deuterium: d_4, 1; d_5, 3; d_6, 6; d_7, 10; d_8, 15; d_9, 17; d_{10}, 17; d_{11}, 14; d_{12}, 9; d_{13}, 4; d_{14}, 2. The nmr spectrum did not show any selective deuterium incorporation. The mass spectrum of **34** showed the following incorporation (d_n, %) of deuterium: d_4, 13; d_5, 20; d_6, 23; d_7, 20; d_8, 13; d_9, 7; d_{10}, 2. The mass spectrum of recovered **27** showed the following incorporation (d_n, %) of deuterium: d_4, 13; d_5, 20; d_6, 23; d_7, 20; d_8, 13; d_9, 7; d_{10}, 2. The nmr spectrum showed the benzylic to aromatic proton ratio to be 6.2:5 compared with 9:5 for nondeuterated **27**.

Exchange of Amino Groups in a Reductive Amination Product.—A mixture of 0.643 g (4.12×10^{-3} mol) of 2,3-dimethylnaphthalene, 1 g (4.12×10^{-3} mol) of **4**, 0.379 g (1.65×10^{-2} g-atom) of sodium, and 16 ml of pyrrolidine were stirred under a nitrogen atmosphere for 12 hr. The amine and hydrocarbon products were separated by the procedure given for the reductive amination of naphthalene with sodium and hexamethylenimine. Gas chromatographic analysis of the volatile hydrocarbon mixture showed the presence of **1** and **3**. Mass spectrometric analysis of the amine mixture which was not volatile to steam showed parent ions at m/e 229 and 201. This latter parent ion corresponds to the molecular weight of **11** or **13**, which can arise only from an exchange of pyrrolidine for the hexamethylenimine group of **4**.

An Attempted Reaction of Cyclooctene with Sodium and Hexamethylenimine.—A mixture of 5.5 g (0.05 mol) of cyclooctene, 4.6 g (0.2 g-atom) of sodium sand, and 150 ml of N-methylpiperazine was stirred at room temperature under a nitrogen atmosphere for 5 hr. No color developed and heat was not evolved from the reaction mixture. The reaction mixture was decanted from the sodium sand onto 400 ml of crushed ice. The aqueous reaction mixture was extracted with ether and the ether layer was extracted with excess 10% HCl. The ether layer was then dried (Na_2SO_4) and gas chromatographed. Only one peak, identical in retention time with that of cyclooctene, in addition to ether was observed. Under these conditions, cyclooctane would have been detected. A similar experiment with cyclohexene failed to produce any cyclohexane.

Reductive Amination of 1,2-Dihydronaphthalene (3) with Sodium and Hexamethylenimine.—A mixture of 5 g (0.04 mol) of **3**, 3.5 g (0.15 g-atom) of sodium, and 150 ml of hexamethylenimine was stirred vigorously at room temperature for 20 hr under a continuous flow of nitrogen. The amine and hydrocarbon products were separated as previously described for the preparation of **4**. The crude, gold-colored product (5.5 g) was distilled to give 5.1 g (58%) of **4**, bp 137° (8 mm). The volatile hydrocarbon fraction was shown by glpc analysis to be a 4:1 mixture of **1** and **3**. A trace of C_{20} hydrocarbon dimers was isolated.

A duplicate run using **2** instead of **3** gave **4** in 66% yield and a 4:1 mixture of volatile hydrocarbons **1** and **3**.

Reaction of 1,2-Dihydronaphthalene (3) and Hexamethylenimine by Means of *n*-Butyllithium.—To a 300-ml, three-necked flask equipped with condenser, stirrer, nitrogen inlet tube, and an addition funnel were added 100 ml of hexamethylenimine. A solution of 8% *n*-butyllithium–hexane (60 ml)[23] was added under nitrogen over a period of 15 min. The temperature of the reaction flask was maintained at 25° by external cooling. A solution

(23) The concentration of *n*-butyllithium was determined by hydrolysis of an aliquot and titration with standard hydrochloric acid.

TABLE V

MASS SPECTRAL DATA OF REDUCTIVE AMINATION PRODUCTS

Compd	Molecular ion peak (intensity as % of Σ)	Peaks by relative intensities fragmentation, *m/e*
4	229 (4.5)	229, 124, 41, 225, 227, 128[a] 230, 229, 228, 227, 226, 225[b]
5	229 (6.0)	186, 130, 131, 229, 41, 56[a] 230, 229, 187, 186, 158, 146[b]
6	231 (3.3)	160, 131, 30, 130, 156, 231[a] 232, 231, 230, 229, 227, 161[b]
7 and **8**	175 (6.7)	175, 56, 130, 28, 131, 104[a] 176, 175, 174, 173, 172, 171[b]
11 and **13**	201 (4.1)	28, 27, 96, 199, 201, 197[a] 202, 201, 200, 199, 198, 197[b]
12	173[c] (2.7)	130, 129, 115, 104, 28, 128[a] 173, 172, 158, 147, 146, 145[b]
14	215 (5.6)	110, 215, 211, 84, 213, 41[a] 216, 215, 214, 213, 212, 211[b]
15	217 (9.5)	217, 130, 112, 28, 131, 129[a] 218, 217, 216, 215, 172, 159[b]
16	245 (8.7)	245, 130, 131, 42, 129, 41[a] 246, 245, 244, 243, 172, 160[b]
17	230 (3.4)	43, 58, 42, 70, 130, 230[a] 231, 230, 229, 228, 186, 172[b]
18	231 (1.7)	202, 131, 198, 27, 43, 41[a] 231, 229, 227, 203, 202, 200[b]
19a and/or **19b**	243 (4.8)	243, 239, 41, 124, 129, 144[a] 244, 243, 242, 241, 240, 239[b]
20a and/or **20b**	243[d] (3.9)	239, 243, 41, 124, 241, 129[a] 244, 243, 242, 241, 240, 239[b]
21a and/or **21b**	285 (3.0)	281, 266, 41, 285, 57, 124[a] 286, 285, 284, 283, 282, 281[b]
22	257 (4.2)	253, 257, 158, 159, 41, 143[a] 258, 257, 256, 255, 254, 253[b]
23	257 (1.8)	98, 28, 253, 41, 255, 30[a] 257, 256, 255, 254, 253, 252[b]
24	271 (3.9)	28, 256, 271, 41, 157, 172[a] 272, 271, 270, 269, 267, 257[b]

[a] Six strongest peaks. [b] Last six peaks with intensities greater than 0.5% of total ion yield. [c] A 0.5% $C_{13}H_{17}N$ impurity was detected. [d] Sample as the hydrochloride when admitted to mass spectrometer.

TABLE VI

ANALYTICAL DATA OF REDUCTIVE AMINATION PRODUCTS

Reductive amination products	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Bp, °C (mm)
4	$C_{16}H_{23}N$	83.78	10.11	6.11	83.56	10.23	6.14	134–136 (0.8)
5	$C_{16}H_{23}N$	83.78	10.11	6.11	83.76	10.25	6.08	129–131 (0(8)
6	$C_{16}H_{25}N$	83.05	10.89	6.05	83.43	11.01	5.79	127–129 (0.8)
7 and **8**	$C_{12}H_{17}N$[a]	82.23	9.78	7.99	82.22	9.64	8.07	66–68 (0.2)
12	$C_{12}H_{15}N$	83.19	8.73	8.09	82.98	8.79	8.02	68–70 (1.5)
11 and **13**	$C_{14}H_{19}N$[b]	83.53	9.51	6.96	83.59	9.58	6.81	107–109 (0.5)
14	$C_{15}H_{21}N$	83.66	9.83	6.51	83.49	9.78	6.61	119–121 (0.8)
15	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.11	8.89	6.43	126–128 (0.8)
16	$C_{16}H_{23}NO$	78.32	9.45	5.71	78.54	9.65	5.64	127–129 (0.8)
17	$C_{15}H_{22}N_2$	78.21	9.63	12.16	78.28	9.75	12.01	133–135 (0.8)
18	$C_{16}H_{25}N$	83.05	10.89	6.05	83.12	10.98	6.02	112–114 (0.8)
19a or **19b**	$C_{17}H_{25}N$	83.89	10.35	5.76	83.67	10.46	5.62	145–147 (0.9)
20a or **20b**	$C_{17}H_{25}N$	83.89	10.35	5.76	83.90	10.36	5.73	136–138 (0.2)
21a or **21b**	$C_{20}H_{31}N$	84.14	10.95	4.91	84.04	11.13	5.15	163–165 (0.6)
22	$C_{18}H_{27}N$	83.99	10.57	5.44	84.18	10.83	5.52	151–153 (0.5)
23	$C_{18}H_{27}N$	83.99	10.57	5.44	84.03	10.23	5.68	147–149 (0.3)
24	$C_{19}H_{29}N$	84.07	10.77	5.16	84.26	10.91	5.00	180–182 (2.0)

[a] This sample is a mixture of **7** and **8** in a ratio of 16:1. [b] This sample is a mixture of **13** and **11** in a ratio of 11:1.

of 6.5 g (0.05 mol) of **3** in 10 ml of hexane was next added over a period of 10 min. The reaction mixture was stirred for 12 hr at 25°. This reaction gave 7.25 g (64%) of **4** and 1.6 g (35%) of unreacted **3**.

Reaction of 1,2-Dihydronaphthalene (3) by Means of *n*-Butyllithium and Thiophenol.—To 80 ml of thiophenol contained in a reaction flask equipped with condenser, nitrogen inlet tube, stirrer, and an addition tube, 30 ml of an 8% solution of *n*-butyllithium–hexane was added over a period of 15 min. A white precipitate formed. To the stirred suspension, 3.25 g (0.025 mol) of **3** was added, and the reaction mixture was stirred at 25°. After a 12-hr period, the reaction mixture was diluted with water and treated with 10% sodium hydroxide solution. This basic solution was extracted with ether and the ether extract was steam distilled to remove unreacted **3** (1.5 g, 48%). The residue from the steam distillation was extracted with ether, dried ($MgSO_4$), and concentrated to 4.0 g of crude dark oil. Evaporative distillation gave 2.92 g (48%) of **36**: nmr ($CDCl_3$) δ 7.19 (m, 5, ArH), 6.92 (s, 4, ArH), 3.32 (m, 1, CH adjacent to S), 2.88 and 2.72 (m, 4, $ArCH_2$), and 1.99 (m, 2, $-CH_2-$ nonbenzylic and not adjacent to S); mass spectrum (70 eV) *m/e* (rel intensity) 240 (34), 131 (100), 130 (71), 129 (39), 115 (29), and 91 (28).

An ether-insoluble, ethyl-acetate-soluble product, mp 59–60°, weighing 1.8 g, was isolated. This was identified as diphenyl disulfide by comparison with authentic material through melting point and mass nmr spectra.

Registry No.—**4**, 23853-47-6; **5**, 23853-48-7; **6**, 23853-49-8; **7**, 19485-86-0; **8**, 23853-51-2; **11**, 23853-52-3; **12**, 23853-53-4; **13**, 23853-54-5; **14**, 23853-55-6; **15**, 23853-56-7; **16**, 23853-57-8; **17**, 23853-58-9; **18**, 23853-59-0; **19a**, 23853-60-3; **19b**, 23890-38-2; **20a**, 23853-61-4; **20b**, 23853-62-5; **21a**, 23853-63-6; **21b**, 23853-64-7; **22**, 23853-65-8; **23**, 23853-66-9; **24**, 23853-67-0; **36**, 23853-68-1.

Acknowledgments.—We are grateful to the American Petroleum Institute for support of API Research Project 58A and to the Research Foundation, Oklahoma State University, for their assistance. We thank Dr. O. C. Dermer for valuable discussions and for having read the manuscript. We are also grateful to the National Science Foundation for support through Grants GY-2420 and 68098.

Synthesis of 3,8-Dihydroxyspiro[4.4]nona-3,8-diene-2,7-dione *via* a Diacyloin Condensation

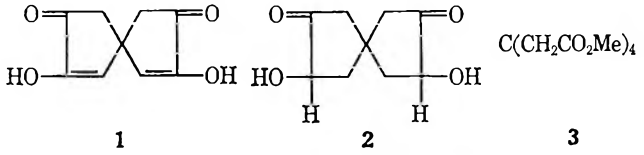
C. AINSWORTH AND FRANCIS CHEN[1]

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received October 16, 1969

Tetramethyl methanetetraacetate and sodium formed an intermediate dienediol that was oxidized by air or iodine to give the title compound. The intermediate in the oxidation with iodine appears to be a disemidione. A modified acyloin condensation, using sodium–liquid ammonia followed by evaporation of the ammonia and the addition of trimethylchlorosilane (TMCS), has been shown to be of particular utility in the synthesis of 2,3,7,8-tetrakis(trimethylsilyloxy)spiro[4.4]nona-2,7-diene.

As a starting material for the synthesis of polyspiro compounds we planned to prepare the title compound **1** from the diacyloin **2**, which was to be synthesized from **3** by the acyloin reaction. Since the last review article[2]



1 **2** **3**

on the reaction, a new procedure[3] has evolved which consists of addition of trimethylchlorosilane (TMCS) as a reactant in a solvent such as xylene. The product of the reaction is the silated enediol, which is easily solvolyzed[3] to acyloin.

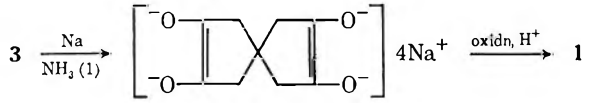
We have developed a modified procedure, which consists of a classical acyloin condensation using liquid ammonia followed by evaporation of the ammonia and the addition of TMCS. In certain instances this procedure cannot be used, but in our reaction it gives higher yield of silated enediol than is obtained by the xylene solvent method.

When the double acyloin condensation of tetramethyl methanetetraacetate (**3**) was attempted using sodium dispersed in xylene with TMCS, nmr studies indicated a small yield of the desired product **4**. Re-

4

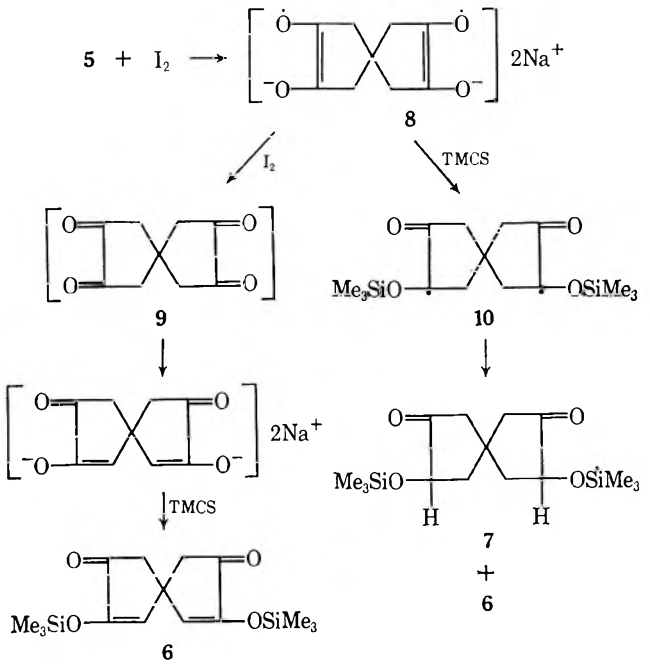
action of **3** with sodium–liquid ammonia followed by TMCS gave an 88% yield of the silated dienediol **4**. Isolation of pure **2** from the silated product was not possible. Compound **2** was shown by nmr studies to be formed by the methanolysis of **4**, but on removal of the methanol the diacyloin **2** polymerized.[4]

It was possible, however, to obtain **1** in 25% yield from the diacyloin condensation of **3**. This was done



5

by formation, from **3** and sodium–liquid ammonia, of the tetrasodium salt of the dienediol intermediate **5**, followed by air oxidation under carefully controlled conditions.[5] A large excess of air gave a low yield of **1**, methanetetraacetic acid, and unidentified material. The oxidation of **5** was also effected by iodine[6] to give **1** in the same yield as by the oxygen method. In order to understand the nature of this reaction, TMCS was added to trap intermediates. When **5** was treated with 2 mol of iodine followed by evaporation of ammonia and addition of TMCS, the silated derivative of **1**, namely compound **6**, was obtained. Treatment of **5** with 1 mol of iodine gave **6** and **7**, the silated derivative of the acyloin **2**. We believe that these results are explained in terms of the following equations.



The electron-transfer reaction of **5** and iodine formed the disemidione **8**, which should be a stable species[7] at low temperature in solution. Reaction of **8** with iodine formed the di-1,2 diketone **9**, which as the enol form[8] was trapped by TMCS as compound **6**. In the absence of iodine for a further electron-exchange reaction, species **8** reacted with TMCS to give the radical **10**

(1) Taken in part from the Ph.D. Thesis of F. M. F. Chen, 1969.

(2) F. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

(3) (a) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964); (b) K. Ruhlmann, A. Seefluth, and H. Becker, *ibid.*, **100**, 3820 (1967); (c) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968).

(4) J. C. Sheehan, R. C. O'Neill, and M. A. White [*J. Amer. Chem. Soc.*, **72**, 3376 (1950)] reported the dimerization of acyloins.

(5) M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).

(6) Use of this reagent was suggested by Larry L. Miller.

(7) Semidiones have been extensively studied by G. A. Russel, *et al.*, *J. Amer. Chem. Soc.*, **89**, 6636, 6781 (1967); **91**, 2813 (1969).

(8) Sodium methylate generated from the condensation served as base.

that underwent disproportion[9] to give the saturated system **7** and the unsaturated compound **6**. No dimer resulting from **10** was formed but a silated residue remained. The silated products **6** and **7** are solids. Compound **7** underwent methanolysis, as does compound **6**.

We also attempted to prepare **1** by the hydrolysis of **4** to give **2** followed by direct oxidation of the diacyloin with cupric acetate. The reaction failed for the reason that **1** is itself oxidized by cupric acetate.

The structure of **1** was confirmed by nmr, ir, and mass spectral data and its conversion into the diquinoxaline derivative. The nmr spectrum of **1** in deuterium oxide–sodium hydroxide was of interest in that all protons exchanged in about 20 min at ambient temperature. On aqueous acidification, the exchanged material showed no proton signal in the nmr.[10]

The tetraester **3** was made from methanetetraacetic acid, which was prepared using a modified procedure of Ingold and Nickolls[11] starting from diethyl acetonedicarboxylate. Rather than following the literature procedure after the preparation of diethyl 3-dicarbethoxymethylglutaconate, the latter was treated with ethyl sodiocyanoacetate to give diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate. The glutaric ester on hydrolysis and decarboxylation gave methanetetraacetic acid.

Experimental Section[12]

Diethyl Acetonedicarboxylate.—Citric acid was converted into acetonedicarboxylic acid,[13] which was esterified.[14] The reported overall yield of the diester was 39–43%. This was raised to 58% by employing anhydrous citric acid and using a connecting 5-l. overflow flask at the stage of addition of citric acid to the cooled fuming sulfuric acid.

Diethyl 3-Chloroglutaconate.—To 101 g (0.5 mol) of diethyl acetonedicarboxylate in a 1-l., round-bottom flask was added, as rapidly as the brisk evolution of hydrogen chloride gas allowed, 105 g (0.5 mol) of phosphorus pentachloride. The mixture was stirred during addition and kept below 50° by means of an ice bath. The solution was poured into 1 kg of ice contained in a large flask, since evolution of hydrogen chloride was vigorous. The red oil at the bottom of the flask was separated and the aqueous layer was extracted with 300 ml of chloroform. The combined oil and chloroform extract was washed with 10% potassium carbonate, followed by saturated salt solution, and then was dried using magnesium sulfate. Distillation gave 78 g (75% yield) of diethyl 3-chloroglutaconate,[15] bp 90° (0.25 mm).

Diethyl 3-Dicarbethoxymethylglutaconate.—The Michael addition reaction was carried out in a 1-l. flask containing 1.1 mol of diethyl sodiomalonate dissolved in 300 ml of ethanol. Diethyl 3-chloroglutaconate (22.5 g, 1 mol) was added dropwise with stirring at such a rate that boiling occurred. After addition, the reaction mixture was heated under reflux for 0.5 hr, cooled, and poured into 1 kg of ice. The oil that formed at the bottom of the flask was separated, and the water layer was extracted with 400 ml of ether. The combined oil and the ether extract was washed with dilute hydrochloric acid, followed by saturated salt solution, and then dried with magnesium sulfate. After removing the ether, the product was heated under reduced pressure at 70° (0.25 mm) to remove the low-boiling impurities. The undistilled residue[16] (*ca.* 70% yield) was nearly pure diethyl 3-dicarbethoxymethylglutaconate and was used in the next step.

Diethyl 2-Carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate.—To a solution of 1 mol of ethyl sodiocyanoacetate and 300 ml of ethanol contained in a 1-l. flask was added, with stirring, 172 g (0.5 mol) of crude diethyl 3-dicarbethoxymethylglutaconate from the previous step. The reaction mixture was heated under reflux for 8 hr, cooled, and poured into 180 ml of 6 *N* ice-cooled hydrochloric acid. The oil that formed at the bottom of the flask was collected and the water layer was extracted with 400 ml of ether. The combined oil and ether extract was washed with 10% potassium carbonate, followed by saturated salt solution, and then dried with magnesium sulfate. Distillation under reduced pressure gave 137 g (60% yield) of diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate, bp 180° (0.5 mm).

Anal. Calcd for $C_{21}H_{31}NO_{10}$: C, 55.13; H, 6.83. Found: C, 54.70; H, 6.64.

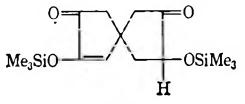
Methanetetraacetic Acid.—A solution of 116 g (0.25 mol) of diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate and 230 ml of concentrated sulfuric acid was allowed to stand at room temperature for 12 hr. The mixture was diluted with twice its volume of water and heated until the vapor reached the boiling point of water. A water condenser was then attached, and the mixture was refluxed for a total reaction period of 48 hr. The mixture was cooled and filtered using a coarse, sintered-glass funnel. The product was recrystallized from water and gave 44 g (70% yield) of methanetetraacetic acid as a white solid, mp 230° (lit.[11] mp 226°).

Tetramethyl Methanetetraacetate (3).—To a solution of 50 g (0.2 mol) of methanetetraacetic acid and 500 ml of absolute methanol in a 1-l., three-neck flask was added slowly with stirring 90 ml of concentrated sulfuric acid. A stream of methanol generated from another flask was passed into the main reaction flask under the liquid surface, and at the same time the main reaction flask was heated. Following removal of about 2 l. of distillate, the mixture was cooled and poured into 1 l. of cold, saturated salt solution. It was extracted three times with 300-ml portions of ether. The ether extract was washed with 10% sodium bicarbonate, followed by saturated salt solution, and dried with magnesium sulfate. Distillation under reduced pressure gave 56 g (93% yield) of tetramethyl methanetetraacetate, bp 155–160° (0.25 mm) [lit.[17] bp 192–195° (12 mm)].

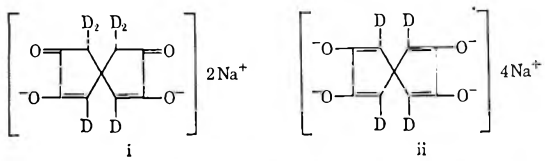
The nmr spectrum (CCl_4) shows peaks at τ 6.35 (12 H) and 7.2 (8 H).

3,8-Dihydroxyspiro[4.4]nona-3,8-diene-2,7-dione (1).—About 75 ml of liquid ammonia was distilled from a commercial cylinder of anhydrous ammonia through a drying tube filled with lump barium oxide into a three-neck flask equipped with mechanical stirrer and a Dry Ice–acetone cooled condenser. Sodium (1.8 g, 0.08 g-atom) cut in small pieces was added to the ammonia. After the system was flushed with helium, a solution of 3 g (0.01 mol) of **3** and 100 ml of anhydrous ether was added over a period of 2 hr. The blue color disappeared at the end of the addition. The Dry Ice was removed from the condenser, and tha ammonia was evaporated using a cold-water bath. The last

(9) Had the species **8** undergone disproportionation to form **5** and **1**, then compound **4** rather than **7** would have resulted. A referee suggested the following structure as a disproportionation product, but we did not observe it.



(10) This finding establishes the salt structure as i rather than ii.



i ii

Ultraviolet studies are in agreement with this conclusion in that there is only a slight bathochromic shift going from neutral to basic solution.

(11) C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, **121**, 1638 (1922).

(12) Melting points were determined with a Fisher-Johns melting point apparatus and boiling points are uncorrected. The nmr measurements were done at ambient temperature using a Varian A-60A spectrometer. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrophotometer. Mass spectra were measured with an AEI Model MS12 spectrometer. The microanalyses were done by Midwest Microlab, Inc., Indianapolis, Ind.

(13) R. Adams and H. M. Chiles, "Organic Syntheses," Coll. Vol. I, 2nd ed, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1941, p 10.

(14) Reference 13, p 237.

(15) This procedure is simpler than Ingold's method.[11]

(16) Distillation at reduced pressure was accompanied with considerable decomposition.[11]

(17) H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **54**, 62 (1935).

traces of ammonia were flushed out by passing helium into the system.

A. **Air Oxidation Method.**—Dry air was passed into the above stirred mixture for 0.5 hr at the approximate rate of 200 ml/min. Then 14 ml of 6 *N* hydrochloric acid was added and the mixture was saturated with ammonium chloride and extracted with three 50-ml portions of tetrahydrofuran (THF). The THF extract was washed with 20 ml of saturated salt solution and dried with magnesium sulfate. After removal of the THF, a yellow solid formed which was recrystallized from water to give 0.45 g (25% yield) of compound **1**: mp 245° dec; nmr (D_2O) τ 3.5 (2 H) and 7.3 (4 H); ir (KBr) 1725 and 1675 cm^{-1}; uv (95% EtOH) λ_{max} 260 mμ (ϵ 13,000) and 225 (broad shoulder) (6000); mass spectrum *m/e* (rel intensity, ion) 180 (65, M), 152 (40, M − CO), 137 (80, M − C_2H_3O), 69 (80), 57 (90), and 55 (base peak).

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.98; H, 4.71.

A sample of compound **1**, *o*-phenylenediamine, and 10 ml of absolute ethanol was refluxed for 5 min. The diquinoxaline derivative that formed was collected, washed with ethanol, and recrystallized from chloroform: mp 310° dec; nmr ($CDCl_3$) τ 2.1 (center of multiplet, 8 H) and 6.6 (8 H); mass spectrum *m/e* (rel intensity) 324 (70, M), 182 (70), 143 (60), 103 (100), and 77 (90).

B. **Oxidation by Iodine.**—Rather than adding air to the above mixture, a solution of 2.5 g (0.01 mol) of iodine and 100 ml of THF was added dropwise with stirring. The same work-up as in the air oxidation method was used and compound **1** was obtained in 25% yield.

3,8-Bis(trimethylsilyloxy)spiro[4.4]nona-3,8-diene-2,7-dione (6).—Procedure B above was completed to the point of adding 2.5 g (0.01 mol) of iodine in THF, and then 10 ml of trimethylchlorosilane (TMCS) was added immediately. The mixture was stirred for 10 min and filtered, and, after removal of the THF from the filtrate, a solid resulted. It was recrystallized from carbon tetrachloride and gave 0.3 g (25% yield) of compound **6**: mp 100°; nmr (CCl_4) τ 3.67 (2 H), 7.42 (4 H), and 9.74 (18 H); ir (Nujol) 1715 and 1610 cm^{-1}; mass spectrum *m/e* (rel intensity) 324 (2, M), 300 (10), 281 (6), 75 (25), and 73 (base peak).[18]

Anal. Calcd for $C_{15}H_{24}O_4Si_2$: C, 55.54; H, 7.46. Found: C, 55.75; H, 7.44.

Compound **6** was converted into **1** by heating a methanol solution of it for 1 hr under a nitrogen atmosphere. After removal of methanol, **1** formed in 95% yield.

3,8-Bis(trimethylsilyloxy)spiro[4.4]nona-2,7-dione (7).—The iodine oxidation procedure (B) was completed to the point of adding 1.2 g (0.005 mol) of iodine in 50 ml of THF, and then 5 ml (0.05 mol) of TMCS was added immediately. The mixture was filtered, and following removal of the THF a solid remained. A sample dissolved in carbon tetrachloride was shown by nmr analysis to contain **6** and **7**, and, on treatment with methanol at reflux for 2 hr, the silyl moieties of both were lost. Recrystallization of the solid from dry Skellysolve B gave **7** in 10% yield: mp 143°; nmr ($CDCl_3$) τ 6.0 (2 H), 7.7 (4 H), 8.5 (4 H), and 9.84 (18 H); ir (Nujol) 1730 cm^{-1}; mass spectrum *m/e* (rel intensity) 328 (2, M), 313 (25), 183 (3), 129 (70), 101 (40), 75 (40), and 73 (base peak).

Anal. Calcd for $C_{15}H_{28}O_4Si_2$: C, 54.86; H, 8.15. Found: C, 54.79; H, 8.42.

2,3,7,8-Tetrakis(trimethylsilyloxy)spiro[4.4]nona-2,7-diene (4).—The procedure described for the preparation of **1** was carried to the point of removing the last traces of ammonia with helium. A solution of 16 ml of TMCS and 100 ml of dry ether was added slowly to the ice-cooled reaction flask and the mixture was stirred for 0.5 hr and filtered. Distillation of the filtrate gave 4.2 g (90% yield) of **4**: bp 126° (0.25 mm); nmr (CCl_4) τ 7.8 (8 H) and 9.8 (36 H); ir (liquid film) 1750, 1700, and 1650 cm^{-1};[19] mass spectrum *m/e* (rel intensity) 472 (1, M), 467 (8), 385 (15), 356 (15), 255 (30), 147 (15), 75 (15), and 73 (base peak).

Anal. Calcd for $C_{21}H_{44}O_4Si_4$: C, 53.33; H, 9.38. Found: C, 53.33; H, 9.19.

Compound **4** was also obtained in a mixture from the acyloin condensation using sodium, TMCS, and xylene heated under reflux. The mixture was separated on a silica gel column using benzene–Skellysolve B to give **4** in 20% yield.

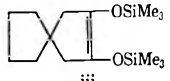
3,8-Dihydroxyspiro[4.4]nona-2,7-dione (2).—A solution of 3 g of **4** and 25 ml of absolute methanol was refluxed under nitrogen for 2 hr. The solution was concentrated to about 6 ml by means of a rotary evaporator. The nmr spectrum of the solution showed chemical shifts typical of an acyloin. Complete removal of the methanol on a rotary evaporator gave a solid polymer that was insoluble in acetone.

Registry No.—**1**, 23936-85-8; **4**, 23936-87-0; **6**, 23936-88-1; **7**, 23936-89-2; diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate, 23936-86-9.

Acknowledgment.—We are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society (Grant 3270-A1) for financial support.

(18) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead [*J. Org. Chem.*, **34**, 2324 (1969)] reported the mass spectra of trimethylsilyl enol ethers.

(19) These unusual absorption bands have been observed in the model compound iii.



iii

The Epoxidation and Cleavage of α,β-Unsaturated Ketones with Alkaline Hydrogen Peroxide

ROBERT D. TEMPLE

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received September 10, 1969

The kinetics of the reaction between 4-phenyl-3-buten-2-one and aqueous alkaline hydrogen peroxide were studied. Four reactions occur in this system: epoxidation by hydroperoxide ion to form 4-phenyl-3,4-epoxy-2-butanone, oxidative cleavage of the epoxide by hydroperoxide to give benzaldehyde, retrograde aldol reaction, and cleavage of the epoxide by hydroxide. The rates of these reactions in water at 25° are 0.22, 0.05, 0.00016, and 0.0032 l. mol^{-1} sec^{-1}, respectively. The influence of substituents in the phenyl ring on reaction rates and the relative reactivities of hydroperoxide and hydroxide ions are discussed in terms of the reaction mechanisms. The oxidative cleavage of α,β-epoxy ketones is mechanistically similar to several recently reported fragmentation reactions. The cleavage reaction was shown to have general synthetic utility in preparing diacids, keto acids, and ketones from α,β-unsaturated ketones, α,β-unsaturated aldehydes, and β diketones.

Treatment with alkaline hydrogen peroxide is the standard method for converting α,β-unsaturated ketones into α,β-epoxy ketones.[1] Our knowledge of the mechanism of this reaction is largely due to the work of Bunton and Minkoff.[2] The observed second-order kinetics and the rate-decreasing effect of methyl substituents at the double bond suggested that the rate-determining step is Michael addition of the hydroperoxide ion to the carbon–carbon double bond. Stereochemical studies also support this mechanism.[3] No general considerations of the reactions of the epoxide products under epoxidation conditions have been reported. In fact, standard references present α,β-epoxy ketones as being stable under basic epoxidation conditions.[4]

We report here additional information on the epoxidation mechanism, along with the rates and probable mechanisms of several competing reactions which occur under epoxidation conditions. α,β-Epoxy ketones undergo oxidative cleavage under these conditions. This reaction has synthetic utility and is mechanistically related to several other recently reported fragmentation reactions.

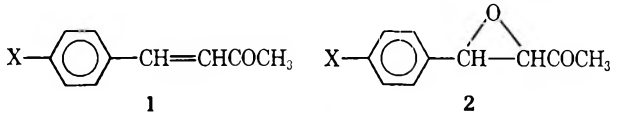
Results

Kinetics.—Bunton and Minkoff[2] found that the epoxidation of 3-penten-2-one and 4-methyl-3-penten-2-one with aqueous alkaline hydrogen peroxide obeyed the rate equation

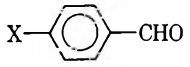
$$\text{initial rate} = k[\text{ketone}][HOO^-]$$

Although the kinetics apparently deviated from second order after long reaction times, these workers did not consider possible side reactions or reactions following the epoxidation.

Our initial results with 4-phenyl-3-buten-2-one (benzalacetone, **1a**) indicated that the reaction was not simply conversion of the α,β-unsaturated ketone into the epoxide. Ultraviolet spectra recorded during a typical run are shown in Figure 1. The intense ketone absorption at 290 nm decreases regularly with time, while the combined ketone and epoxide maximum near 225 nm decreases much more slowly, as expected for formation of epoxide with disappearance of ketone. However, the lack of a simple isosbestic point near 250 nm and the subsequent appearance of a strong peak in this region accompanied by the disappearance of the epoxide 225-nm maximum show that the epoxide is being converted into a new product. This product was identified as benzaldehyde by ultraviolet and infrared spectroscopy, boiling point, and preparation of the *p*-nitrophenylhydrazone derivative. Analysis of the spectra shown in Figure 1 and other spectra recorded during this run shows that the concentrations of the three species vary as shown by the points in Figure 2. Kinetic and stoichiometry studies, discussed later in detail, indicated that reactions 1–4



1 **2**



3

a, X = H; **b**, X = Cl; **c**, X = OCH_3

$$\mathbf{1} + HOO^- \xrightarrow{k_1} \mathbf{2} + HO^- \quad (1)$$

$$\mathbf{2} + HOO^- \xrightarrow{k_2} \mathbf{3} + P \quad (2)$$

$$\mathbf{1} + HO^- \xrightarrow{k_3} \mathbf{3} + P \quad (3)$$

$$\mathbf{2} + HO^- \xrightarrow{k_4} \mathbf{3} + P \quad (4)$$

take place in this system, where **1** = α,β-unsaturated ketone, **2** = epoxide, **3** = benzaldehyde, and P represents cleavage products containing three carbon atoms. Reaction 1 is the expected epoxidation reaction. Most of the benzaldehyde is produced by the epoxide fragmentation (reaction 2). Some benzaldehyde is also produced by reaction 3, the retrograde aldol reaction, and by cleavage of the epoxide by base (reaction 4). Reactions 3 and 4 are orders of magnitude slower than 1 and 2.

For a complete kinetic treatment of this system, the rapid degradation of product P must also be considered. Stoichiometry studies suggest that the de-

(1) E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921).
(2) C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, **1949**, 665.
(3) H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 2428 (1958); H. E. Zimmerman and G. A. Zimmerman, Abstracts, 149th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1965, p 8P.
(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 466.

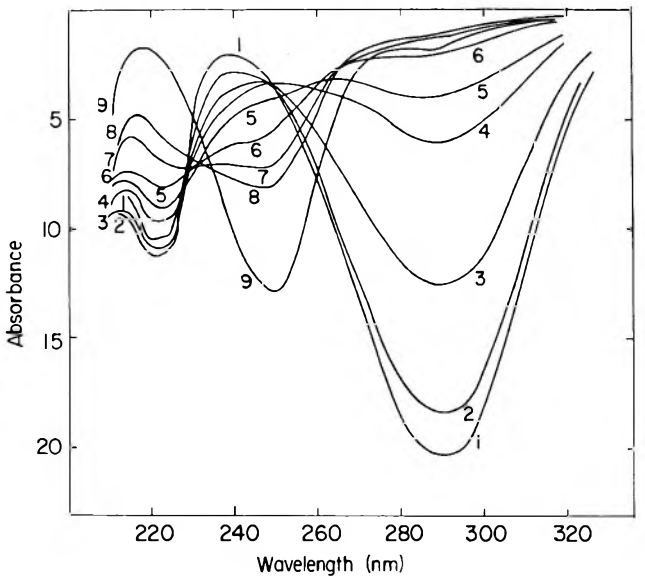


Figure 1.—Spectra recorded during reaction of benzalacetone (initially 0.001075 *M*) with hydrogen peroxide (0.00497 *M*) and sodium hydroxide (0.00644 *M*) in water at 25°. Spectra were recorded at the following times (in seconds): 1, 0; 2, 320; 3, 1020; 4, 2480; 5, 3700; 6, 7130; 7, 12,600; 8, 21,100. Spectrum 9 is a spectrum of 0.001075 *M* benzaldehyde.

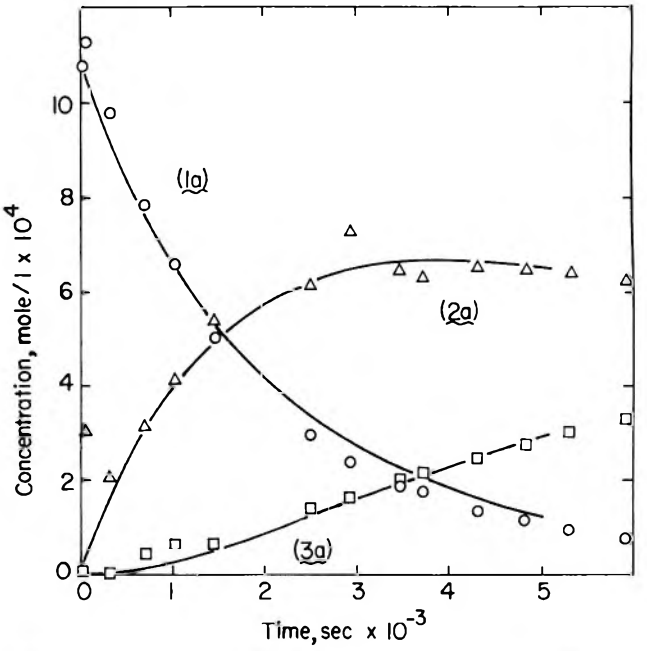


Figure 2.—Zero-order kinetic plot of the run shown in Figure 1. The symbols are experimental points. The solid lines are calculated as described in text: **1a**, ○; **2a**, △; **3a**, □.

struction of P consumes *ca.* 1 equiv each of base and peroxide, as in reaction 5.

$$P + HOO^- \longrightarrow Q \qquad (5)$$

The total titrable base ($HO^- + HOO^-$) stoichiometry results shown in Table I indicate that *ca.* 2 mol of base are used up for every 1 mol of epoxide converted into aldehyde. This agrees with the stoichiometry required by reactions 2 (or 4) and 5. Product Q has not been identified, but by stoichiometry is likely an equimolar mixture of $HCOO^-$ and CH_3COO^-.

TABLE I

BASE STOICHIOMETRY IN REACTION 2[a]

Time, sec	Δ[2a][b]	Δ[3a][b]	Δ[NaOH][b]	Δ[NaOH]/Δ[2a]	Δ[NaOH]/Δ[3a]
330	3.51	2.81	7	2.0	1.8
500	5.05	4.49	9	1.8	2.0
990	5.90	6.36	14	2.4	2.2
1090	6.05	6.74	14	2.3	2.1
1480	7.39	6.65	17	2.3	2.6
1570	6.95	7.55	17	2.4	2.2
2000	7.40	7.38	19	2.6	2.6
2180	7.78	7.96	19	2.4	2.4
2600	8.25	7.49	20	2.4	2.7
3120	7.94	7.63	21	2.5	2.6
				2.3 (avg)	2.3 (avg)

[a] In water at 25.0°. Initial concentrations: 2a, 9.30 × 10^{-4} *M*; H_2O_2, 4.07 × 10^{-2} *M*; NaOH, 1.68 × 10^{-2} *M*. [b] Δ[X] is the change in concentration of compound X at the time given. All values are 10^{-4} *M*.

The hydrogen peroxide acid–base equilibrium (reaction 6) must also be included in the kinetic scheme. The equilibrium constant for reaction 6 can be obtained from literature data: $K_6 = K_p/K_w = 222$, where K_p is the ionization constant of hydrogen peroxide (2.24 × 10^{-12})[5] and K_w is the self-ionization constant of water. Finally, the base-catalyzed decomposition of hydrogen peroxide (reaction 7) cannot be ignored in our system. The value of k_7 in control

$$H_2O_2 + HOO^- \longrightarrow H_2O + O_2 \qquad (7)$$

runs averaged *ca.* 5 × 10^{-3} l. mol^{-1} sec^{-1}. Fast, irregular peroxide decomposition rates were occasionally encountered, probably owing to adventitious catalytic impurities. Kinetic runs in which such rapid decomposition was evident were discarded.

The complete set of differential equations describing reactions 1–5 and including the acid–base equilibrium of reaction 6 cannot be solved explicitly and subjected to the usual kinetic analysis. However, the rates of reactions 3 and 4 can be determined accurately, independent of the other processes. The rate constants obtained for the reaction of hydroxide ion with α,β-unsaturated ketones **1a–1c** and with the epoxide **2a** are given in Table II. Adherence to second-order kinetics was excellent in every case, and ultraviolet spectra showed that the corresponding aldehyde, **3a–3c**, was always the reaction product.

Rough estimates of the rate constants for reactions 1 and 2 can be obtained from pseudo-first-order (in **1** or **2**) plots or second-order (in **1** or **3** and hydroperoxide) plots of kinetic data from runs with peroxide, base, and compound **1** or **2** initially present. The averages of several runs suggested that k_1 was *ca.* 0.3 in the **a** series, 0.4 in the **b** series, and 0.1 in the **c** series, and that k_2 was *ca.* 0.03 in the **a** series (all rate constants in l. mol^{-1} sec^{-1}). These values were refined and the validity of the entire reaction scheme was checked through the use of a computer simulation technique. An analog model of the proposed scheme was set up on an IBM 360/44 computer using a modified IBM

(5) M. G. Evans and N. Uri, *Trans. Faraday Soc.*, **45**, 224 (1949).

TABLE II
RATES OF REACTIONS 3 AND 4. CLEAVAGE OF UNSATURATED KETONES (1) AND EPOXIDES (2) BY HYDROXIDE ION[a]

	Initial concn, mol/l. × 10³		Rate constant, l. mol⁻¹ sec⁻¹ × 10⁴	
Substrate	Substrate	NaOH	k_2	k_4
1a	0.524	17.2	1.40	...
1a	0.685	25.2	1.76	...
1a (avg)			1.6	
2a	0.730	17.2	...	33
2a	0.620	25.2	...	29.8
2a	0.688	11.2	...	32.2
2a (avg)				32
1b	0.668	25.2	5.27	...
1b	0.445	25.2	7.09	...
1b (avg)			6.2	
1c	0.775	25.2	1.94	...
1c	0.388	31.5	1.78	...
1c (avg)			1.9	

[a] In water at 25.0°.

Continuous System Modeling Program (CSMP).[6] Reactions 1–7 were included in the model system, with the exception that reaction 7 was replaced for simplicity by a pseudo-reaction, 8. The accurately known rate and equilibrium constants discussed previously were used in the CSMP without modification. Reaction 5

$$HOO^- \longrightarrow HO^- + {}^1/_2O_2 \qquad (8)$$

was assigned an arbitrary rapid rate, $k_5 = 1.0$ l. mol^{-1} sec^{-1}. It was found that $k_8 = 1.0 \times 10^{-5}$ sec^{-1} worked well in most cases to account for peroxide disappearance; this would typically be equivalent to *ca.* 5×10^{-3} l. mol^{-1} sec^{-1} for k_7. Starting with the estimated values given above, k_1 and k_2 were varied systematically until the CSMP-calculated concentration–time data agreed with the observed concentrations of compounds **1**–**3** (compounds **1** and **3** only in the **b** and **c** series). The rate constants which give the best fit to data from several different kinetic runs are given in Table III. A typical fit of calculated

TABLE III
RATES OF REACTIONS 1 AND 2. REACTION OF HYDROPEROXIDE ION WITH UNSATURATED KETONES (1) AND EPOXIDES (2)[a]

	Rate constant, l. mol⁻¹ sec⁻¹	
Series[b]	k_1	k_2
a	0.22	0.05
b	0.28	0.06
c	0.08	0.03

[a] In water at 25.0°. [b] Series **a**, unsubstituted benzalacetone; **b**, *p*-chloro; **c**, *p*-methoxy.

to experimental data is shown by the solid lines in Figure 2. Peroxide and total base concentrations calculated using the constants in Tables II and III are in satisfactory agreement with the observed values.[7]

(6) International Business Machines Corp., "1130 Continuous System Modeling Program (1130-CX-13X) Program Reference Manual," IBM No. H20-0282-0, White Plains, N. Y., 1966.

(7) For examples of the use of similar computer techniques for determining rate constants in complex reactions, see D. F. DeTar, *J. Amer. Chem. Soc.*, **89**, 4058 (1967); J. E. Leffler and R. D. Temple, *ibid.*, 5235 (1967).

Mechanism and Substituent Effects.—Our results are consistent with a mechanism for reaction 1 which involves nucleophilic addition of perhydroxide ion to the activated double bond of the α,β-unsaturated ketone as the rate-determining step. This is essentially the mechanism outlined by earlier investigators,[2,3] and is very similar to the Michael addition of various other nucleophiles to activated double bonds, including the retrograde aldol reaction (3). A close inspection of the rate constants given in Tables II and III, however, reveals some apparent anomalies which call for a detailed discussion of the rates and mechanisms of reactions 1–4.

The logarithms of the three rate constants (series **a**–**c**) for reaction 1 correlate roughly with the Hammett σ values[8] of the *para* substituents, with a slope (ρ value) of *ca.* +1.2. This value suggests that considerable negative charge is developed in the neighborhood of the double bond on passing from reagents to transition-state species, and is thus consistent with the suggested mechanism. Rate constants for reaction 2 are also correlated roughly, with a ρ value of *ca.* +0.6. With reaction 3, however, the straight-line correlation breaks down completely: the order of reactivity is H < *p*-OCH_3 < *p*-Cl instead of *p*-OCH_3 < H < *p*-Cl as required by the Hammett relationship. Since we have suggested that reactions 1 and 3 are similar, yet substituent effects are different, an apparent anomaly exists.

The problem is readily resolved by considering the details of the mechanism. The retrograde aldol reaction (3) is represented in more detail by the following scheme.

$$ArCH{=}CHCOCH_3 + HO^- \underset{k_B}{\overset{k_A}{\rightleftharpoons}} \left[ArCH(OH)CH(-)COCH_3 \rightleftharpoons ArCH(O^-)CH_2COCH_3 \right] \xrightarrow{k_C} ArCH(=O) + {}^-CH_2COCH_3 \qquad (3)$$

By applying the steady-state approximation (*i.e.*, $k_A \ll k_B + k_C$) to the enolate intermediate, it can easily be shown that the observed second-order rate constant, k_3, is a composite given by

$$k_3 = \frac{k_A k_C}{k_B + k_C}$$

From this relationship it can then be shown that the observed ρ value is also a composite given by

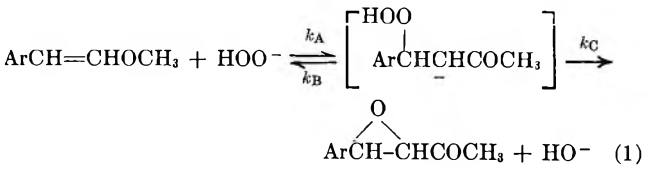
$$\rho_3 = \rho_A + \rho_C - \delta_R \log (k_B + k_C)$$

where δ_R is the substituent stabilization operator.[8] A complex ρ of this type is not in general a constant; instead, in the case in which $k_B \geq k_C$, a U-shaped Hammett plot should result. Since we have only three data points, a detailed consideration of substituent effects on the rate of reaction 3 would be inappropriate, but

(8) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963.

the points can clearly be placed on a U-shaped ρ–σ plot.[9]

The epoxidation reaction (1) is similarly represented by the following mechanism.



(1)

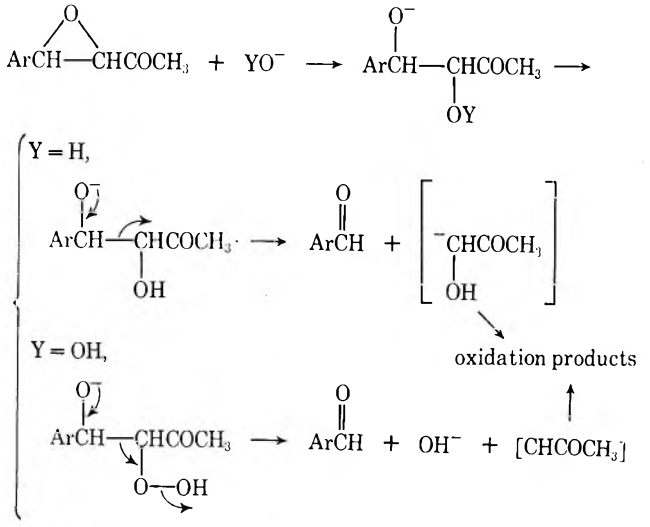
The observed k_1 and ρ values are again composites, as in reaction 3. The results become explicable if we postulate that $k_B \ll k_C$, instead of $k_B \geq k_C$ as suggested for reaction 3. It is reasonable that k_C/k_B for reaction 1 should be larger than for reaction 3. Other workers[10] have suggested that the elimination of hydroxide from β-hydroxy ketone carbanions (analogous to the k_B step in reaction 3) is rapid relative to retro aldol cleavage (the k_C step in reaction 3). The intramolecular displacement of HO^- (k_C) in reaction 1 should be easier than the carbon–carbon bond cleavage in reaction 3, and k_C in reaction 1 does not depend on the position of an intermediate prototropic equilibrium as it does in reaction 3. If $k_B \ll k_C$, the expression for ρ_1 can be simplified as follows.

$$\rho_1 = \rho_A + \rho_C - \delta_R \log (k_B + k_C)$$

$$\cong \rho_A + \rho_C - \delta_R \log k_C = \rho_A$$

The Hammett plot for reaction 1 should then be approximately rectilinear, as observed.

Another apparent anomaly appears when we compare the relative reactivities of hydroxide and perhydroxide, respectively, with substrates **1a** and **2a**. The relative reactivity with **1a** is $k_1/k_3 = 1400$, while with **2a** it is $k_2/k_4 = 16$. The relative reactivities of HOO^- and HO^- can vary widely with substrate,[11] but a



(9) A referee has suggested as an alternative explanation that the *p*-methoxy compound is oxidized more rapidly owing to a competing Dakin or Baeyer–Villiger reaction. This possibility is ruled out by product analysis. No *p*-methoxyphenol, *p*-methoxyphenylacetic acid, or *p*-methoxycinnamic acid was found, though as little as a few per cent of any one could easily have been detected (nmr).

(10) M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 71 (1963); B. W. Rockett, T. M. Harris, and C. R. Hauser, *ibid.*, **85**, 3491 (1963); J. Warkentin and L. K. M. Lam, *Can. J. Chem.*, **42**, 1676 (1964).

TABLE IV

PRODUCTS FROM THE REACTION OF α,β-UNSATURATED CARBONYL COMPOUNDS WITH ALKALINE HYDROGEN PEROXIDE

Compd	Product[a]	Yield, %[b]
2-Cyclohexen-1-one	Glutaric acid	72
1-Acetyl-1-cyclohexene	Adipic acid	67
Isophorone	3,3-Dimethyl-5-keto-hexanoic acid	84
Pulegone	3-Methyladipic acid	60
Verbenone	Pinononic acid[c]	85
Citral	2-Methyl-2-hepten-6-one	77[d]
5,5-Dimethyl-1,3-cyclohexanedione	3,3-Dimethylglutaric acid	80

[a] Reaction conditions and product identification are given in the Experimental Section. [b] No attempt to optimize yield was made in most cases. [c] Mixture of *cis* and *trans* isomers, *ca.* 1:1. [d] By gas chromatography.

factor of 100 seems excessive for reactions postulated to be similar. We suggest that $k_2/k_4 = 16$ for the epoxide cleavage is of the order of magnitude of a "normal" reactivity ratio,[12] and that the mechanisms of reactions 2 and 4 are in fact very similar.

The high k_1/k_3 ratio can be accounted for by the suggested complex nature of the measured rate constants. As postulated for reaction 1, $k_B \ll k_C$, and

$$k_1 = \frac{k_A k_C}{k_B + k_C} \cong \frac{k_A k_C}{k_C} = k_A$$

so the observed rate is a good approximation for the actual rate of nucleophilic attack by HOO^- on the unsaturated ketone. For reaction 3, however, k_B is approximately equal to or greater than k_C, and the observed rate constant $k_3 = k_A k_C/(k_B + k_C)$, which can be much smaller than k_A itself. We thus attribute the large k_1/k_3 ratio to the contribution of the factor $k_C/(k_B + k_C)$ to k_3.

Scope and Synthetic Utility.—The epoxidation and cleavage sequence of reactions 1 and 2 seems to be a general one and to have synthetic utility. A variety of α,β-unsaturated aldehydes and ketones (Table IV) were converted in good yield into the products expected on the basis of this sequence. 1,3 diketones react similarly, presumably *via* epoxidation of the enol.

The alkaline hydrogen peroxide epoxidation–cleavage reaction has advantages over the use of base alone (reaction 3), which sometimes yields the same products. For example, the cleavage of citral to 2-methyl-2-hepten-6-one in 1 *M* aqueous methanolic sodium hydroxide at 25° is *ca.* 50 times faster when the solution is made 1 *M* in hydrogen peroxide. In addition, the reaction mixture assumes a deep yellow color when base alone is used, while no noticeable colored by-products are formed when peroxide is present.

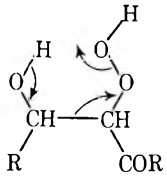
The alkaline peroxide treatment often yields products different from those obtained on cleavage with base alone. Cleavage by peroxide of the α-dicarbonyl compounds obtained on initial oxidative epoxide cleavage is an obvious example. Treatment of α,β-epoxy ketones with base often leads to products of benzylic

(11) (a) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962). (b) R. G. Pearson and D. N. Edgington, *ibid.*, **84**, 4607 (1962).

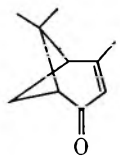
(12) For example, in the displacement of bromide from benzyl bromide, $k(HOO^-)/k(HO^-) = 34$ (ref 11); from α-bromo-*p*-toluic acid, $k(HOO^-)/k(HO^-) = 11$ (J. E. McIsaac, Jr., H. A. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968).

acid type rearrangement[13] or Favorskii rearrangement,[14] not cleavage as in reaction 2.

The production of pinononic acid from verbenone in high yield probably rules out a cyclic mechanism such as **4** for the cleavage reaction (2). The rigid geometry



4



5

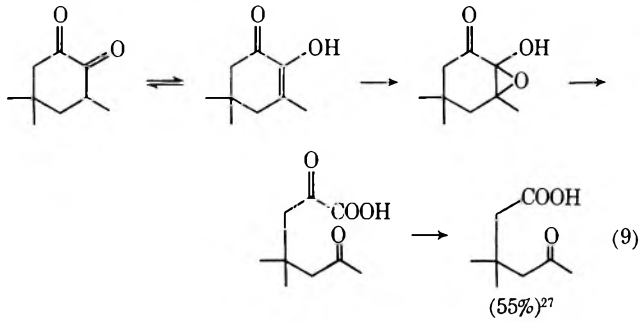
of the intermediate *trans*-β-hydroxyhydroperoxide derived from verbenone (**5**) precludes a transition state of this type.

Discussion

Two groups of workers[15] have observed specific examples of epoxidation–cleavage reaction sequences, one in a keto steroid and one in a cyano olefin. The generality of the reaction, however, has apparently not been appreciated. Two other reactions in which epoxides are cleaved by hydrogen peroxide are reported in the literature. Thus α-methylstyrene oxide is slowly converted into acetophenone on treatment with alkaline hydrogen peroxide,[16] and 3,4-epoxy-4-methyl-2-pentanone reportedly reacts with hydrogen peroxide without solvent or added base to give acetone, acetic acid, and formic acid.[17] The cleavage with neutral peroxide is surprising. α-Methylstyrene oxide is not cleaved in the absence of added base,[16] and we also find that little or no cleavage product results from epoxides and hydrogen peroxide alone. An acid-catalyzed analog of reaction 2 has been proposed recently.[18]

In larger context, the mechanism of reaction 2 is typical of a class of heterolytic fragmentation mechanisms reviewed recently.[19] Similar peroxide fragmentations, presumably proceeding by the same mechanism, have been reported in the cases of β-hydroxy peroxides,[20,21] α-peroxycarboxylic acids,[21,22] the ozonide of an α,β-unsaturated carboxylic acid,[23] and β-amino peroxides.[24] The instability of β-halohydroperoxides to base has recently been documented also.[25,26] Both elimination and carbon–carbon bond cleavage can occur with these compounds.[26] We suggest that the latter reaction may proceed *via* hydrolysis to the β-hydroxy compound followed by cleavage as in reaction 2.[26b]

Certain α diketones[27] and β-dicarbonyl compounds[28] reportedly react with alkaline hydrogen peroxide to give cleavage products very much like those obtained from α,β-unsaturated ketones in this work. We suggest that these reactions may proceed *via* epoxidation of the enol followed by oxidative cleavage of the epoxide by hydroperoxide ion (*e.g.*, reaction 9). A similar mechanism could also account for the recently reported oxidative cleavage of phenyl-2-propanone.[29]



(55%)[27] (9)

Experimental Section[30]

Materials.—Reagents were obtained from commercial sources, with the exceptions of 4-*p*-chlorophenyl-3-buten-2-one (**1b**), bp 105–108° (0.35 mm), mp 58.5–59.5° (lit.[31] mp 59–59.5°), which was prepared by Claisen–Schmidt condensation of *p*-chlorobenzaldehyde with acetone; 4-phenyl-3-epoxy-2-butanone (**2a**), bp 88–90° (0.08 mm), mp 44–45°, mmp 10–15° with 4-phenyl-3-buten-2-one (**1a**) (lit.[1] mp 52–53°), prepared by oxidation of **1a** with alkaline methanolic hydrogen peroxide at 0–5°; and verbenone, obtained from Dr. W. F. Erman of these laboratories. Commercial samples of **1a** and 4-*p*-methoxyphenyl-3-buten-2-one (**1c**) were recrystallized from hexane, mp 41–42° (lit.[32] mp 40–42°) and 74–75.5° (lit.[32] mp 72–74°), respectively. Compounds **1a** and **2a** were the *trans* isomers, as indicated by their nmr spectra: **1a**, vinyl protons at τ 2.51 and 3.33 (d, J = 16 Hz); **2a**, oxirane protons at τ 6.05 and 6.58 (d, J = 2 Hz). Hydrogen peroxide (30%, Matheson Coleman and Bell) and sodium hydroxide (Baker Analyzed Reagent) were used without further purification.

Kinetic Methods.—In a typical kinetic run, the required amounts of water, aqueous α,β-unsaturated ketone or α,β-epoxy

(13) C. J. Collins and O. K. Neville, *J. Amer. Chem. Soc.*, **73**, 2471 (1951), and references cited therein.

(14) H. O. House and W. F. Gilmore, *ibid.*, **83**, 3972 (1961); G. W. K. Cavill and C. D. Hall, *Tetrahedron*, **23**, 1119 (1967); W. Reusch and P. Mattison, *ibid.*, **23**, 1953 (1967).

(15) W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, **85**, 1669 (1963); L. J. Bollyky, R. H. Whitman, R. A. Clarke, and M. M. Rauhut, *J. Org. Chem.*, **32**, 1663 (1967).

(16) J. Hoffman, *J. Amer. Chem. Soc.*, **79**, 503 (1957).

(17) V. S. Etlis and L. M. Degtyareva, *Zh. Org. Khim.*, **3**, 1430 (1967).

(18) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

(19) C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1 (1967). A general formulation of the peroxide fragmentation reaction is also given by A. Rieche, *ibid.*, **78**, 496 (1966).

(20) B. Witkop, *J. Amer. Chem. Soc.*, **72**, 1428 (1950); M. Schulz and H. Steinmaus, *Angew. Chem.*, **75**, 918 (1963); H. H. Wasserman and M. B. Floyd, *Tetrahedron Lett.*, 2009 (1963); M. Schulz and H.-F. Boeden, *ibid.*, 2843 (1966); M. Schulz and L. Somogyi, *Angew. Chem.*, **79**, 145 (1967); M. Schulz, H.-F. Boeden, and P. Berlin, *Jutus Liebigs Ann. Chem.*, **703**, 190 (1967); S. Marmor and M. M. Thomas, *J. Org. Chem.*, **32**, 252 (1967).

(21) M. M. Rauhut, D. Sheehan, R. A. Clarke, B. G. Roberts, and A. M. Semsel, *ibid.*, **30**, 3587 (1965).

(22) M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **85**, 1655 (1963); W. H. Richardson and R. S. Smith, *ibid.*, **89**, 2230 (1967); **91**, 3610 (1969).

(23) D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956).

(24) L. A. Cohen and B. Witkop, *J. Amer. Chem. Soc.*, **77**, 6595 (1955), and references cited therein; E. Schmitz, A. Rieche, and A. Stark, *Chem. Ber.*, **101**, 1035 (1968).

(25) W. H. Richardson, J. W. Peters, and W. P. Konopka, *Tetrahedron Lett.*, 5531 (1966); M. Schulz, A. Rieche, and K. Kirschke, *Chem. Ber.*, **100**, 370 (1967).

(26) (a) K. R. Kopecky, J. H. van de Sande, and C. Mumford, *Can. J. Chem.*, **46**, 25 (1968). (b) Unpublished results by K. R. Kopecky and coworkers indicate that this mechanism does not operate in at least one case. Instead, cleavage of 3-bromo-2-methyl-2-butyl hydroperoxide proceeds *via* an isolable 1,2-dioxetane intermediate. We wish to thank Professor Kopecky for this information.

(27) G. B. Payne, *J. Org. Chem.*, **24**, 719 (1959).

(28) L. P. Vinogradova and S. I. Zav'yalov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2050 (1961); L. P. Vinogradova, B. A. Rudenko, and S. I. Zav'yalov, *ibid.*, 1436 (1962).

(29) D. D. Jones and D. C. Johnson, *J. Org. Chem.*, **32**, 1402 (1967).

(30) Melting points are corrected. Infrared and ultraviolet spectra were recorded using Perkin-Elmer Models 137 and 202 spectrophotometers, respectively. A Varian HA-100 instrument was used to determine the nuclear magnetic resonance spectra. Chemical shifts in $CDCl_3$ are reported in parts per million downfield from internal tetramethylsilane. Gas chromatography was carried out with a Varian-Aerograph Model 202-IC instrument using a 5 ft × 1/4 in. 20% SE-30 on Chromosorb W column.

(31) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, Jr., J. D. Smith, and J. W. Wilson, III, *J. Org. Chem.*, **14**, 982 (1949).

(32) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p 69.

ketone solution, and sodium hydroxide solution were pipeted into a volumetric flask immersed in a constant-temperature bath at 25.0 ± 0.05°. The mixture was shaken and allowed to equilibrate for a few minutes, and then hydrogen peroxide solution was added to initiate the reaction. Samples were withdrawn periodically and analyzed as described in the next section.

Rate constants were first estimated graphically from second-order or pseudo-first-order kinetic plots, then refined by use of the CSMP digital analog simulation technique discussed in the text.

Analytical Methods.—Hydrogen peroxide solutions were analyzed titrimetrically with potassium permanganate in acidic solution. In kinetic runs in which peroxide concentration was followed, samples were withdrawn periodically and the titanium(IV)–hydrogen peroxide complex was determined spectrophotometrically at 405 nm.[33] Base concentration was followed in some runs by titration with standard 0.05 *N* hydrochloric acid.

The organic compounds were determined spectrophotometrically. The ultraviolet spectra of aqueous solutions of the benzalacetones, epoxides, and aldehydes were determined, and extinction coefficients were calculated from the optical densities of at least five different samples of each compound. Adherence to Beer's Law was excellent in every case. The extinction coefficients are given in Table V. The spectra of all three classes of

TABLE V

EXTINCTION COEFFICIENTS OF COMPOUNDS 1–3

Compd	Wavelength, nm						
	225	250	260	285	290	300	320
1a	8750	2700	...	...	19000	...	...
1b	...	...	5620	...	...	23140	...
1c	...	...	...	8410	...	...	20370
2a	10600	770	...	...	170	...	...
3a	2050	12400	...	...	1270	...	...
3b	...	...	15710	...	...	575	...
3c	...	...	...	15520	...	...	820

compounds (1a–3a) were followed in the a series (X = H), and the concentrations of 1 and 3 were followed in the b and c series. Approximate correction for overlapping of the absorption bands was made using a computer program which solves the matrix equation

$$\begin{Bmatrix} A(\lambda_1) \\ A(\lambda_2) \\ A(\lambda_3) \end{Bmatrix} = \begin{Bmatrix} \epsilon(\lambda_1, 1) & \epsilon(\lambda_1, 2) & \epsilon(\lambda_1, 3) \\ \epsilon(\lambda_2, 1) & \epsilon(\lambda_2, 2) & \epsilon(\lambda_2, 3) \\ \epsilon(\lambda_3, 1) & \epsilon(\lambda_3, 2) & \epsilon(\lambda_3, 3) \end{Bmatrix} \begin{Bmatrix} c(1) \\ c(2) \\ c(3) \end{Bmatrix}$$

where A is the absorbance, ϵ is the extinction coefficient, c is the concentration, λ's designate three wavelengths, and boldface numerals stand for the three compounds. The wavelengths used with each series of compounds can be inferred from Table V.

Preparative Oxidation Procedure.—To a solution of 0.01 mol of the α,β-unsaturated carbonyl compound in 50 ml of methanol, 12 ml of 30% aqueous hydrogen peroxide and then 30 ml of 1 *N* aqueous sodium hydroxide solution were added with cooling. The mixture was then stirred overnight at 40–50° (1 hr at 40° for the reaction with citral). The resulting solution was evaporated to about half the original volume on a rotary evaporator and then washed with ether. The aqueous solution was made acidic with sulfuric acid, saturated with sodium sulfate, and extracted thoroughly with ether. The extract was treated with $FeSO_4$ or Na_2SO_3 to destroy peroxides, dried ($MgSO_4$), and evaporated. The residue, which was essentially pure product, was recrystallized, distilled, or converted into a suitable derivative as outlined below.

Identification of Products.—The above treatment converted **2-cyclohexen-1-one** into **glutaric acid**, mp and mmp 94–95°.

1-Acetyl-1-cyclohexene yielded **adipic acid**, mp and mmp 150–151°.

Isophorone was converted into **3,3-dimethyl-5-ketohexanoic acid**, a slightly yellowish oil (lit.[34] mp 28°). This product showed a positive iodoform test and gave a crystalline semicarbazone, mp 167–169° (lit.[34] mp 170–172°).

Oxidation of **pulegone** gave **3-methyladipic acid**. A sublimed sample had a melting point of 86–87.5° (lit. mp 85–89°,[35] 92–94°[36]) and an ir spectrum identical with that reported.[36]

Verbenone was oxidized to a mixture (*ca.* 1:1) of *cis*- and ***trans*-pinononic acid** (3-acetyl-2,2-dimethylcyclobutanecarboxylic acid). The nmr spectrum of the noncrystalline product mixture clearly indicated an essentially pure mixture of the two isomers. The most important features were two sets of three methyl singlets: τ 7.9, 8.5, and 9.0 (*cis* acid) and τ 7.8, 8.6, and 8.8 (*trans* acid). The spectrum of the authentic *cis* acid[37] has singlets at τ 7.9, 8.5, and 9.0. The mass spectrum of the methyl ester mixture obtained by treating the acids with diazomethane showed a parent peak at *m/e* 184 (calcd mol wt 184). Important fragment ions were *m/e* 139, 152, 141, 124, and 114.

Citral (*ca.* 40:60 mixture of geranial and neral) yielded **2-methyl-2-hepten-6-one**, a colorless liquid with a characteristic odor. The ir and nmr spectra and the gas chromatographic retention time were identical with those of authentic material.

5,5-Dimethyl-1,3-cyclohexanedione was oxidized to **3,3-dimethylglutaric acid**, mp and mmp 96–100°.

Registry No.—Hydrogen peroxide, 7722-84-1; **1a**, 122-57-6; **1b**, 3160-40-5; **1c**, 943-88-4; **2a**, 6249-79-2; **3a**, 100-52-7; **3b**, 104-88-1; **3c**, 123-11-5.

Acknowledgment.—The author wishes to acknowledge the capable assistance of Mr. H. H. Lorance in the experimental part of this work.

(33) G. M. Eisenberg, *Ind. Eng. Chem., Anal. Ed.*, **15**, 327 (1943).

(34) T. Henshall, W. E. Silbermann, and J. G. Webster, *J. Amer. Chem. Soc.*, **77**, 6656 (1955).

(35) E. J. Eisenbraun and S. M. McElvain, *ibid.*, **77**, 3383 (1955).

(36) R. Stevens, *J. Chem. Soc.*, 1118 (1960).

(37) Obtained from Dr. T. W. Gibson of these laboratories.

Metalation Reactions. V. The Metalation of Octadecadienyl Alcohols and Methyl Ethers

J. KLEIN, S. GLILY, AND D. KOST

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

Received May 28, 1969

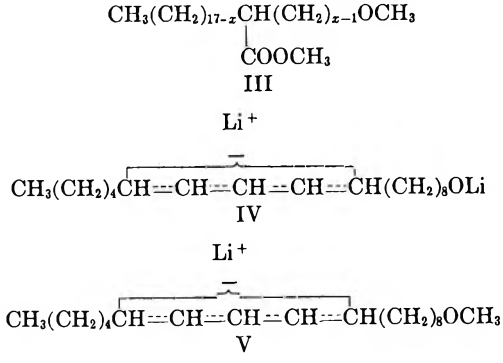
Linoleyl alcohol and methyl ether are metalated by butyllithium, the first compound more easily than the second. Carbonation of the metalated product gives a mixture of carboxylic acids, and the position of carbonation is influenced by the methyl ether function and even more so by the lithium alkoxide group. An intramolecular isomerization of the metalated product occurs. Linoleyl alcohol and methyl ether are isomerized at room temperature with dimsylsodium in DMSO to conjugated dienes. These dienes are not metalated by butyllithium in ether, but in hexane they undergo in presence of TMEDA an addition of butyllithium to one of the double bonds. This addition depends on the stereochemistry of the double bond.

The metalation of olefins is very slow relative to that of aromatic compounds.[1-3] Alkylsodium compounds and prolonged reaction periods are usually employed to carry out these reactions. We found some years ago[4] that linoleyl alcohol (I) and linoleyl methyl ether (II) undergo metalation with amylsodium and butyllithium. We report now the details of these reactions. Metalation of other aliphatic 1,4-dienes with butyllithium were reported recently.[5]

Linoleyl alcohol (I) was metalated in hexane solution with amylsodium and treated with Dry Ice to give a mixture of carboxylic acids. A similar reaction could be obtained in ethyl ether using butyllithium as metalating agent. The latter reaction was studied in detail, because of the commercial availability and safer handling of the lithium reagent. The carboxylic acids obtained on carbonation of the metalation product were separated from the neutral compounds, then esterified, and etherified with diazomethane.[6]

The metalation was relatively fast and a high yield of products was obtained after 6 hr in the studied conditions (Table I). The lower yields after longer reaction periods were probably due to the partial decomposition of the anion. Diesters were obtained in some cases on metalation and carbonation of I. Their formation is probably due to a metalation[7] of the initial product of carbonation by excess butyllithium present in solution and a repeated carbonation. This explanation is supported by the structure of the diesters which were found to be disubstituted malonates.

The obtained unsaturated esters showed a strong absorption at 235 mμ with an extinction coefficient of *ca.* 16,000 and no bands at higher wavelengths. The conjugation revealed by these spectra could be attributed either to two double bonds in 1,3 positions or to one double bond α,β to the ester function. However, the second possibility was excluded by the presence of a strong band at 1740 cm^{-1} in the infrared. It could therefore be concluded that the carbanion IV, formed during the metalation, is attached by carbon dioxide preferentially at the extremities and not at the central position of the pentadienylic system, giving in this manner two conjugated double bonds. This mode of attack is different from the course of protonation of cyclohexadienyl systems.[8-10] The absence or low extent of conjugation with the ester group proved also that no isomerization occurred during the carbonation and work-up procedures. The position of the carboxyl group could therefore be assumed to determine the location of the double bonds in the products. The mixture of isomers formed in these reactions gave rise to inordinate analytic difficulties. Direct separation of the isomers was impossible even by glpc. Various methods of degradative oxidation, *e.g.*, by ozonolysis or by permanganate–periodate treatment did give some of the expected products in low yields or not at all. The following analytical procedure was therefore adopted. The ester–ethers obtained were distilled, hydrogenated, and purified by glpc; the composition of the saturated esters III was analyzed by mass spectrometer techniques, using the ratio of the fragments $[CH_3(CH_2)_{18-x}$-



$COOCH_3]^+$ with varying x to evaluate the ratio of the isomeric ethers III having the carboxyl group at the position x. This method was found to give a good picture[11] of the ratio of the studied isomeric esters III. The esters III formed in this reaction could also be separated and identified by tlc, but quantitative evaluation of the relative amount of the isomers formed has proved very difficult by this method. Glpc could not afford the separation of the isomers. The relative amounts of the isomers III with the carboxyls at different positions as determined by mass spectrometer

(1) R. A. Benkeser, D. J. Foster, D. M. Sauve, and J. F. Nobis, *Chem. Rev.*, **57**, 870 (1957).
(2) H. Gilmand and J. W. Morton Jr., *Org. React.*, **8**, 258 (1954).
(3) M. Schlosser, *Angew. Chem. Int. Ed. Engl.*, 287, 362 (1964).
(4) Annual Research Report (1965) to the U. S. Department of Agriculture, Agricultural Research Service.
(5) R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 205 (1967).
(6) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *ibid.*, No. 6, 36 (1959).
(7) A. A. Morton, F. Fallwell, Jr., and L. Palmer, *J. Amer. Chem. Soc.*, **60**, 1426 (1938).
(8) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950).
(9) R. B. Bates, R. H. Carnighan, and C. E. Staples, *J. Amer. Chem. Soc.*, **85**, 3032 (1963).
(10) R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 199 (1967).
(11) J. Klein and E. Gurfinkel, *J. Org. Chem.*, **34**, 3952 (1969).

TABLE I

COMPOSITION[a] OF THE PRODUCTS OF METALATION–CARBONATION OF LINOLEYL ALCOHOL (I) AND LINOLEYL METHYL ETHER (II)

Run	Starting material (mmol)	BuLi, mmol	Method	Solvent, ml	TMEDA, mmol	Duratn of metalatn, hr	Yield of III, %	Relative amounts of III, with x = 6	7	8	9	10	11	12	13	14	15	16
1	I (10)	50	B	40		24	60[d]			0.3+	1.0+	0.5+	0.8+	0.7+	2.9+	0.7		
2	I (20)	70	C	60		20	60			0.1	1.0	0.2	1.3	0.2	3.3	0.3	0.1	
										0.1	1.0+	0.2	1.3+	0.3	3.3+	0.3	0.1	
3[b,c]	I (10)	40	B	35		24	40			0.3	1.0+	0.5	0.9+	0.7	2.0+	0.6	0.2	
										0.3	1.0	0.5	0.7	0.6	2.0	0.6	0.2	
4	I (10)	40	D	30	38	96	60[e]	0.5+	0.5+	0.7+	1.0+	1.4+	1.7+	1.5+	1.7+	1.4	1.0	0.8
								0.5	0.6	0.7	1.0	1.7	1.9	1.6	1.9	1.4	1.1	0.8
5	I (10)	45	B	25		6.5	75			0.1	1.0+	0.2	0.6+	0.2	2.1+	0.2	0.1	
6	I (10)	45	B	25		1.5	12				1.0+	0.1	0.5+	0.1	2.0+	0.1	0.1	
7	II (25)	60	A	120		24	28			0.2+	1.0+	0.4+	1.0+	0.4+	1.5+	0.4	0.1	
8	II (10)	40	D	30	29	72	46	0.6	0.6	0.8	1.0	1.5	1.6	1.6	1.7	1.4	0.9	
								0.4+	0.5+	0.8+	1.0+	1.5+	1.6+	1.5+	1.6+	1.5	0.8	
9	II (10)	24	B	20		48	44	0.1+	0.1+	0.4+	1.0+	0.6+	0.7+	0.6+	1.5+	0.6	0.1	
10	II (10)	45	B	45		120	60	0.3+	0.5+	0.7+	1.0+	1.2+	1.3+	1.2+	1.6+	1.2	0.7	
11	II (10.7)	50	C	45		108	54	0.5+	0.6+	0.9+	1.0+	1.5+	1.5+	1.3+	1.5+	1.5	1.0	
12	II (10)	45	D	29	32	48	68	0.3+	0.5+	0.8+	1.0+	1.6+	1.8+	1.7+	1.9+	1.6	1.1	0.5
13	II (10)	60	B	35		216	70[f]	0.3+	0.4+	0.9+	1.0+	1.1+	1.3+	1.1+	1.7+	1.0	0.7	0.4
14	II (10)	45	D	28	32	200	75	0.3+	0.4+	0.5+	1.0+	1.1+	1.3+	1.1+	1.8+	1.0	0.8	0.5
15	II (10)	45	D	28	32	5	65[g]			0.3+	1.0+	0.4+	0.6+	0.4+	1.7+	0.4	0.1	0.1
16	II (10)	45	D	28	32	1	65			0.1+	1.0+	0.2	0.4	0.2	2.0+	0.2	0.1	0.1

[a] A + signifies detection of the isomer by tlc. [b] Determined on the product obtained from the precipitate formed during the metalation. [c] Determined on the product obtained from the supernatant on the precipitate formed during the metalation. [d] Contains *ca.* 10% diesters. [e] Contains *ca.* 3% diesters. [f] Contains *ca.* 15% diesters. [g] Contains, 10% diesters.

analysis are recorded in Table I. The isomers detectable by tlc are also marked for comparison.

The distribution of the carboxyl group at the different positions of the chain of linoleyl alcohol is of interest. The high reactivity of I relative to other olefins in the metalation reaction must be connected with the methylene group located between the two double bonds. The relative rates[12] of proton abstraction from the methylene of 1,4-pentadiene and an allylic methylene is 10^6. It is expected, therefore, that a proton from this group was abstracted to give a stabilized pentadienyl anion IV. Attack of this anion was expected to occur at the positions 9, 11, and 13. This was observed after short reaction times. However, these three positions did not react with carbon dioxide with the same rate, in spite of all of these carbons being secondary. There was a strong discrimination in favor of position 13, where the carbonation is three times faster than at each of the two other positions. This effect has to be attributed to the long range interaction with the alkoxide group, present in the molecule. The sum of isomers formed by attack of IV at the extremities of the pentadienyl system (positions 9 and 13) is much larger (84%) than the amount formed by attack at the central position 11 (16%) and is in agreement with the uv data.

Longer metalation periods resulted in the formation of additional isomeric esters III and in a more even distribution of the isomers. This was clearly a result of an isomerization of the anion IV, proceeding either directly or by a protonation–metalation route (see below). Isomerizations were faster in hexane–TMEDA than in ether.

Metalations of linoleyl methyl ether (II) and subsequent carbonation were performed in a manner similar to that of I (Table I). These reactions were slower than the corresponding reaction of I in ether, and were an additional confirmation of the catalytic effect of alkoxides on the rates of metalation.[13-15] The reactions in hexane catalyzed by tetramethylethylenediamine[16] (TMEDA) were fast, and high yields of products were obtained after 1 hr of metalation. Long reaction periods in ether or hexane did not result in the destruction of the anion IV and high yields of esters were obtained. It seems also that the isomerization of the anion V was faster than that of IV. However, these isomerizations apparently stopped after reaching position 6 at one side and 15 at the other. Although very short time metalations of II in ether were not carried out, because of the slowness of this reaction, it could nevertheless be observed that the discrimination observed in the case of I between the positions 9, 11, and 13 during carbonation persisted here also, but was lower than in the case of the alcohol I. The nature of this discriminating effect is not clear. An electron-withdrawing group could polarize by an inductive effect the negative charge of the pentadienylic anion, concentrate it at the position nearer to this group, and favor carbonation at this point. However, a stronger inductive effect would be expected for the methoxy than for the alkoxy group. A field effect of the negative charge of the alkoxide should have an opposite effect to that of the methoxy group. The most probable explanation for the position discrimination is that the oxygen of the functional group helps after coiling the chain to solvate the lithium cation in the ion pair with the carbanion and keeps it in such a position that most of the charge of the anion is located at position 13.

(12) A. Schriesheim, C. A. Rowe, Jr., and L. Neslund, *J. Amer. Chem. Soc.*, **85**, 2111 (1963).

(13) A. A. Morton and A. E. Brachman, *ibid.*, **73**, 4363 (1951); A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955).

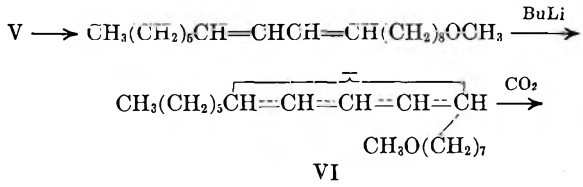
(14) M. Schlosser, *J. Organometal. Chem.*, **8**, 9 (1967).

(15) R. A. Benkeser, T. F. Crimmins, and W. Tong, *J. Amer. Chem. Soc.*, **90**, 4366 (1968).

(16) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).

The isomerization of the pentadienylic anion could proceed by a proton transfer from the solvent to the anions IV or V with the formation of isomeric conjugated dienes and subsequent renewed metalation of these dienes, *e.g.*, Scheme I. The new anion VI formed

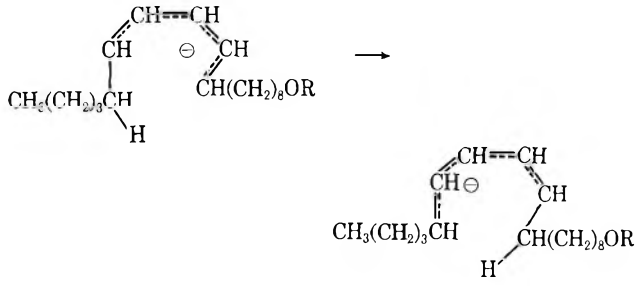
SCHEME I



carboxyls at 8, 10, or 12

could give on carbonation three isomeric acids. The anion VI in its turn could be isomerized in the same way. However, the conjugated dienes derived from linoleyl alcohol (I) and linoleyl methyl ether (II) did not undergo metalation with butyllithium in ether solution and an addition to the diene system occurred in hexane in the presence of TMEDA with formation of butyl-substituted allylic anions (see below). These results exclude the two-step mechanism of Scheme I. We conclude therefore that the isomerizations are intramolecular and a proton is transferred from a position α to the pentadienyl system to a carbon of this system. This is an unencountered sigmatropic rearrangement, to which the rules of Woodward and Hoffmann[17] could be applied. The most probable course taken by the isomerization is a 1,6-sigmatropic migration since in this case a new pentadienylic system is formed from the original one (Scheme II). According to the rules,[17,18]

SCHEME II



an antarafacial migration of hydrogen is predicted for this system. Such a migration will be accompanied by some strain in the transition state but can be performed even on molecular models.

The intramolecular isomerization is favored for carbanions that are not coordinated to the lithium cation, as in the TMEDA catalyzed reaction. It is of interest that the rate of this isomerization drops very strongly when the pentadienylic system reaches the fifth carbon from one of the extremities of the chain. There is a possibility that in this position the anionic sites are exposed to the solution and therefore less apt to isomerize. This explanation infers that the pentadienylic system in locations nearer the center of the molecule is protected from the solvent during the isomerization by coiling the chain around it.

This intramolecular isomerization by proton transfer resulting in a migration of a pentadienylic anion along an aliphatic chain could be observed only in a long-chain molecule. The fact that this isomerization stopped at the positions 6 and 15 at one and the other end of the molecule, respectively, requires a minimum number of 14 carbons in the chain to make this process observable. The long molecules should therefore not be regarded as an inert extension of short-chain compounds, but the aliphatic chain itself has the properties of a functional group.

Isomerization of linoleyl methyl ether (II) was performed at room temperature with solutions of dimsylsodium in DMSO.[19] The reaction was fast and terminated after a few minutes resulting in the formation of conjugated products, as shown by their uv absorption at 233 mμ. Linoleyl alcohol is isomerized more slowly. A mixture of 9,11- and 10,12-dienes was obtained from I and II. The two dienes were obtained in similar amounts as evidenced by the ratio of capraldehyde and heptaldehyde obtained on ozonolysis of the mixture of products of the isomerization (Table II).

TABLE II

OZONOLYSIS OF THE ISOMERIZATION PRODUCTS OF LINOLEYL ALCOHOL AND LINOLEYL METHYL ETHER IN DMSO

Starting compound	Duratn of the isomerizn, hr	Ratio of products —of ozonolysis— Capraldehyde/heptaldehyde	VII/VIII	Compositn of the isomerizn product	Ratio of absorbance at 985 and 947 cm^{-1} in the product
II	1	0.9	1.2	XIb + XIIb	1.1
II[a]	40	0.9	1 3	IXb + Xb	4.0
I	40	1		XIa + XIIa[b]	2.0

[a] The product of ozonolysis contains also approximately 10% $CHO(CH_2)_7OCH_3$ and 10% $CHO(CH_2)_{10}OCH_3$. [b] This product contains a considerable amount of IXa and Xa.

The relative amounts of the two ω-methoxyaldehydes VII and VIII formed in this reaction confirmed these

$CH_3O(CH_2)_8CHO$ VII $\qquad$ $CH_3O(CH_2)_9CHO$ VIII

results. The obtained dienes contain *cis* and *trans* double bonds, since two bands of similar intensity were found in the infrared at 985 cm^{-1} and 947 cm^{-1}. Prolonged treatment of I and II with larger amounts of dimsylsodium produced a product rich in the *trans-trans*-dienes IX and X, as revealed by the ratio of intensities of the bands at 985 cm^{-1} and 947 cm^{-1}. Ozonolysis of the *trans-trans* isomers gave a product composed predominantly of capraldehyde and heptaldehyde and only 10% 8-methoxyoctaldehyde and 10% 11-methoxyundecaldehyde, showing that migration of the double bonds occurred to a small extent. This result indicates that metalation at an allylic position is not the exclusive mechanism for the *cis-trans* isomerization of the conjugated dienes, since protonation of the

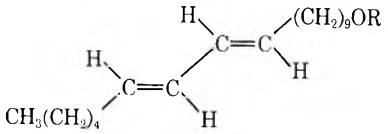
(17) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

(18) R. B. Woodward, Special Publication No. 21, The Chemical Society, London, 1967, p 217; R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

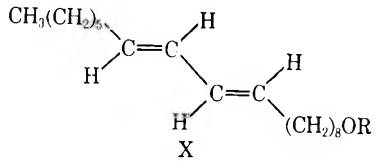
(19) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

pentadienylic anion should produce in this case 33% double-bond migration. We conclude therefore that the *cis–trans* isomerization of the conjugated dienes proceeded differently from that of the 1,4 isomers by addition of dimsylsodium to one double bond with formation of an allylic anion that subsequently eliminated dimsylsodium. Similar additions of dimsylsodium to conjugated olefins were observed by Cram.[20]

The disposition of the substituents around the double bonds in the 9,11- and 10,12-octadecadienols and octadecadienyl methyl ethers was of interest. The product could have been a mixture of *cis–cis*-, *trans–trans*-, and *cis–trans*-dienes or composed of *cis–trans*-dienes only. The selective reactivity of one bond in each diene (see below) led us to assume that it was

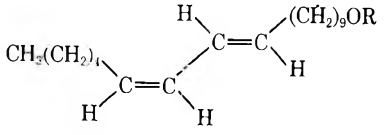


IX

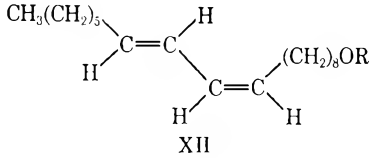


X

a, R = H
b, R = CH_3



XI



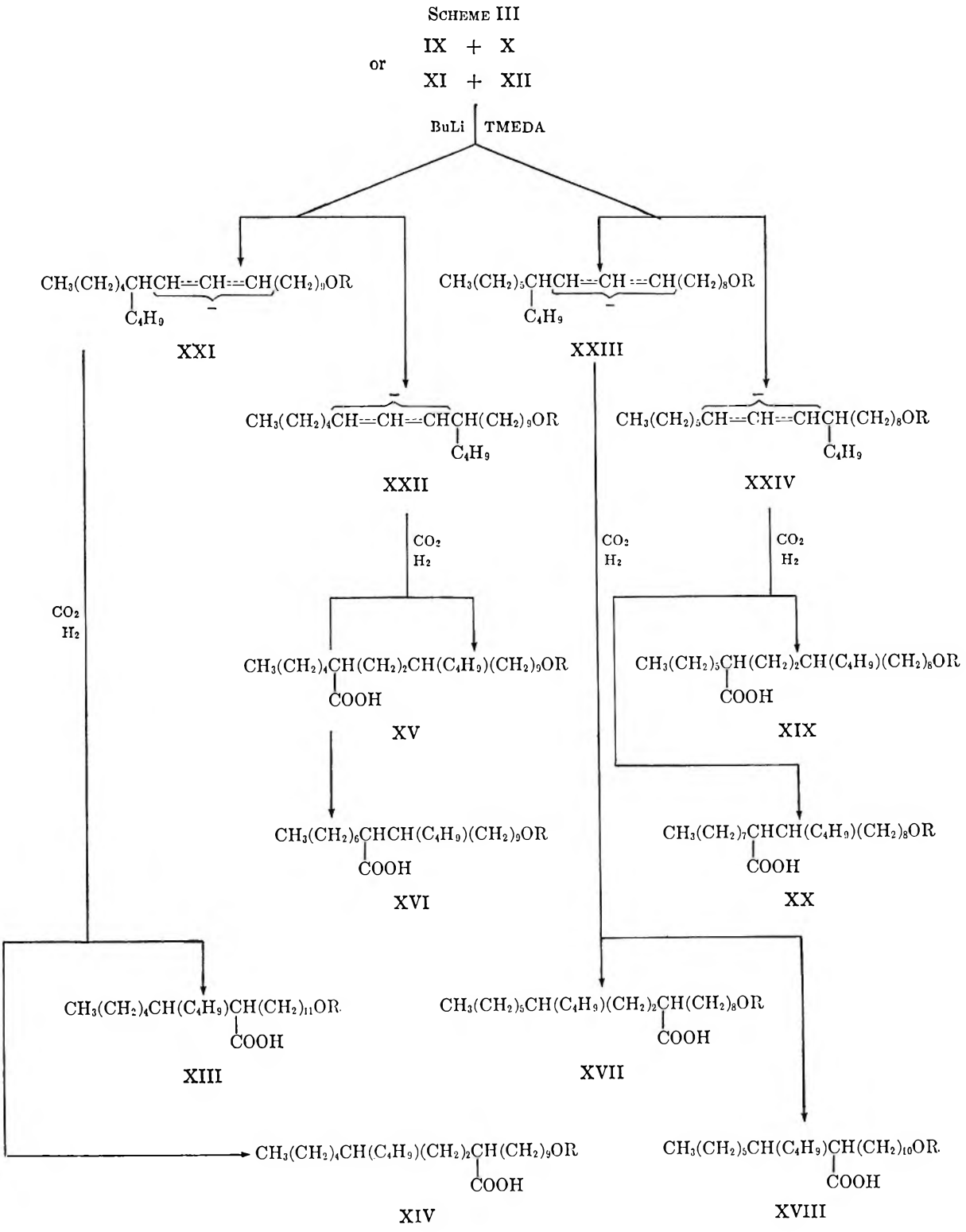
XII

constituted of *cis–trans*-dienes predominantly. The structures XI and XII were tentatively attributed to the alcohols and ethers formed after short-time isomerization reactions on the assumption of a *trans* configuration around the double bond that migrated, whereas the double bond, that did not change its position, was assumed to retain its original *cis* configuration. This was not a very safe conclusion. Allylic anions are known to retain their configuration[21] for some time, and the pentadienylic anion formed during the isomerization is in the essentially protic DMSO (certainly a short-lived species) and is expected to retain its configuration around the nonmigrating bond. However, *cis* olefins are known to be formed kinetically in base-catalyzed migrations of double bonds,[22,23] and it could also be argued that it was the migrating bond that had the *cis* configuration since the kinetic product was isolated after short reaction time. We preferred, nevertheless, the first assignment of XI and XII to the short-time isomerization products, since the explanation (assuming a more stable *cis* than *trans* conformation in the allylic anion[23]) advanced previously for the preferential formation of *cis* products during the protonation of these anions has proved to be inaccurate in the case of pentadienylic,[5] phenylallylic,[20] or pentenynylic[22] anions, where *trans* conformations were found by nmr, or product study and kinetic methods. In order to support this assignment we subjected the isomerization products to a partial epoxidation and subsequent ozonolysis. Analysis of the formed aldehydes showed that the double bond, to which the *cis* configuration was assigned, was attacked to a greater extent than the *trans* one. A higher reactivity of *cis* relative to *trans* olefins was found before in the reaction with disiamylborane,[24] or in the Simmons–Smith reaction.[25,26] Epoxidation,[27] having a mechanism similar to that of the last reaction, should show also a similar discrimination between the *cis* and *trans* bonds.

The compounds obtained either after short (XI + XII) or prolonged (IX + X) isomerization times of I or II did not undergo metalation with butyllithium in ether. Only traces of carboxy derivatives of I and II were obtained, and these were formed probably from small amounts of unisomerized I or II present in the starting material. However, metalation of the same compounds in hexane solution in presence of N-tetramethylethylenediamine (TMEDA) and subsequent carbonation gave a good yield of monocarboxylic acid, that contained a butyl group in the chain (elemental analysis). A small amount (less than 20% of the product) of the carboxylated linoleyl alcohol or methyl ether exempt of an additional butyl group was also obtained. The butyl-substituted acidic product was a mixture of several isomeric compounds. Their methyl esters could be separated analytically by tlc, but isolation of the individual esters for further study was very difficult. Only traces of butyl-substituted acids were obtained on metalation of unisomerized linoleyl alcohol or linoleyl methyl ether in hexane in presence of TMEDA, and these were formed probably from traces of conjugated isomers in the starting material.

The formation of butyl-substituted acids was rationalized by an addition of butyllithium to the conjugated system of the double bonds. If this occurred, eight isomeric acids (XIII, XIV, XV, XVI, XVII, XVIII, XIX, and XX) could be obtained after carbonation and hydrogenation (Scheme III). It was assumed that the butyl group added always to one of the extreme carbons of the conjugated system to give an allylic anion. Since the separation of the isomers was difficult, mass spectrometer techniques were used for the analysis of the composition of this acidic product after hydrogenation (in the form of methyl ethers and esters) and also to evaluate the relative amounts of the isomeric esters. This method was proved itself in the analysis of the isomeric x-methoxycarbonyloctadecyl

(20) D. H. Hunter and D. J. Cram, *J. Amer. Chem. Soc.*, **88**, 5765 (1966).
(21) D. H. Hunter and D. J. Cram, *ibid.*, **86**, 5478 (1964).
(22) J. Klein and S. Brenner, unpublished work.
(23) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *ibid.*, **87**, 3224 (1965).
(24) H. C. Brown and A. W. Moerikofer, *ibid.*, **85**, 2063 (1963).
(25) H. E. Simmons and R. D. Smith, *ibid.*, **80**, 5323 (1958); **81**, 4256 (1959).
(26) E. P. Blanchard and H. E. Simmons, *ibid.*, **86**, 1337 (1964); H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).
(27) B. Rickborn and J. E. H. Chan, *J. Org. Chem.*, **32**, 3576 (1967).



methyl ethers,[11] since the relative abundance of the fragments $[CH_3(CH_2)_{18-z}COOCH_3]^+$ was in a 1:1 correspondence with the relative amounts of the corresponding synthetic esters $CH_3(CH_2)_{17-z}CH(COOCH_3)(CH_2)_{z-1}OCH_3$.

β cleavage[28] of the butyl-substituted esters can give rise to four kinds of fragments, depending on the position of the butyl relative to that of the ether and ester groups. Two of these fragments, $[C_{18-z}H_{36-2z}(C_4H_9)COOCH_3]^+$ and $[C_zH_{2z-1}(C_4H_9)(COOCH_3)OCH_3]^+$, are of low abundance due to additional bond breaking on the branched carbon. The ratio of the intensities of the unbranched fragments $[CH_3O(CH_2)_zCOOCH_3]^+$ and $[CH_3(CH_2)_{18-z}COOCH_3]^+$ was therefore used to determine the relative amounts of the isomeric esters.

The relative abundances of the $[CH_3O(CH_2)_zCOOCH_3]^+$ fragments with m/e of 216, 230, 244, and 258 derived from the esters of XVII, XIV, XVIII, and XIII, respectively, were 24:6:8:2 for the products of metalation of the mixture of the *cis-trans*-dienes XIb and XIIb and 14:9:8:4, respectively, for the product of metalation of the mixture containing predominantly

(28) R. Ryhage and H. Stenhagen in "Mass Spectrometry," F. W. McLafferty, Ed., McGraw-Hill Book Co., New York, N. Y., 1962.

the *trans–trans*-dienes IXb and Xb. Similarly, the relative abundances of the $[CH_3(CH_2)_{18-x}COOCH_3]^+$ fragments with *m/e* of 172, 158, 144, and 130 derived from the esters of XX, XVI, XIX, XV, respectively, was 24:20:100:4, respectively, for the products of metalation of the mixture XIb and XIIb, and 36:50:67:21 for the products of the mixture rich in IXb and Xb.

In the case of the butyl-substituted esters no pure compounds were available to verify the 1:1 correspondence between the relative amounts of these esters and the relative intensities of the mentioned fragments. Such a correspondence was nevertheless assumed and it was supported by the following internal evidence. Each allylic anion formed by addition of butyllithium to the diene gave rise to two carboxylic acids, one with the carboxyl on a carbon vicinal and another with the carboxyl in a position three carbons away from the butyl group. The ratio of these two acids should be similar for all allylic ions, since the environment in the chain is similar. In fact, the ratios of the fragments 28 mass units apart and arising from the same anion are between 1:2 and 1:3 for all anions. Thus, the 3:1 ratio of the intensities of the fragments $[CH_3OCO(CH_2)_xOCH_3]^+$ with *m/e* 216 and 244 formed from the esters of the acids XVII and XVIII, both derived from the anion XXIII formed during the metalation of the *cis–trans*-diene mixture XIb and XIIb, is the same as the ratio of *m/e* 230 and 258 derived from the anion XXI *via* the acids XIV and XIII, although their absolute intensities are different. This supports the use of the concentration–intensity correspondence at least to determine qualitatively the ratio of components in the mixture. The ratio of the two acids from the same anion reflects the greater hindrance to carbonation on the vicinal than on the carbon more remote from the butyl group.

The fivefold difference in the intensities of the fragments derived from the anions XXIV and XXI formed during the metalation of the mixture XIb and XIIb is significant, particularly when it is observed that a similar fivefold difference is observed between the sum of the intensities of the $[CH_3(CH_2)_{18-x}COOCH_3]^+$ fragments (*m/e* 144 and 172) obtained from the esters of XV and XVI derived from the anion XXII during the metalation of XIb and XIIb and that of similar fragments obtained from the esters of XIX and XX (*m/e* 158 and 186) derived from the anion XXIV. This difference is not due to a lack of correspondence between the intensities of the fragments and the amounts of the esters, since a ratio of only 2:1 instead of 5:1 of these fragments is observed during the mass spectral analysis of the same esters formed from the product of metalation of the *trans–trans*-dienes IXb and Xb. It is reasonable to expect that the symmetrical dienes IXb and Xb will be attacked equally well from both extremities of the conjugated system and the comparable intensities of the fragments confirm again the assumption of an approximate 1:1 correspondence between the intensities of the fragments and the amounts of the corresponding esters. Therefore, the difference in the intensities of the fragments from the products of metalation of XIb and XIIb has to be ascribed to the preferential attack of butyllithium on one of the double bonds of the *cis–trans*-dienes. It can be seen that the bond attacked is the one that has migrated during the isomerization and to which the *trans* configuration was ascribed. The selectivity of the attack of butyllithium is not due to the influence of the methoxyl group, since the olefinic carbon nearest to this group in XIb, but the furthest in XIIb was attacked by butyllithium. The 2:1 ratio of the fragments obtained from the products of metalation of IXb and Xb is probably due to the presence of XIb and XIIb in this mixture. Since the mixture of XIb and XIIb contains also probably *cis–cis*- and *trans–trans*-dienes that should not exhibit preferential attack on one of the two double bonds, it can be assumed that the ratio of rates of attack of the *trans* and *cis* double bonds is higher than 4:1.

The reason for selective attack of butyllithium on *cis–trans*-dienes is not clear. One possibility is the faster formation of an allylic anion with a *cis* conformation that is assumed to be more stable.[23]

Experimental Section

Linoleyl alcohol (I) was prepared by reduction[29] of methyl linoleate.

Linoleyl Methyl Ether (II).—A solution of diazomethane in dichloromethane[6] (prepared from 13.8 g of nitrosomethylurea) was added dropwise to a solution of 10 g of linoleyl alcohol in 20 ml of dichloromethane containing 8 drops of 40% HBF_4. The temperature of the reaction was not allowed to exceed 0° during the addition. The acid was then neutralized by a solution of KOH. The organic layer was washed with water and distilled, yielding 10 g, bp 128° (0.2 mm).

Metalation of I with Amylsodium.—Amylsodium in hexane was prepared from 9.2 g of Na by the method described by Schlosser.[3] A solution of 13.3 g of I in 25 ml of hexane was then added dropwise at 10°. The reaction mixture was left for 1 hr at room temperature and excess Dry Ice was then added in pieces. Water was added after several hours. The layers separated; the aqueous solution was acidified and extracted with ether. Evaporation of the solvent and of the caproic acid *in vacuo* left 6 g of an acid, showing by titration a molecular weight of 300.

Metalation of I with Butyllithium.—A solution of 26.5 g of I in 50 ml of ether was added dropwise to a solution of butyllithium[30] prepared from 7 g of lithium. The solution was left for 24 hr at room temperature, then added dropwise to a stirred suspension of powdered Dry Ice in ether. Water and hydrochloric acid were added; the ether layer was washed with aqueous NaOH. Acidification of the alkaline solution gave the acid that was extracted with ether and esterified with diazomethane. Distillation gave 60% yield of hydroxy esters, boiling at 175–185° (0.4 mm): $\tilde{\nu}_{max}$ 1740, 1710 (sh), 3350 cm^{-1}; λ_{max} 234 mμ (ε 16,000).

Anal. Calcd for $C_{26}H_{36}O$: C, 74.07; H, 11.11. Found: C, 74.21; H, 11.15.

Metalation with Butyllithium. See Table I. Method A (Run 7).—A solution of 7 g of linoleyl methyl ether (II) in 100 ml of ether was added under nitrogen to 40 ml of 1.6 *M* butyllithium in hexane. The solution was left at room temperature for 24 hr, then added dropwise to a suspension of Dry Ice in ether and left overnight. Water and hydrochloric acid was added, the organic layer was washed with 10% NaOH, and the aqueous solutions were acidified and extracted with ether. Esterification with diazomethane yielded 1.8 g of the unsaturated ester: $\tilde{\nu}_{max}$ 1740 cm^{-1}; λ_{max} 231 mμ (ε 17,000).

Anal. Calcd for $C_{21}H_{38}O_3$: CH_3O, 18.34. Found: CH_3O, 18.02.

Hydrogenation of 1 g of the unsaturated methoxy esters, in acetic acid in presence of PtO_2, yielded 1 g: bp 160° (0.4 mm); $\tilde{\nu}_{max}$ 1740 cm^{-1}.

(29) S. P. Lighthelm, E. Von Rudloff, and D. A. Sutton, *J. Chem. Soc.* 3187 (1950).

(30) R. G. Jones and H. Gilman, *Org. React.*, **6**, 352 (1951).

Anal. Calcd for $C_{21}H_{42}O_3$: CH_3O, 18.1. Found: CH_3O, 17.5.

Method B (Run 5).—The solvent was distilled off *in vacuo* from 30 ml of 1.6 *M* butyllithium in hexane and the residue was dissolved in 25 ml of dry ether. Linoleyl alcohol (2.7 g, 0.01 mol) was then added and the solution left 6.5 hr at room temperature. Carbonation, separation of the acid, esterification, and finally etherification[8] gave 2.6 g: bp 160–170° (0.5 mm); $\bar{\nu}_{max}$ 1740 cm^{-1}; λ_{max} 234 mμ (ϵ 16,200). Hydrogenation gave pure saturated esters.

The neutral fraction gave on distillation 0.6 g of I: bp 140° (0.2 mm); $\bar{\nu}_{max}$ 3250–3450 cm^{-1}; λ_{max}^{EtOH} 233 mμ (ϵ 1950).

Method C (Run 2).—Linoleyl alcohol (5.4 g, 0.02 mol) was added to 60 ml of an ether solution of butyllithium prepared from 1 g of lithium. The usual work-up gave a 60% yield of unsaturated ether–esters: bp 170–180° (0.5 mm); $\bar{\nu}_{max}$ 1740 cm^{-1}; λ_{max}^{EtOH} 233 mμ (ϵ 21,000). Hydrogenation in acetic acid gave the saturated esters: bp 165° (0.5 mm); $\bar{\nu}_{max}$ 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{42}O_3$: C, 73.68; H, 12.25. Found: C, 73.67; H, 12.30.

Distillation of the neutral fraction gave 0.8 g of I: bp 148–155° (0.5 mm); $\bar{\nu}_{max}$ 3300–3400 cm^{-1}; λ_{max}^{EtOH} 233 mμ (ϵ 1180).

Method D (Run 8).—Tetramethylethylenediamine (3.4 g) was added to 28 ml of 1.6 *M* butyllithium in hexane. Linoleyl methyl ether (2.8 g) was then added to the solution; the reaction mixture was left for 72 hr at room temperature and carbonated. The acids were separated, hydrogenated, esterified, and re-etherified with diazomethane, giving 46% yield of the saturated product. This product was purified from a small amount of diester by glpc.

Isomerization of Linoleyl Methyl Ether (II).—II (2.8 g) was added to 5 ml of dimsylsodium in DMSO;[19] the solution was left for 1 hr, then poured on dilute HCl. The product was extracted with hexane and the hexane solution washed several times with water, and distilled, yielding 2.5 g of XIb + XIIb, boiling at 148° (0.4 mm): λ_{max}^{EtOH} 230 mμ (ϵ 25,000), 268 (190), 279 (155). This compound showed ir bands at 985 and 947 cm^{-1}; the ratio of absorbances at these wavelengths is 1.1.

II (2.8 g) was left for 24 hr with 15 ml of dimsylsodium solution,[19] an additional 15 ml of the catalyst solution was added, and the reaction mixture was left for another 24 hr. Work-up as above yielded 2.5 g of IXb + Xb: bp 140° (0.4 mm); λ_{max} 233 mμ (ϵ 25,000). The ratio of absorbances at 985 and 947 cm^{-1} was 4.0.

Isomerization of Linoleyl Alcohol (I).—I (5 g) was added to 30 ml of dimsylsodium in DMSO[19] and the solution left for 3 hr. Water was then added. Work-up as for II gave 4.6 g of XIa + XIIa, boiling at 148–150° (0.4 mm): λ_{max}^{EtOH} 234 mμ (ϵ 16,300), 247 (270), 280 (280). The ratio of absorbances at 985 and 947 cm^{-1} was 1.1.

The product (4.6 g) obtained in the preceding experiment and 20 ml of the catalyst solution was left overnight at room temperature. Work-up as above gave 3.6 g IXa + Xa + XIa + XIIa: bp 142° (0.4 mm); λ_{max} 233 mμ (ϵ 18,300). The ratio $A_{985\ cm^{-1}}/A_{947\ cm^{-1}} = 2.0$.

I (3 g) and 60 ml of the catalyst solution were left overnight at room temperature. Then 30 ml of the same catalyst solution was added and the reaction mixture left for 24 hr. Work-up as above gave 2.8 g of IXa + Xa + XIa + XIIa: bp 142° (0.4 mm); λ_{max} 233 mμ (ϵ 23,000). The ratio $A_{985\ cm^{-1}}/A_{947\ cm^{-1}} = 2.0$.

Ozonolysis.—Ozone was bubbled through a solution of 20 mg of the product in 1.5 ml of dichloromethane cooled to −70° until a blue coloration appeared. Excess ozone was then removed by passing a stream of N_2 through the solution and 200–300 mg of triphenylphosphine[31] was then added. The reaction mixture was left until it reached room temperature, $MgSO_4$ was added, the solution was filtered and concentrated to 0.5 ml by passing a stream of N_2, and the products were analyzed by glpc. The ratio of hexanal to heptanal was analyzed on a 2 m × 0.25 ft column of 10% polydiethylene glycol succinate on Chromosorb and the methoxyaldehydes on a 1 m × 0.25 ft column of 20% SE-30 on Chromosorb. The ratio of hexanal to heptanal did not change when the solution was analyzed before concentration. Linoleyl alcohol and linoleyl methyl ether were ozonolyzed in the same conditions for comparison.

Epoxidation.—A solution of 77 mg of *m*-chloroperoxybenzoic acid in 1 ml of CH_2Cl_2 was added to a solution of 103 mg of the mixture of XIb and XIIb in 0.5 ml of CH_2Cl_2[32] and the reaction mixture was left for 20 min at room temperature. This solution was then washed with 10% aqueous sodium metabisulfite, then with $NaHCO_3$ solution, and the solvent was evaporated. The product showed a *trans* double bond at 970 cm^{-1}. Ozonolysis of this product gave a 1:2 ratio of capraldehyde to heptaldehyde and of VII to VIII instead of the 1:1 ratio of these compounds in the ozonolysis of the conjugated dienes.

Metalation of Isomerized Linoleyl Methyl Ether.—The solvent was distilled off *in vacuo* from 25 ml of 1.6 *M* butyllithium in hexane. The residue was dissolved in 25 ml of dry ether. The *cis–trans* isomers XIb and XIIb (1.5 g) were then added and the solution was left for 184 hr at room temperature. Carbonation, separation of the acids, their esterification, and distillation of methyl valerate left only a trace of an ester. Only a part of the neutral fraction could be distilled since some polymerization occurred.

TMEDA (1.7 g, 15 mmol) was added to 10 ml of butyllithium (15 mmol) in cyclohexane, followed by 1.4 g (5 mmol) of the mixture of VIIIb and IXb. The reaction mixture was left for 2 days under N_2, then added dropwise, with stirring, to a suspension of Dry Ice in anhydrous ether. The mixture was left overnight, then water and dilute acid were added, and the ether layer was separated. The organic layer was washed with dilute NaOH and the alkaline solution was acidified and extracted with ether. The carboxylic acid was esterified with diazomethane yielding 0.9 g of esters: λ_{max}^{EtOH} 233 mμ (ϵ 4000); $\bar{\nu}_{max}$ 1730 cm^{-1}. Hydrogenation of these esters in acetic acid in presence of PtO_2 gave a product which was separated by glpc—on 1.5 m × 0.25 ft column of 10% stabilized polydiethylene glycol succinate on Chromosorb—into two fractions. The first fraction (18% of the product) was a mixture of *x*-methoxycarbonyloctadecyl methyl ethers, identified by tlc and mass spectrometer analysis. The second fraction (82%) was composed of octadecyl methyl ethers having butyl and carboxy substituents.

Anal. Calcd for $C_{25}H_{50}O_3$: C, 75.65; H, 12.56. Found: C, 75.88; H, 12.45.

The mixture of IXb and Xb (2.8 g) was added to 15 ml of butyllithium in hexane (25 mmol), containing 2.8 g of TMEDA. The solution was left for 72 hr, then worked up as above, yielding 1.1 g of saturated esters that were separated as above into two fractions, the first (13%) containing carboxy-substituted octadecyl methyl ethers and the second (87%) composed of octadecyl methyl ethers having butyl and carboxyl substituents.

Metalation of Isomerized Linoleyl Alcohol.—Metalation of 2.6 g of the mixture of XIa and XIIa with butyllithium in ether for 72 hr as described above yielded 0.3 g of esters.

The mixture of isomerized linoleyl alcohols (1.5 g, 6 mmol), λ_{max} 233 mμ (ϵ 18,300), was metalated in 16 ml of butyllithium (26 mmol) in hexane for 79 hr. Carbonation, esterification of the acids, then etherification,[6] and hydrogenation yielded 1.1 g of saturated esters that were separated by glpc into two fractions, the first (21%) being the product of metalation and the second (79%) that of butyllithium addition as in the case of the ethers IXb and Xb.

Registry No.—I, 506-43-4; II, 23405-45-0.

Acknowledgment.—We are grateful to the U. S. Department of Agriculture, Agricultural Research Service, for the support of this work.

(31) R. A. Stein and N. Nicolaides, *J. Lipid Res.*, **3**, 476 (1962).

(32) V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2509 (1966).

The Effect of Tetramethylethylenediamine on the Metalation of *o*-and *p*-N,N-Dimethyltoluidines with *n*-Butyllithium. Deuteration and Electrophilic Condensation of Intermediate Lithioamines[1]

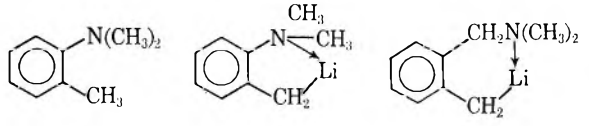
ROBERT E. LUDT, GARY P. CROWTHER, AND CHARLES R. HAUSER

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received August 26, 1969

When compared with *n*-butyllithium alone, *n*-butyllithium–N,N,N′,N′-tetramethylethylenediamine (TMEDA) reagent was shown to be better for effecting the lithiation of *o*- and *p*-N,N-dimethyltoluidine. Upon treatment with *n*-butyllithium in ether–hexane, N,N-dimethyl-*o*-toluidine (**1**) undergoes metalation predominantly in the 2-methyl position to form lithioamine **2**; small amounts of ring metalation were also detected. When *n*-butyllithium–TMEDA in hexane was used as a metalating agent, a more rapid and selective metalation of **1** occurred to give a better yield of intermediate lithioamine **2**. With the same reagent, N,N-dimethyl-*p*-toluidine (**26**) undergoes only *ortho* ring metalation to give lithioamine **27**. Positions and extent of metalation were determined by deuteration and by condensation with electrophilic compounds. These results indicate a *n*-butyllithium–TMEDA complex sufficiently electrophilic so that the neighboring nitrogen still influences the site of metalation. The synthetic advantages of TMEDA as a butyllithium activator in metalations influenced by a neighboring tertiary aromatic amine are also presented.

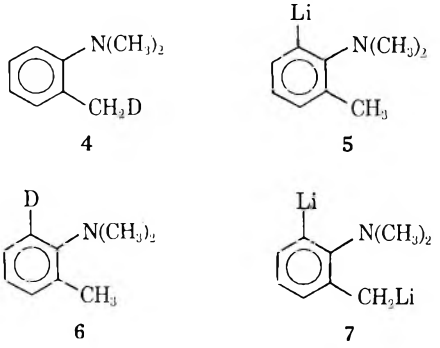
The use of nitrogen as a neighboring heteroatom to effect selective metalations with *n*-butyllithium has been widely investigated.[2-7] Benzyldimethylamine undergoes exclusive *ortho* ring metalation with *n*-butyllithium, as evidenced by condensation with electrophilic compounds in excellent yields.[2-3] Similarly, 2-methylbenzyldimethylamine has been shown to undergo exclusive 2-methyl (side chain) metalation to afford lithioamine **3**, which was condensed with electrophiles in excellent yields.[4] N,N-Dimethylaniline has been metalated with alkyllithium reagents,[5,6] but the yields were low, possibly owing to some delocalization of the free electron pair on nitrogen decreasing the coordination ability of the nitrogen and also decreasing the acidity of the ring protons. It was anticipated that N,N-dimethyl-*o*-toluidine (**1**) should undergo metalation with *n*-butyllithium at the 2-methyl position, since the 2-methyl protons are more acidic than the ring protons and a five-membered intermediate (**2**) could be formed.



1 **2** **3**

Metalation of N,N-Dimethyl-*o*-toluidine with *n*-Butyllithium in Ether–Hexane.—We have found that N,N-dimethyl-*o*-toluidine (**1**) undergoes preferential metalation at the 2-methyl position with *n*-butyllithium in ether–hexane to form mainly lithioamine **2**, as shown by deuteration and condensation studies. Some ring metalation also occurs, presumably at the *ortho* position,[8] although this does not necessarily arise by direct metalation of amine **1** (see below).

Deuteration of the metalation mixtures was conducted to determine the site and extent of lithiation in amine **1**. The results (see Table I) show that, when 1 equiv or an excess of reagent was employed in ether–hexane, the ratio of side-chain to ring deuterium incorporation varied from 3.1:1 to 1.5:1 (expt 1–4) and, more significantly, that this ratio decreased as the metalation period was increased (*cf.* expt 1 and 2, and 3 and 4). This decrease in ratio with time might be explained in one of the following three ways: (A) by isomerization of side-chain lithio derivative **2** to form the *o*-lithio derivative **5**; (B) by a slower competitive direct *ortho* metalation of **1** to give intermediate lithioamine **5**; or (C) by further metalation of the monolithioamine **2** to give dilithioamine **7**. The first explanation seems unlikely, since the amount of 2-methyl metalation did not decrease with time (see Table I). Moreover, not only is the carbanion in **2** probably a weaker base than in **5**,[9] but the five-membered ring in **2**, having lithium coordinated with nitrogen, should be more stable than the corresponding four-membered ring that might be assumed in **5**. Such a side-chain to ring isomerization has been observed previously with α-lithiobenzyldimethylamine to form *o*-lithiobenzyldimethylamine,[7] but this was accompanied by the formation of a relatively stable five-membered ring.



4 **5** **6** **7**

No direct evidence was found to distinguish between the latter two possibilities.

(1) Supported by the U. S. Army Research Office (Durham) and by the Public Health Service Research Grant No. CA04455-11 from the National Cancer Institute.

(2) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

(3) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

(4) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 1387 (1964).

(5) A. R. Lepley, W. A. Khan, A. B. Guimanini, and A. G. Guimanini, *ibid.*, **31**, 2047 (1966).

(6) G. Wittig and W. Merkle, *Chem. Ber.*, **75**, 1491 (1942).

(7) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

(8) The results only establish that some ring metalation occurred in the case of N,N-dimethyl-*o*-toluidine. Since ring metalation of the *para* isomer was proven unequivocably to be in the *ortho* position, it is assumed that the ring metalation in amine **1** was also in the *ortho* position.

(9) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York and London, 1965, p 19.

TABLE I

METALATION OF N,N-DIMETHYL-o-TOLUIDINE WITH n-BUTYLLITHIUM AT 25–30° AND DEUTERATION WITH DEUTERIUM OXIDE

Expt no.	Ratio of C_4H_9Li to amine 1	Solvent	Metalation time, hr	Extent of deuteration: Total	At CH_3-2	On ring	Ratio of 2-CH_3 to ring
1	1:1	Ether–hexane	11	0.49	0.37	0.12	3.1:1
2	1:1	Ether–hexane	20	0.63	0.39[a]	0.24	1.6:1
3	2:1	Ether–hexane	12	0.68	0.45[a]	0.23	2.0:1
4	2.5:1	Ether–hexane	40	0.94	0.57[a]	0.37	1.5:1
5[b]	2.5:1	Ether–hexane	40	0.45	0.15	0.30	1:2[c]
6	1.5:1	Hexane–TMEDA[d]	4	0.88	0.80[e]	0.08	10:1
7	2.5:1	Hexane–TMEDA	4	1.11	1.01[e]	0.10	10:1
8	3.0:1	Hexane–TMEDA	18	1.02	0.72[f]	0.30	2.4:1
9	3.0:1	Hexane–TMEDA	40	1.1	0.85[f]	0.26	3.3:1

[a] In the nmr spectrum of this sample, the peak for the side-chain methyl does show some splitting, although the best description would be a broad singlet. [b] Reaction mixture quenched with less than 1 equiv of deuterium oxide, rather than the usual excess. [c] The accuracy of the estimation of deuterium incorporation is presumably 0.1–0.2 D; the measurement is accurate enough to show that the extent of deuterium incorporation into the ring in expt 5, relative to the deuteration of the 2-methyl group, is markedly greater than was observed in expt 4. [d] N,N,N′,N′-Tetramethylethylenediamine. [e] In the nmr spectrum of this sample, the peak for the side-chain methyl is clearly a triplet (J = 2 cps). [f] In the nmr spectrum of this sample, the signal for the side-chain methyl appears as a quartet (J = 2 cps).

TABLE II

METALATION OF N,N-DIMETHYL-o-TOLUIDINE WITH n-BUTYLLITHIUM. CONDENSATION AT THE 2-METHYL GROUP OF AMINE 1 WITH BENZOPHENONE TO FORM CARBINOLAMINE 8

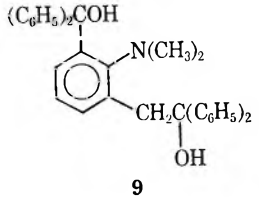
Expt no.	Ratio of LiC_4H_9 to 1	Solvent	Temp, °C	Metalation time, hr	Ratio of $(C_6H_5)_2CO$ to 1	Yield of 8, %
1	1.1:1	Ether–hexane	25–30	18–20	1.1:1	47–50
2	1.5:1	Ether–hexane	25–30	30	1.5:1	51
3	2.0:1	Ether–hexane	25–30	40[a]	2.0:1	59–62
4	2.0:1	Hexane	69	72	2.0:1	71
5	1.5:1	Hexane–TMEDA	25–30	4	1.5:1	65–71
6	2.0:1	Hexane–TMEDA	25–30	3	2.0:1	90–94
7	1.1:1	Hexane–THF[b]	25–30	10–20	1.1:1	0

[a] One equivalent of reagent was added initially. After the solution had been stirred for 20 hr, a second equivalent was introduced (see Experimental Section). [b] Tetrahydrofuran.

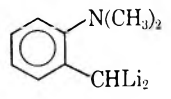
When the metalation mixture produced under the conditions of Table I, expt 5, was treated with only 50 mol % deuterium oxide (instead of the usual excess), so that presumably preferential deuteration of the more basic site would occur, the ratio of side-chain to ring deuterium incorporation was much less (only 1:2) than that observed (1.5:1) when the metalated amine mixture was treated with excess deuterium oxide. Either dilithioamine **7** or a mixture of lithioamines **2** and **5** would be consistent with these deuteration results.

Table II summarizes the yields of carbinolamine **8** obtained when amine **1** was metalated with *n*-butyllithium in ether–hexane under various conditions and the resulting lithioamine **2** was treated with excess benzophenone. This table shows that carbinolamine **8** was obtained in fair to good yields (47–71%) when the metalation of amine **1** was effected in ether–hexane or hexane alone (expt 1–4). In Table II, expt 3, the crude reaction product was indicated by tlc to consist of two components with radically different retention ratios. The compound with the higher R_f value was shown to be adduct **8**, which was isolated in 62% yield. The other component, not positively identified, was shown by its mass spectrum to have a much higher molecular weight than adduct **8**, and is thought to be diadduct **9**, arising from twofold condensation of dilithioamine **7** with the ketone. No benzophenone adduct arising from lithioamine **5** was ever isolated or detected in any experiment. The absence of such an adduct leads us to believe that the third possibility (see above), formation of dilithioamine **7**, best accounts for the observation of deuterium incorporation into the ring of amine **1** with longer metalation periods.

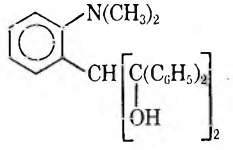
8



9



10



11

Metalation of N,N-Dimethyl-o-toluidine with *n*-Butyllithium–TMEDA in Hexane.—Since the discovery that certain tertiary amines greatly increase the activity of *n*-butyllithium, many aromatic hydrocarbons known to be inert to *n*-butyllithium alone have been metalated in good to excellent yield by the use of the proper tertiary amine catalyst.[10–12] However, this technique seems to have had limited application in effecting metalations of compounds containing

(10) J. F. Eastham and C. G. Screttas, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).
(11) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).
(12) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 1741 (1965).

TABLE III

CONDENSATIONS AT THE 2-METHYL GROUP OF N,N-DIMETHYL-*o*-TOLUIDINE (1) WITH ELECTROPHILIC COMPOUNDS (E) IN ETHER–HEXANE (METHOD A) AND IN TMEDA–HEXANE (METHOD B)

	Method A[a]			Method B[b]				
					Direct method		Indirect method	
Electrophilic compd (E)	Ratio of E to 1	Product	Yield, %	Ratio of E to 1	Product	Yield, %	Product	Yield, %
Benzophenone	2:1	**8**	47–61	1.5:1	**8**	50–70	**8**	90–94
Benzaldehyde	1.5:1	**12**	41–48	1:1, 1.5:1	**12**	25–30	**12**	78–79
					15b	10–15	**15b**	0–5
Phenylisocyanate	1:1	**13**	30	...	...	...	...	...
Benzonitrile	1:1	**14**[c]	41–43	1:1	**14**[c]	45–48	**14**	48–54
					16	5–10	**10**	15–20
Methyl benzoate	1:2	**14**	48–52	1:2	**14**	47	**14**	32
					17	18–20	**17**	28
Benzyl chloride	1:1	**21**	16–17	2:1	**21**	41	**21**	33–42
	2:1	**21**	33					
Benzyl bromide	2:1	**21**	36–38	...	...	...	...	...
1,4-Dibromo-butane	1:2	**22**	42					
		23	...	1:2	**22**	5–14	**22**	10–15
					23	50	**23**	45–50

[a] Metalation time 40 hr in ether–hexane. [b] Metalation time 3–4 hr in TMEDA–hexane. [c] Ketone obtained after acid hydrolysis of the crude reaction mixture.

heteroatoms;[13,14] in many instances the use of such catalysts is unnecessary.

When N,N-dimethyl-*o*-toluidine was treated with *n*-butyllithium–TMEDA in hexane, not only did metalation occur much more rapidly and selectively than with *n*-butyllithium alone, but the overall yield was also increased (see Tables I and II). For example, in Table I, expt 7, 1.1 equiv of deuterium was incorporated into the molecule on quenching with deuterium oxide after only 4 hr of metalation. Moreover, the ratio of side-chain to ring deuterium incorporation had increased to 10:1. The incorporation of more than 1 equiv of deuterium is direct evidence of some dilithiation. In this instance, though, we believe the dilithio intermediate to be **10**, rather than **7**. Evidence for the presence of **10** was afforded by the nmr spectrum of the deuterated samples of Table I, expt 8 and 9, which showed very complex splitting for the side-chain methyl signal. Chemical evidence for the α,α'-dilithio intermediate is presented in the next section. Similar dilithio intermediates have been postulated in related instances.[15]

The synthetic advantages of using TMEDA are apparent from the condensation results with benzophenone (Table II). By employing short metalation periods, indicated by deuteration studies to give the best selectivity, 90–94% yields of adduct **8** were realized (see Table II, expt 6).[16] In the *o*-toluidine system TMEDA can be utilized to give more active *n*-butyllithium, which not only metalates more quickly and in better overall yield than the lithium reagent alone, but also exhibits increased selectivity, a trait uncommon in a more reactive reagent.

We believe that the results employing TMEDA support the conclusions drawn in the preceding section, namely, that metalation of amine **1** occurs initially at the 2-methyl group to form lithioamine **2** and not on the ring to give **5**. It also appears that **2** may undergo further metalation to afford a dilithioamine, possibly **7** or **10**; the results suggest that dilithiamine **7** is formed preferentially when *n*-butyllithium in ether–hexane is the metalation reagent (Table I, expt 5), whereas **10** is the predominant dilithio intermediate with *n*-butyllithium–TMEDA in hexane.

Condensation of Lithioamine 2 with Various Electrophilic Compounds. Synthetic Methods.—As a result of the observations discussed in the previous sections, two general procedures were employed in the study of the condensation of lithioamine **2** with various electrophilic compounds. These involved (A) metalation of amine **1** with the lithium reagent in ether–hexane for 40 hr (method A), and (B) metalation with *n*-butyllithium–TMEDA in hexane for 3–4 hr (method B). It should be noted that there were two methods of mixing the reagents in method B: the direct method, adding premixed *n*-butyllithium–TMEDA to amine **1**, and the indirect method, adding amine **1** to *n*-butyllithium–TMEDA. Most of the condensations were carried out using both of these metalation procedures. However, only in the case of the carbonyl addition reactions was a difference in yields noted (Table III) between the direct and indirect procedures of method B (see Experimental Section).

Early reports on the use of *n*-butyllithium–TMEDA claimed that a 1:1 mol ratio of these components was necessary to give maximum yields of the condensation products.[11] Other workers, though, have shown that the extent of metalation was the same with a 4:1 and 1:1 mol ratio of *n*-butyllithium to TMEDA.[15] In the present study, a 4:1 mole ratio was found to give best results. Not only were the yields of the condensation products the same as when a 1:1 ratio of these reagents was employed, but also purification of the desired product was easier with less TMEDA in the reaction mixture.

The yields of the condensation products of lithioamine **2** with the various electrophilic compounds employing methods A and B are summarized in Table III.

Lithioamine **2** underwent addition reactions not only with benzophenone to form carbinolamine **8**, but also

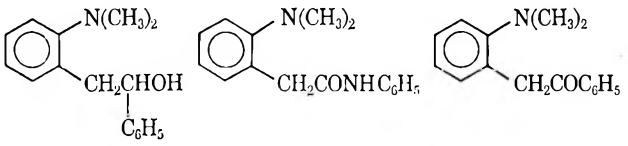
(13) D. J. Peterson, *J. Organometal. Chem.*, **8**, 199 (1967).

(14) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).

(15) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **90**, 2656 (1968).

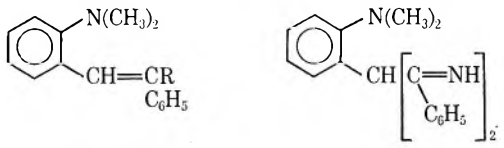
(16) In Table II, expt 5, the crude reaction product was indicated by tlc to consist of three components. The compound with the highest R_f value was adduct **8**, which was isolated in 65–71% yield. The other two compounds had much lower R_f values, similar to the compound detected by tlc in Table II, expt 3. Though neither compound was positively identified, possible structures would be diadducts **9** and **11**.

with benzaldehyde, phenyl isocyanate, and benzonitrile to give carbinolamine **12**, amide amine **13**, and keto amine **14** (after hydrolysis of intermediate imine),



12 **13** **14**

respectively. Carbinolamines **8** and **12** were dehydrated with acid to afford olefin amines **15a** and **15b**, respectively. Part of carbinolamine **12** produced by method B was also converted into olefin amine **15b** during the condensation reaction or work-up (see Table III). Beside keto amine **14**, some diimine (15–20%) **16** was obtained from benzonitrile in method B (see Table III). The formation of **16** affords further evidence for the presence of α,α-dilithioamine **10**.[17]

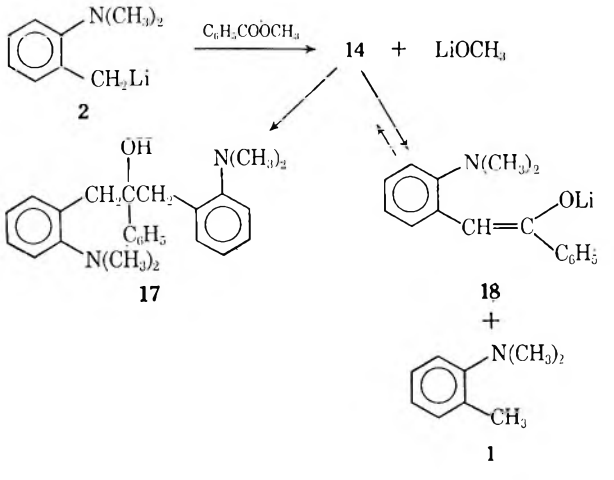


15a, R = C_6H_5
b, R = H

16

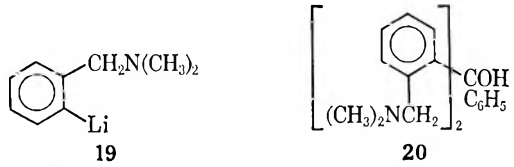
Lithioamine **2** underwent benzoylation with methyl benzoate to form mainly keto amine **14**, a relatively small amount of which reacted further with **2** to give carbinoldiamine **17**. This arresting of the reaction at the ketone stage presumably occurs because much of the ketone is converted into its enolate **18** by lithioamine **2**, thereby minimizing the amount of ketone or its lithium methoxide addition complex available for further conversion into carbinoldiamine **17** (Scheme I).

SCHEME I



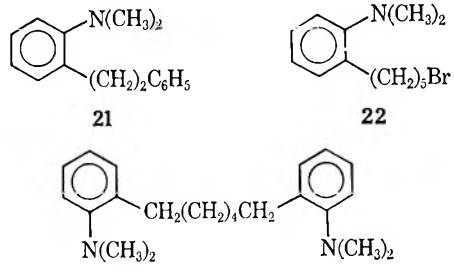
2 **17** **18** **1**

This result is to be contrasted with the reaction of lithioamine **19** with methyl benzoate, which has been observed to afford carbinolamine **20** under similar conditions; none of the keto amine corresponding to **14** was isolated.[3]



19 **20**

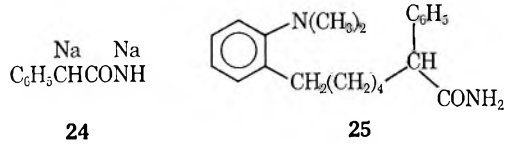
Lithioamine **2** underwent alkylation with benzyl chloride to form benzyl derivative **21**. When a 1:1 mol ratio of amine **1** to benzyl chloride was used, the yield of **21** was only 16%. When a 1:2 mol ratio of these reagents was used, a 34% yield of alkylated product was realized. In an attempt to further improve the yield of **21**, lithioamine **2** was alkylated with benzyl bromide, but the change in halogen increased the yield only to 36–38%. Lithioamine **2** also underwent alkylation with 1,4-dibromobutane to give halo amine **22** and the bis derivative **23**. Interestingly, **22**, which still contains bromine, was the main product in method A, whereas the main product in method B was **23** (see Table III).



21 **22**

23

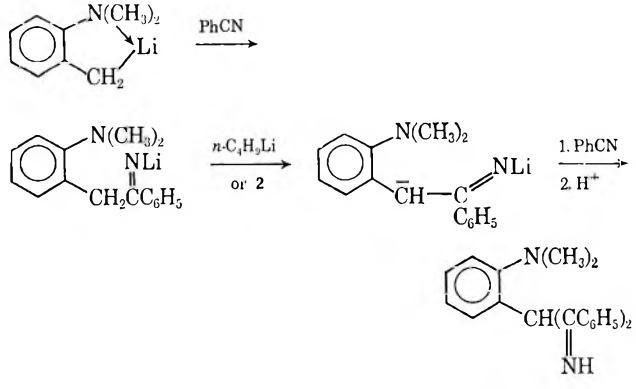
Halo amine **22** reacted as an alkylating agent when added to disodiophenylacetamide (**24**) in liquid ammonia to form amide amine **25**; disodio salt **24** was prepared from phenylacetamide and sodium amide.[18]



24 **25**

All of the products described above are new. Their structures were supported by analyses and absorption spectra. For example, the nmr spectra of carbinolamine **8** has a singlet at δ 2.72 (6 H) assigned to the N-methyl protons and another singlet at δ 3.62 (2 H)

(17) A rapid two-step condensation might be postulated to account for the formation of **16**. Such a sequence appears unlikely, since an excess of benzonitrile was quickly added to the metalation mixture.



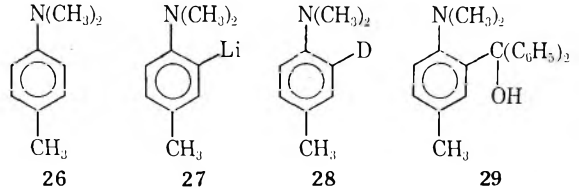
(18) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **29**, 722 (1964).

assigned to the benzylic methylene protons. The 3:1 integration ratio confirms structure **8** and eliminates the other possibility, the *o*-benzophenone adduct from lithioamine **5**. Also, special attention should be given to the nmr spectra of mono- and bisalkylated amines **22** and **23**. In each of these nmr spectra, the triplet assigned to the benzylic methylene protons is hidden for the most part under the large singlet of the N-methyl protons. The N-methyl "singlet" at δ 2.62 integrates for eight protons in the nmr spectrum of **22**, and that in the nmr spectrum of **23** (δ 2.6) integrates for 16.2 protons. The structure of the diimine adduct **16** was established from the nmr spectrum, which showed a one-proton singlet at δ 6.2 assigned to the methine proton along with the expected N-methyl and aromatic peaks (see Experimental Section). Also, the ir spectrum of **16** does not have any absorption bands corresponding to 1,2,3 trisubstitution. Thus the diadduct was established as structure **16** arising from dilithio compound **10** and not from reaction of dilithio amine **7**.

Based on the results of Table III, it must be concluded that, when the major products were the same in methods A and B, the latter method is generally preferable, since not only did it usually afford better yields, but the lithiation was complete in much less time. However, as shown in the alkylation reaction with 1,4-dibromobutane, metalation under the conditions of method A is still useful.

Metalation of N,N-Dimethyl-*p*-toluidine.—The foregoing section showed that the metalation of amine **1** (method A) occurred in fair yield at the 2-methyl position, as shown by deuteration and condensation studies. More significant, it was shown that the use of the TMEDA-activated reagent (method B) not only greatly facilitated the rate of metalation of amine **1**, but also enhanced the ratio of side-chain to ring metalation (see Table I).

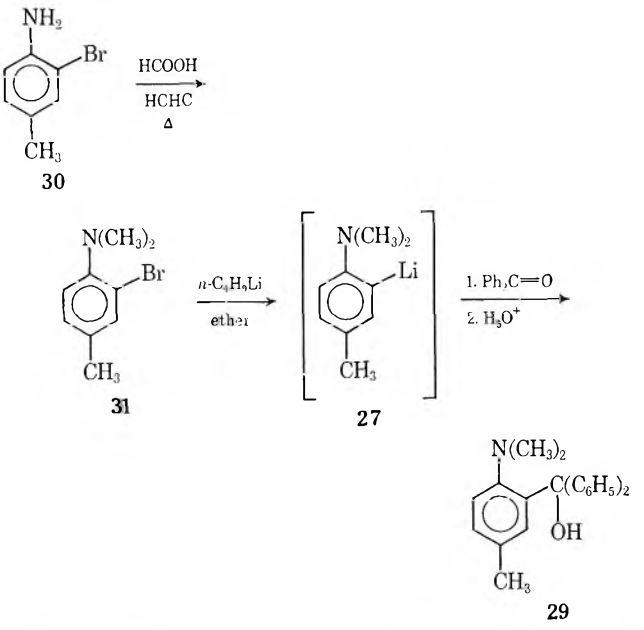
In contrast to amine **1**, which underwent preferential metalation at the 2-methyl group, amine **26** was found to undergo exclusive ring metalation with either *n*-butyllithium or its TMEDA complex, as shown by deuteration and condensation with benzophenone to form deuterioamine **28** and carbinolamine **29**, respectively.



That the deuterium was incorporated into the ring, presumably *ortho* to the dimethylamino group, was supported by ir and nmr spectra. Similarly, the structure of the benzophenone adduct **29** was supported by elemental analysis and absorption spectra.

In view of the proposed coordination mechanism for similar metalation reactions of tertiary amines,[19] it seems improbable that either deuterium or benzophenone was incorporated *ortho* to the *p*-methyl group of amine **26**. However, the analysis and absorption spectra used to verify structure **29** would also be consistent with the structure of the product which would have resulted from the condensation of amine **26** with benzophenone *ortho* to the *p*-methyl group. In order to verify the proposed structure of adduct **29**, then, this carbinolamine was synthesized by another method (Scheme II). Thus bromo amine **31**, obtained by methylating commercially available 2-bromo-4-methyl-

SCHEME II



aniline (**30**) with excess formic acid and formaldehyde,[20] was treated with 3 molar equiv of *n*-butyllithium in ether, and then with excess benzophenone.[21] The product was shown to be identical with carbinolamine **29** by mixture melting point and spectral data. Again, metalation of amine **26** with the TMEDA-activated reagent provided a better yield of adduct **29** in much less time than did metalation and condensation of amine **26** with *n*-butyllithium alone; metalation of amine **26** in refluxing hexane for 72–80 hr with *n*-butyllithium alone gave a 60% yield of **29**, while metalation with TMEDA–*n*-butyllithium for 3–4 hr afforded nearly an 80% yield of this carbinolamine.

The above results indicate that amine **26** is being lithiated only in the *ortho* position. However, it is possible that **26** was metalated initially at the *p*-methyl position followed by isomerization to form *o*-lithioamine **27** or that with longer metalation times **27** might isomerize to form the *p*-methyl lithio derivative. When the metalation reaction of amine **26** with *n*-butyllithium–TMEDA in hexane was quenched with deuterium oxide after 30 min, the nmr spectrum of the deuterated amine showed very little deuterium incorporation; less than 0.1 D was present at the *p*-methyl position and a maximum of 0.24 D was present in the ring. When the same reaction was quenched with D_2O after 36 hr, the nmr showed *ca.* 0.8 D in the ring and essentially no deuterium at the *p*-methyl position. These deuterations further substantiate that amine **26** is metalated nearly exclusively in the *ortho* position. No significant *p*-methyl metalation was detected.

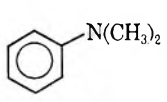
Based on the good yields of metalation observed in the *o*- and *p*-dimethyltoluidines, it was of interest to

(19) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **32**, 1479 (1967).

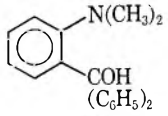
(20) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 723.

(21) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

apply the TMEDA method to N,N-dimethylaniline (**32**) to determine whether or not *ortho* derivatives could be attained in better yields than previously reported. Treatment of amine **32** with *n*-butyllithium–TMEDA in hexane for 3–4 hr followed by condensation with benzophenone afforded carbinolamine **33** in 71% yield. The best yield of adduct **33** previously obtained with *n*-butyllithium alone was 40% (56% crude).[5]



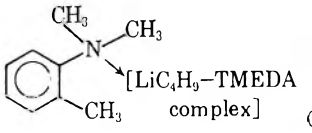
32



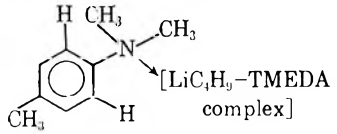
33

Summary.—The *n*-butyllithium–TMEDA complex has been shown in this study to be a better metalating reagent of N,N-dimethyl tertiary aromatic amines than *n*-butyllithium alone. The complex is not only an effectively stronger base, as suggested by better yields and shorter metalation periods, but also, unexpectedly, a more selective base, as shown by the results with N,N-dimethyl-*o*-toluidine (**1**).

In the metalation of the *p*-amine **29**, no comparison of selectivities is possible, since both reagents give only *ortho* metalation. Since the *n*-butyllithium–TMEDA complex metalates toluene nearly quantitatively in the α position,[11] some metalation at the 4-methyl position of amine **26** might be expected; yet with amine **29** only *ortho* metalation is observed. This clear-cut preference indicates that the *n*-butyllithium–TMEDA complex is apparently still sufficiently electrophilic to coordinate with the free electron pair of nitrogen in the aromatic amine. Such a coordination complex between the reagent and the amine would form an intermediate in which the potential *n*-butyl carbanion is directed to a methyl hydrogen in amine **1**, but to an *ortho* hydrogen in amine **26**, as indicated in **34** and **35**, respectively.



34



35

Thus, although a protophilic mechanism does probably operate to form a weaker base in both cases, the potential lithium cation must play an important role in determining the site of metalation.[22] If initial coordination of the TMEDA complex was not an important factor in directing the site of metalation, it is difficult to explain why the more acidic 4-methyl group of amine **26** was not metalated preferentially.

Synthetically, the TMEDA method has been shown to be excellent for effecting substitution at the 2-methyl position of N,N-dimethyl-*o*-toluidine and at the *ortho* positions of N,N-dimethyl-*p*-toluidine and N,N-dimethylaniline. Currently, studies are underway to apply this method to other systems.

(22) A. A. Morton has long stressed the influence of the metallic cation in the mechanism of metalations: A. A. Morton, "Solid Organoalkali Reagents," Gordon and Breach, Inc., New York, N. Y. 1964.

Experimental Section

Melting points were taken in open capillary tubes on a Thomas–Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and by M–H–W Laboratories, Garden City, Mich. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids and sodium chloride plates for the liquids. The nmr spectra were obtained on a Varian A-60 spectrometer. All chemical shifts are reported in parts per million downfield from a tetramethylsilane standard.

Vpc analysis was done with an F & M Model 700 vapor phase chromatograph using a 6-ft column packed with 10% SE-30 on 80–100 Diataport S. Mass spectra were measured at the Research Triangle Institute for Mass Spectrometry, Durham, N. C., on a MS-902 mass spectrometer.

Unless otherwise stated, the metalation reactions were done in a 500-ml, round-bottom flask fit with a Claisen adapter. A dropping funnel was placed directly above the flask, and a condenser was placed in the other side of the adapter. The entire apparatus was predried and kept under a nitrogen atmosphere.

The various metalation conditions are described below. However, only one procedure will be described for the condensation reactions of lithioamine **2** with the different reagents, unless different products were obtained in method A and method B metalations (see Table II and III for yields). Analytical and spectral data for the condensation products are summarized in Tables IV and V.

TABLE IV

ANALYSES FOR CONDENSATION PRODUCTS AND DERIVATIVES

Compd	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
8	$C_{22}H_{23}NO$	83.24	7.30	4.41	83.03	7.40	4.48
12	$C_{16}H_{19}NO$	79.63	7.94	5.81	79.47	7.95	5.86
13	$C_{16}H_{18}N_2O$	75.65	7.10	11.02	76.04	7.40	11.13
14	$C_{16}H_{17}NO$	80.40	7.12	5.80	79.95	7.07	5.93
15a	$C_{22}H_{21}N$	88.30	7.02	4.68	88.13	7.21	4.70
15b	$C_{16}H_{17}N$	86.08	7.63	6.28	85.84	7.85	6.27
16	$C_{23}H_{23}N_3$	80.90	6.79	12.30	80.61	6.71	12.58
17	$C_{25}H_{30}N_2O$	80.20	8.08	7.48	80.05	8.07	7.18
21	$C_{16}H_{19}N$	85.40	8.44	6.22	85.32	8.48	6.21
22	$C_{13}H_2ONBr$	57.95	7.41	5.18	58.17	7.53	5.10
23	$C_{22}H_{32}N_2$	81.43	9.94	8.63	81.14	10.19	8.48
25	$C_{21}H_{28}N_2O$	77.8	8.64	8.64	77.78	8.47	8.60
29	$C_{22}H_{23}NO$	83.24	7.30	4.41	83.42	7.50	4.48

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine in Ether. Method A.—A solution of 5.0 g (0.038 mol) of N,N-dimethyl-*o*-toluidine in 200–250 ml of anhydrous ether was placed into a 500-ml, round-bottomed flask. To this stirred solution was syringed 27 ml (0.038 mol) of *ca.* 1.55 *M* *n*-butyllithium in hexane. This mixture was stirred under a nitrogen atmosphere for 20 hr, when another 27 ml (0.038 mol) of *n*-butyllithium was syringed into the yellow solution. Stirring of this mixture was continued for another 20–25 hr before deuteration or condensation with the designated electrophile. Lithioamine **2** usually precipitated from the ether medium over this latter period of stirring.

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine Using TMEDA. Method B. Direct Method.—A solution of 5.0 g (0.038 mol) of N,N-dimethyl-*o*-toluidine in 150 ml of dry hexane was placed into a 500-ml, round-bottom flask. Next a solution of 2.2–8.7 g (0.019–0.075 mol) of TMEDA in 20–30 ml of dry hexane was placed in the dropping funnel. To this TMEDA solution was syringed 25–33 ml (0.056–0.075 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. The resulting cloudy solution was allowed to stand for 10–15 min, during which time the *n*-butyllithium–TMEDA complex usually precipitated. The premixed solution was then added to the stirred hexane solution of amine **1**. Stirring of the resulting mixture was continued for 3–4 hr before deuteration or condensation. Lithioamine **2** usually precipitated from the hexane medium during the metalation period.

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine Using TMEDA. Method B. Indirect Method.—A solution of 2.2 g (0.019 mol) of TMEDA in 100 ml of dry hexane was placed

TABLE V

SPECTRAL PROPERTIES OF CONDENSATION PRODUCTS AND DERIVATIVES

	Ir, cm^{-1}				Nmr,[a] δ		
Compd	$N(CH_3)_2$[b] stretching	*ortho* substitution	Monoaromatic substitution	Other	$N(CH_3)_2$ (type, integration)	Aromatic (type, integration)	Other[c] (assignment) (type, integration)
8[d]	1060 935	767	756		2.71 (s, 5.9 H)	7.0–7.5 (m, 14.1 H)	3.62 ($PhCH_2$) (s, 2 H) 6.54 (OH) (broad s, 1.1 H)
12	1065 939	773	759 700	3350 (OH)	2.38 (s, 6 H)	6.7–7.2 (m, 9.1 H)	2.86 ($PhCH_2$) (d,[e] 2.1 H) 4.67 (CHOH) (t,[f] 0.91 H) 5.54 (OH) (broad s, 0.97 H)
13	1045 943	770	755 690	3310 (NH), 1652 (amide I) 1610 (amide I)	2.74 (s, 6 H)	6.8–7.55 (m, 10.3 H)	3.65 ($PhCH_2$) (s, 2 H)
14	1050 950	768	756 690	1682 (C=O)	2.45 (s, 6 H)	6.9–8.0 (m, 9 H)	4.18 ($PhCH_2$) (s, 1.83 H)
15a	1050 946	770	755 697	...	2.78 (s, 6 H)	7.05–7.45 (m, 13.5 H)	6.4–6.6 [Ph(C=)H] (m, 1 H)
15b	1052 948	763	758 692	...	...[g]		
16[d]	1032 947	763	750 697	3410 and 1565 (NH imine) 1640 (C=N)	2.79 (s, 6 H)	6.7–7.9 (m, 16 H)	6.23 (methine) (s, 0.96 H)
17[d]	1052 945	770	765 705	3380 (OH)	2.58 (s, 12 H)	6.7–7.45 (m, 14.3 H[h])	2.97 and 3.28 [$CH_2C(OH)CH_2$] (AB pattern,[i] 4.1 H)
21	1045 945	764	749 697		2.55 (s, 6.1 H)	7.0–7.2 (m, 9 H)	2.88 ($PhCH_2CH_2$) (s, 3.9 H)
22	1050 947	768	...		2.62 (broad s, 8 H)	6.9–7.1 (m, 4 H)	1.27–1.95 (CH_2) (m, 5.94 H) 3.3 (CH_2Br) (t,[j] 1.93 H)
23	1048 950	768	...		2.6 (broad s 16.2 H)[k]	6.82–7.17 (m, 8.2 H)	1.32–1.87 (CH_2) (m, 8 H)
25	1048 950	763	748 702	3420 and 3210 (NH), 1650 (amide I) 1605 (amide II) 1415 (amide III)	2.58 (broad s, 8 H)[k]	6.6–7.6 (m, 9.8 H)[l]	1.0–2.8 (CH_2) (m, 8.8 H[l]) 3.23 (methine) (t, 1.1 H[m])
29	...[n]	...	...	3350 (OH)	2.29 (s, 6 H)	6.95–7.4 (m, 12.6 H)	2.21 (*p*-CH_3) (s, 2.96 H) 6.45 (OH) (broad s, 1 H)
31[o]	915	...	...	870 and 812 (1,2,4-trisubstitution)	2.63 (s, 6 H)	6.88 and 7.35 (two broad s, 1.98 and 0.85 H)	2.11 (*p*-CH_3) (s, 3.1 H)

[a] Nmr spectra determined in carbon tetrachloride unless noted otherwise. [b] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, *C*, 3674 (1959). [c] Ph = *o*-N,N-dimethylaminophenyl. [d] Nmr solvent deuteriochloroform. [e] J = 5.5 Hz. [f] J = 5.5 Hz. [g] Nmr spectrum not determined. [h] Aromatic integration includes hydroxyl proton. [i] AB_{obsd} = 14 Hz. [j] J = 6–8 Hz. [k] Peak and integration also include $PhCH_2$ protons. [l] Integration was not accurate enough to determine position of protons on amide nitrogen. [m] J = 7 Hz. [n] Unable to determine correlations. [o] Nmr spectrum determined on neat liquid.

into a 500-ml, round-bottom flask. To this stirred solution was syringed 33 ml (0.075 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. This mixture was stirred for 10–15 min, during which time the TMEDA–*n*-butyllithium complex usually precipitated. Then a hexane solution of 5.0 g (0.038 mol) of N,N-dimethyl-*o*-toluidine was added *via* the dropping funnel over a 2–10 min interval. Stirring of the resulting mixture was continued for 3 hr. Lithioamine **2** precipitated during this time affording a yellow-white suspension.

Deuteration of Lithioamine 2 with Deuterium Oxide.—To the stirred yellow-white suspension of lithioamine **2** was added a 2–3 molar excess of deuterium oxide (99.8% deuterium) *via* the dropping funnel. (In one instance, less than 1 molar equiv of deuterium oxide was employed; see Table I, expt 5.) Stirring was continued until a clear yellow solution resulted (5–60 min). The organic layer was filtered free of the solid which had separated, dried ($MgSO_4$), and concentrated to give deuterated amine **1**. The recovery of undistilled deuterated amines was 75–100%. The crude liquids were fractionated at reduced pressure through a 15-cm Vigreux column [65–70° (12–13 mm), a midcut being collected for deuterium analysis (see Table I). The TMEDA employed in certain metalations was distilled at atmospheric pressure and 120–123° or at slightly reduced pressure.

Deuteration of Lithioamine 2 with Less than 1 Equiv of Deuterium Oxide (See Table I, Expt 5.)—To the stirred yellow-white suspension of lithioamine **2** was added 0.4 g (0.020 mol) of deuterium oxide (99.8% deuterium) *via* the dropping funnel. After the solution had been stirred for 1 hr, excess water was added and stirring was continued until a clear yellow solution resulted. Subsequent work-up of the deuterated sample was the same as described above.

The nmr spectra of the deuterated amines were run either neat or as carbon tetrachloride solutions. The integration data was obtained by comparing the integrating areas of the signal in the nmr spectra of the deuterated samples with the analogous absorption peaks in the nmr spectrum of undeuterated amine **1**. In each instance, the dimethylamino singlet (6 H) was used as an internal standard. The ir spectra of the deuterated samples were taken neat.

Condensation of Lithioamine 2 with Benzophenone.—To the yellow suspension of **2** was added an ethereal solution of 13.4

g (0.075 mol) of benzophenone, dropwise, over a 15-min interval. The resulting green solution was stirred for 5–30 min and then poured into a solution of 5.0 g (0.083 mol) of glacial acetic acid in 30 ml of ether. After the solution had been stirred for several minutes, 50 ml of water was added. The resulting suspension was filtered, affording a white, crystalline solid, yield 0.0–11.0 g, mp 149–152°. The filtrate was extracted with 10% hydrochloric acid (solid hydrochloric salt of product precipitated). The resulting aqueous suspension was made basic with NaOH pellets, liberating the solid free amine, which was collected by filtration to give up to 7.91 g of crude benzophenone adduct **8**, mp 148–151°. (This solid was subjected to tlc analysis.) One recrystallization from benzene–hexane gave 6.85 g of white needles, mp 151.5–154°. The basic filtrate was extracted with ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated. Distillation of this oil gave 0–0.8 g (16% recovery) of **1**, bp 35° (0.25 mm). Cooling the high-boiling residue gave 0.8 g of adduct **8**, mp 148–151°. The total yield of pure adduct **8** was 60–94%. Further recrystallization of **8** from benzene–hexane afforded an analytical sample, mp 153–155°.

Dehydration of Benzophenone Adduct 8 with 20% Sulfuric Acid.—Into a 100 ml, round-bottom flask were placed 3.17 g (0.01 mol) of **8** and 20 ml of 20% sulfuric acid. This solution was refluxed for 2 hr, cooled in an ice bath, and then carefully poured into a precooled solution of 8 g of NaOH in 20 ml of water. The basic solution was extracted with ether; the combined ether extracts were dried ($MgSO_4$) and concentrated to a yellow oil which solidified on standing overnight. Recrystallization of the crude product from petroleum ether (bp 30–60°) gave 2.0 g (70%), mp 73–75°, of olefin amine **15a**. Further recrystallizations from petroleum ether gave an analytical sample, mp 75–77°.

Dehydration of Benzophenone Adduct 8 with Acetic Acid–Sulfuric Acid.—Into a 100-ml, round-bottom flask were placed 4.0 g (0.0126 mol) of carbinolamine **8** along with 45 ml of glacial acetic acid. Stirring was initiated until all the solid had dissolved. Then 5 ml of concentrated sulfuric acid were added with immediate development of red color. After stirring for 2 min, the reaction mixture was poured into ice contained in a 250-ml beaker. The resulting slurry was neutralized with NaOH pellets, liberating a gummy, yellow solid which was taken up in petroleum ether. Cooling and scratching afforded 3.35 g (88%) of white solid (**15a**), mp 74–76°.

Condensation of 2 with Benzaldehyde.—To the milky yellow slurry of lithoamine **2** was added 8.0 g (0.075 mol) of benzaldehyde–hexane. After stirring for 30 min, the clear yellow solution was inversely neutralized into acetic acid–ether. Following usual acid–base work-up procedure, the ether layer was dried ($MgSO_4$) and concentrated to a yellow oil which was distilled under reduced pressure, yielding 2.45 g of yellow liquid, bp 105–125° (0.35 mm), and 7.07 g (78–79%) of yellow oil (**12**), bp 155–160° (0.35 mm). The yellow liquid was a mixture of a TMEDA–*n*-butyllithium condensation adduct and a smaller amount of the dehydrated benzaldehyde adduct (**15b**). Treatment of the yellow oil **12** with hexane afforded a white, crystalline solid, mp 66–68°.

Dehydration of Carbinolamine 12 with 20% Sulfuric Acid.—Into a 200-ml, round-bottom flask were placed 1.4 g (0.006 mol) of carbinolamine **12** and 20 ml of 20% sulfuric acid. After refluxing for 2 hr, the solution was cooled and then treated in the same manner as in the dehydration of carbinolamine **8**. The concentrated ether layer was distilled under reduced pressure to give 0.68 g (50%) of a light yellow liquid (**15b**), bp 130–135° (0.2 mm). Two further distillations gave a colorless liquid, bp 130–132° (0.2 mm). In contrast to carbinolamine **12**, the dehydrated product **15b** does not solidify when treated with hexane.

Condensation of 2 with Phenyl Isocyanate.—To the milky yellow slurry of **2** was added an ether solution of 6.7 g (0.055 mol) of phenyl isocyanate. After the initial exothermic reaction had subsided, the semiclear solution was refluxed for 4 hr and then inversely neutralized into an acetic acid–ether solution. This solution was washed with sodium bicarbonate, and then the ether layer was dried ($MgSO_4$) and concentrated. Distillation of the ether residue (complicated by the presence of a subliming white solid) gave 1.0 g of **1** and sublimed white solid and 1.5 g of unidentified yellow oil, bp 100–105° (0.3 mm) (also contaminated with white solid). The resulting high boiling point residue was taken up in hexane–ether, which on cooling gave 7.0 g of yellow-white precipitate, mp 74–84°. This precipitate was dissolved in ether and extracted with 10% hydrochloric acid. The acid washings were neutralized with NaOH pellets and extracted with ether. Evaporation of the ether gave a residue which was taken up in absolute ethanol. Cooling afforded 3.2 (33%) of white solid (**13**), mp 103–105°. Recrystallization from acetonitrile gave an analytical sample, mp 104–105°, of amido amine **13**.

Condensation of 2 with Benzonitrile.—To the yellow-white slurry of **2** was added 4.65 g (0.045 mol) of benzonitrile–hexane. After the resulting mixture had been stirred for 3 hr, the light orange solution was neutralized directly with 100 ml of water. As neutralization proceeded, a white precipitate formed. The solid was filtered and then recrystallized from absolute ethanol, yielding 1.0 g (10%), mp 168–172°, of amine diimine **16**. The filtrate was extracted with 10% hydrochloric acid. The combined acid extracts were then heated under reflux for 45–240 min, cooled, and then neutralized with NaOH pellets, liberating a yellow oil. This oil was extracted into ether, dried ($MgSO_4$), concentrated, and distilled under reduced pressure to give 3.42 g (48%) of keto amine **14**, bp 130–140° (0.2 mm). Further distillation of keto amine **14** afforded an analytical sample.

When the solid was determined to be diimine amine **16**, a longer metalation period, 16 hr, employing 2.5 equiv of *n*-butyllithium and 0.6 mol of TMEDA, was used in order to maximize the yield of the diadduct. Following the above procedures, a 15–20% yield of diadduct **16** was realized, along with 48–54% of keto amine **14**, after hydrolysis of the intermediate monoimine adduct. Recrystallization of diimine adduct **16** from benzene–hexane afforded an analytical sample as white needles, mp 167.5–169.5°.

Benzoylation of 2 with Methyl Benzoate.—To the yellow-white slurry of **2** was added 2.6 g (0.019 mol) of methyl benzoate in ether. After the resulting mixture had been stirred for 35 min, the orange-yellow suspension was inversely neutralized into acetic acid in ether. Following the usual acid–base work-up, the resulting yellow liquid was distilled under reduced pressure, giving 2.5–2.6 g (50%) of recovered amine **1**, 1.42 g (32%) of keto amine **14**, bp 150–165° (0.075 mm), and 1.41 g of carbinoldiamine **17**, bp 180–195° (0.075 mm). The high-boiling point residue was dissolved in petroleum ether and afforded 0.7 g of yellow-white solid. This solid was dissolved in 95% ethanol along with the liquid distilled at 180–195°. Cooling gave 2.0 g (28%) of white solid (**17**), mp 103–105°.

Alkylation of 2 with Benzyl Chloride.—To the yellow-white slurry of **2** was added 9.0 g (0.071 mol) of benzyl chloride–hexane. After this mixture had been stirred at room temperature for 2 hr (or refluxed for 4 hr), the white slurry was neutralized with 60 ml of water. After work-up in the usual manner, distillation of the resulting yellow liquid afforded 1.3 g (26%) of recovered amine **1**, 2.84 g (34%) of alkylated amine **21**, bp 114–120° (0.1 mm), a yellow oil, bp 135–150° (0.1 mm), and a viscous liquid, bp 175–185° (0.1 mm). The yellow oil fraction was found by vpc analysis to contain three components, of which one was the alkylated product **21**. Of the two other components, the larger one may be a 1,1 diadduct similar to that isolated in the condensation with benzonitrile. The retention time of the minor component was the same as that for the viscous liquid. Neither of these two compounds was purified sufficiently for identification.

Alkylation of 2 with 1,4-Dibromobutane. Method A.—To the milky yellow suspension of **2** was added an ether solution of 8.1 g (0.0375 mol) of 1,4-dibromobutane, dropwise, over a 5–10-min period. During this addition, mild reflux was initiated and continued throughout the reaction. After *ca.* 20 min, the yellow-white solution cleared but became cloudy as refluxing continued. After 7 hr, the solution was neutralized and worked up in the usual manner, giving 1.3 g (26% recovery) of **1**, 4.22 g (42%) of colorless liquid **22**, bp 110–113° (0.22 mm), and 1.0 g of high-boiling residue. Using the same procedure with either 4.0 g (0.019 mol) or 2.0 g (0.0094 mol) of 1,4 dibromobutane, only the monoalkylated product **22** and recovered **1** were isolated.

When the reaction was neutralized after only 30 min of ether reflux, less than 10% **22** was isolated, whereas, after 1 hr of refluxing, the yield of isolated **22** was increased to 21%.

Alkylation of 2 with 1,4-Dibromobutane. Method B.—To the yellow-white slurry of **2**, prepared using a 1:1 mol ratio of *n*-butyllithium to TMEDA (1.5 equiv), was added 4.12 g (0.079 mol) of 1,4-dibromobutane in hexane. After stirring for 6 hr, the resulting mixture was neutralized by adding 100 ml of water. Following the usual work-up procedure, the yellow liquid was distilled under reduced pressure, yielding 1.63 g (26%) of recovered amine **1**, 0.75 g (14%) of monoadduct **22**, and 3.03 g (49.2%, based on moles of dihalide used) of alkylated product **23**, bp 160–

165–180° (0.25 mm). Further distillations gave an analytical sample as a yellow liquid, bp 160–163° (0.2 mm).

Formation of the Dipotassium Salt of Phenylacetamide.[18] Alkylation of Haloamine 22.—To a stirred solution of 0.033 mol of potassium amide in 300 ml of liquid ammonia was added 2.0 g (0.015 mol) of solid phenylacetamide. The resulting dark green solution was stirred for 30 min, when an ether solution of 4.0 g (0.0148 mol) of **22** was added during 1.5 min. After stirring for 20 min, the yellow solution was neutralized with excess ammonium chloride. The ammonia was replaced by ether, and the resulting ether layer was filtered and then extracted with 10% hydrochloric acid. Normal work-up gave a light yellow oil which was taken up in benzene–hexane. After the solution had been cooled to room temperature, the solid which had formed was removed by filtration to give 0.62 g of crystalline solid, mp 155–160° (31% recovery of phenylacetamide). Cooling the filtrate in an ice bath, with scratching, gave 3.0 g (63%) of white, powdery solid (**25**). Recrystallization from acetonitrile gave a white, crystalline solid, mp 79–81°.

Lithiation of Amine 26 by *n*-Butyllithium in Refluxing Hexane. Condensation with Benzophenone.—Into a 500-ml, round-bottom flask were placed 5.0 g (0.0375 mol) of N,N-dimethyl-*p*-toluidine dissolved in 250 ml of dry hexane. To this stirred solution was syringed 25 ml (0.037 mol) of *ca.* 1.55 *M* *n*-butyllithium in hexane. This mixture was stirred with mild refluxing for 24 hr, when 25 ml (0.037 mol) of *n*-butyllithium was syringed into the dropping funnel and added dropwise to the reaction mixture. Stirring with mild reflux was continued for 72 hr, when an ether solution of 9.1 g (0.05 mol) of benzophenone was introduced dropwise over a period of 15 min. This mixture was stirred for 4 hr, and then the dark blue reaction mixture was inversely neutralized into acetic acid in ether. This neutralized solution was extracted with three 50-ml portions of 10% hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide pellets, liberating a solid which was collected by filtration, yield 6.4 g (52%), mp 169–173°. The basic filtrate was extracted with ether, which was dried over $MgSO_4$ and then concentrated to give 0.85 g (8%) of solid, mp 163–170°. Recrystallization of the combined product from benzene–hexane gave a white, crystalline solid, mp 171.5–172.5°.

Lithiation of Amine 26 by *n*-Butyllithium–TMEDA in Hexane.—Using the previously described apparatus, 4.0 g (0.0296 mol) of N,N-dimethyl-*p*-toluidine was dissolved in 250 ml of dry hexane and then placed in a 500-ml, round-bottom flask. To this stirred solution was added a premixed (10–15 min) suspension of 5.2 g (0.045 mol) of TMEDA and 20 ml (0.045 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. The resulting mixture was stirred for 4 hr.

Deuteration of Lithioamine 27.—Quenching the lithioamine prepared as described above with deuterium oxide was done in the same manner as described for deuteration of lithioamine **2**. Undistilled deuterated amine **26** was recovered in greater than 90% yield. The crude amine was distilled under reduced pressure through a 15-cm Vigreux column [54–56° (0.4 mm)], a midcut being collected for deuterium analysis. The three experimental conditions are outlined below.

A. **Metalation for 30 min** resulted in the following data: ir (neat) identical with that of undeuterated amine **26**; nmr (neat) δ 2.2 (s, 2.9, C_6H_5–CH_3), 2.62 [s, 6.0, $N(CH_3)_2$], and 6.4–7.1 (AB quartet, 3.76, J = 4 Hz, aromatic).

B. **Metalation for 3 hr** resulted in the following data: ir (neat) 2300 (ring D), 950 [$N(CH_3)_2$], and 878 and 806 cm^{-1} (1,2,4-triaromatic substitution); nmr (neat) δ 2.21 (s, 2.98, *p*-$C_6H_5CH_3$), 2.60 [s, 6, $N(CH_3)_2$], and 6.4–7.2 (m, 2.94, aromatic).

C. **Metalation for 36 hr** resulted in the following data: ir (neat) 2290 (ring D), 951 and 1054 [$N(CH_3)_2$], and 808 and 878 cm^{-1} (1,2,4-triaromatic substitution); nmr (neat) δ 2.21 (s, 2.96, *p*-$C_6H_5CH_3$), 2.61 [s, 6.0, $N(CH_3)_2$], and 6.4–7.1 (m, 3.2, aromatic).

Condensation with Benzophenone.—To a stirred solution of lithioamine **27** was added an ether solution of 8.2 g (0.045 mol) of benzophenone. Stirring was continued for 20 min after addition of benzophenone. Then the clear yellow solution was inversely neutralized into acetic acid–ether. Normal acid–base work-up afforded 6.92 g (74%) of white solid, mp 160–172°, on neutralization with sodium hydroxide. Concentration of the ether washings afforded another 0.6 g (6.5%) of carbinolamine **29**. The total yield was 80%.

Independent Synthesis of Alcohol Amine 29. Methylation of 2-Bromo-*p*-toluidine.[20]—A 3.38-g sample (0.675 mol) of 90% formic acid was placed in a 500-ml, three-necked, round-bottom flask. Then 25 g (0.135 mol) of 2-bromo-*p*-toluidine was added to the acid with stirring. After the solution had been stirred for 5 min, 30.5 ml (0.405 mol) of 37% formaldehyde solution was added cautiously, resulting in vigorous gas evolution. After addition was complete, the flask was introduced into an oil bath (90–100°). The reaction mixture was kept at 95–100° for 8 hr and then cooled. After the mixture had cooled to room temperature, 69 ml of 4 *M* hydrochloric acid was introduced into the reaction mixture. The resulting mixture was concentrated on Buchi Rota-Vac to *ca.* 30 ml of orange-red liquid plus some white precipitate. Next, 50 ml of water was added and then 30 g of sodium hydroxide in 60 ml of water. The resulting solution was extracted with ether and benzene; the organic extracts were dried ($MgSO_4$), concentrated, and distilled at reduced pressure. The desired product was collected as a light yellow liquid at 90–93° (1.5 mm), leaving a higher boiling, yellow-orange liquid which solidified on cooling. The yield of halo amine **31** was 35–38%.

Lithiation, *via* Metal–Halogen Exchange, of Halogen Amine 31.[20] Condensation with Benzophenone.—Into a 500-ml, round-bottom flask fit with a Claisen adapter were placed 4.28 g (0.02 mol) of 2-bromo-N,N-dimethyl-*p*-toluidine and 150 ml of anhydrous ether. To this stirred solution was syringed 27 ml (0.06 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. The resulting solution was stirred for 1 hr, when an ether solution of 7.5 g (0.04 mol) of benzophenone was added dropwise to the light yellow solution. After stirring at room temperature for 1.5 hr, the red-brown solution was inversely neutralized into an ether solution of acetic acid. Normal acid–base work-up afforded an orange-white solid, which was dissolved in absolute ethanol. After cooling, the suspension was filtered to give 5.5 g (74%) of crystalline, white solid, mp 169–172°. No depression of melting point occurred on admixture with carbinolamine **29**.

Lithiation of Amine 34 by *n*-Butyllithium–TMEDA in Hexane. Condensation with Benzophenone.—A solution of 4.0 g (0.033 mol) of N,N-dimethylaniline in 250 ml of hexane was placed into the 500-ml, round-bottom flask. To this stirred solution was added a premixed (10–15 min) suspension of 7.68 g (0.066 mol) of TMEDA and 31 ml (0.069 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. The resulting mixture was stirred for 4 hr, when an ether solution of 9.1 g (0.05 mol) of benzophenone was added over a 5-min interval. After stirring for 30 min, the reaction mixture was inversely neutralized into an ether solution of acetic acid. Normal acid–base work-up afforded 7.1 g (71%) of crystalline carbinolamine **35**, mp 157–160° (lit.[4] mp 160.5–161.5°).

Registry No.—Tetramethylethylenediamine, 110-18-9; *n*-butyllithium, 109-72-8; N,N-dimethyl-*o*-toluidine, 609-72-3; **8**, 23666-96-8; **12**, 23666-97-9; **13**, 23754-32-7; **14**, 23666-98-0; **15a**, 23666-99-1; **15b**, 23667-00-7; **16**, 23667-01-8; **17**, 23667-02-9; **21**, 23667-03-0; **22**, 23667-04-1; **23**, 23829-35-8; **25**, 23754-33-8; **29**, 23667-05-2; **31**, 23667-06-3.

Halomethyl Metal Compounds. XXXI. Phenyl(fluorodichloromethyl)mercury. A Useful Source of Fluorochlorocarbene[1]

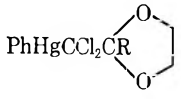
DIETMAR SEYFERTH AND KIRK V. DARRAGH[2]

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

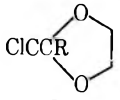
Received September 8, 1969

Phenyl(fluorodichloromethyl)mercury, $PhHgCCl_2F$, can be prepared in moderate yield by the reaction of phenylmercuric chloride, fluorodichloromethane, and potassium *t*-butoxide in diethyl ether at −25° with high-speed stirring. Diphenylmercury is an unavoidable and inseparable contaminant (*ca.* 20%) but does not interfere in the CFCl transfer reactions of $PhHgCCl_2F$. A number of *gem*-fluorochlorocyclopropanes have been prepared in high yield by the thermolysis of $PhHgCCl_2F$ in the presence of the appropriate olefin in benzene solution at 80° for 48 hr (Table I). The olefins thus successfully converted include base-sensitive acrylonitrile and vinyl acetate and the poorly nucleophilic vinyltrimethylsilane. Insertion of $PhHgCCl_2F$-derived CFCl into the C–H bond of 2,5-dihydrofuran, the Si–H bond of triethylsilane, and the Sn–Sn bond of hexamethylditin also have been observed. An alternate and also preparatively useful method for releasing CFCl from $PhHgCCl_2F$ involves treating this mercurial with sodium iodide in DME in the presence of the olefin. This procedure proceeds rapidly (within 5 hr at 80–85°, within 48 hr at room temperature) and gives good yields of *gem*-fluorochlorocyclopropanes.

We have developed a number of organomercury compounds which serve as effective divalent carbon transfer agents: $PhHgCCl_2Br$ and $PhHgCCl_3$ (CCl_2 sources);[3] $PhHgCClBr_2$ (a CClBr source);[3] $PhHgCBr_3$ (a CBr_2 source);[3] PhHgCClXH (X = Cl or Br)[4,5] and $PhHgCBr_2H$,[5] which transfer CHCl and CHBr, respectively; $Hg(CH_2Br)_2$ and ICH_2HgI,[1,6] both CH_2 transfer agents; $PhHgCCl_2CO_2Me$ and $PhHgCBr_2CO_2Me$, sources of $ClCCO_2Me$ and $BrCCO_2Me$, respectively;[7] $PhHgCClBrCF_3$ (a source of $ClCCF_3$);[7] $(Me_3SiCCl_2)_2Hg$, which transfers Me_3SiCCl;[8] and **1** (R = H, Me, Ph), sources of carbenes[9] of type **2**. Notably absent from this list is a fluorocarbene of type FCX. Current studies are devoted to providing organometallic precursors for fluorocarbenes. We have recently reported concerning a new CF_2-generating system, the Me_3SnCF_3 + NaI reagent,[10] and in the present report we describe the preparation and some reactions of phenyl(fluorodichloromethyl)mercury, $PhHgCCl_2F$, a precursor for fluorochlorocarbene.



1



2

All of the previously known methods for the generation of fluorochlorocarbene utilize either the action of strong base on a CCl_2F^- anion source or the high-temperature reaction of fluorodichloromethane with ethylene oxide in the presence of a catalytic quantity of tetraethylammonium bromide.[11] Among the precursors, the treatment of which with base generated CFCl, were fluorodichloromethane,[12–16] methyl fluorodichloroacetate,[17,18] and *sym*-difluorotetrachloroacetone.[17,19–23] A further procedure for CFCl generation which is as yet not well developed is based on the photolysis of fluorochlorodiazirine.[24] Clearly, a CFCl precursor which releases this carbene in neutral medium under mild temperature conditions would be a useful reagent.

Preliminary experiments showed that direct adaptation of the Reutov–Lovtsova procedure[25,26] for phenyl(trihalomethyl)mercury preparation (eq 1) to the

$$PhHgCl + CHX_3 + Me_3COK \xrightarrow{\text{benzene, } 0^\circ} PhHgCX_3 + KCl + Me_3COH \quad (1)$$

synthesis of $PhHgCCl_2F$ was not possible. This mercurial was obtained in trace yields at best when fluorodichloromethane was used in the reaction described by eq 1. The finding that diethyl ether could replace benzene as solvent in reaction 1[27,28] permitted the preparation of phenyl(fluorodichloromethyl)mercury in moderate yield. The reaction of phenylmercuric

(1) Part XXX: D. Seyferth, R. M. Turkel, M. A. Eisert, and L. J. Todd, *J. Amer. Chem. Soc.*, **91**, 5027 (1969).

(2) National Institutes of Health Predoctoral Fellow.

(3) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(4) D. Seyferth, H. D. Simmons, Jr., and L. J. Todd, *J. Organometal. Chem.*, **2**, 282 (1964).

(5) D. Seyferth, H. D. Simmons, Jr., and G. Singh, *ibid.*, **3**, 337 (1965).

(6) D. Seyferth, M. A. Eisert, and L. J. Todd, *J. Amer. Chem. Soc.*, **86**, 121 (1964).

(7) D. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *ibid.*, **91**, 1562 (1969).

(8) D. Seyferth and E. M. Hanson, *ibid.*, **90**, 2438 (1968).

(9) D. C. Mueller and D. Seyferth, *ibid.*, **91**, 1754 (1969).

(10) D. Seyferth, H. Dertouzos, R. Suzuki, and J. Y.-P. Mui, *J. Org. Chem.*, **32**, 2980 (1967).

(11) P. Weyerstahl, D. Klamann, C. Finger, F. Nerdel, and J. Buddrus, *Chem. Ber.*, **100**, 1858 (1967).

(12) J. Hine, A. D. Ketley, and K. Tanabe, *J. Amer. Chem. Soc.*, **82**, 1398 (1960).

(13) W. E. Parham and R. R. Twelves, *J. Org. Chem.*, **22**, 730 (1957).

(14) G. C. Robinson, *Tetrahedron Lett.*, 1749 (1965).

(15) M. Schlosser and G. Heinz, *Angew. Chem.*, **79**, 617 (1967).

(16) H. Reimlinger, *Chem. Ber.*, **97**, 339 (1964).

(17) R. A. Moore and R. Levine, *J. Org. Chem.*, **29**, 1883 (1964).

(18) T. Ando, H. Yamanaka, S. Terabe, A. Horike, and W. Funasaka, *Tetrahedron Lett.*, 1123 (1967).

(19) B. Farah and S. Horensky, *J. Org. Chem.*, **28**, 2494 (1963).

(20) J. P. Oliver, U. V. Rao, and M. T. Emerson, *Tetrahedron Lett.*, 3419 (1964).

(21) L. Ghosez, G. Slinckx, M. Glineur, P. Hoet, and P. Laroche, *ibid.*, 2773 (1967).

(22) R. A. Moss and R. Gerstl, *Tetrahedron*, **23**, 2549 (1967).

(23) R. A. Moss and R. Gerstl, *J. Org. Chem.*, **32**, 2268 (1967).

(24) R. A. Mitsch, E. W. Neuvar, R. J. Koshar, and D. H. Dybvig, *J. Heterocycl. Chem.*, **2**, 371 (1965).

(25) O. A. Reutov and A. N. Lovstova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1716 (1960); *Dokl. Akad. Nauk SSSR*, **139**, 622 (1961).

(26) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).

(27) E. K. Euranto, A. Noponen, and T. Kujanpaa, *Acta Chem. Scand.*, **20**, 1273 (1966).

(28) D. Seyferth, J. Y.-P. Mui, and R. Damrauer, *J. Amer. Chem. Soc.*, **90**, 6182 (1968).

chloride (or bromide) with fluorodichloromethane and potassium *t*-butoxide–*t*-butyl alcohol monosolvate in 1:6.5:2 molar ratio in anhydrous diethyl ether at −25° with high-speed stirring gave this mercurial in ~35% yield. This marked effect of solvent on reaction 1 when $CHCl_2F$ is the haloform used may be rationalized in terms of more effective solvation (hence stabilization) of the intermediate CCl_2F^- anion in diethyl ether and somewhat greater solubility of phenylmercuric chloride in ether.

Closer examination of the product obtained in the $PhHgX–CHCl_2F–Me_3COK$ reaction showed it to be contaminated with diphenylmercury. Using the conditions specified above, the product was shown by means of exhaustive brominolysis to contain *ca.* 20% diphenylmercury. No change in reaction conditions prevented formation of this contaminant, and the best product purity to be achieved was 85%. Neither fractional crystallization nor chromatographic techniques could effect separation of diphenylmercury from phenyl(fluorodichloromethyl)mercury and, indeed, such separation was not required for the synthetic utilization of this reagent. A pure sample of $PhHgCCl_2F$ was obtained by treating the $PhHgCCl_2F–Ph_2Hg$ mixture with gaseous hydrogen chloride (eq 2). Fluorodi-

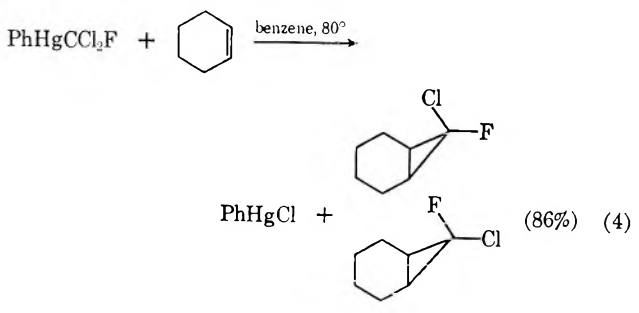
$$\left.\begin{matrix}PhHgCCl_2F\\ +\\ Ph_2Hg\end{matrix}\right\} \xrightarrow[\text{benzene}]{HCl} \begin{matrix}C_6H_6 + ClHgCCl_2F\\ C_6H_6 + PhHgCl\end{matrix} \quad (2)$$

chloromethylmercuric chloride was recovered in 88% yield after column chromatographic separation from phenylmercuric chloride and subsequently was allowed to undergo substituent redistribution with diphenylmercury (eq 3). Pure $PhHgCCl_2F$ was isolated in 45% yield.

$$Ph_2Hg + ClHgCCl_2F \text{ (excess)} \longrightarrow PhHgCl + PhHgCCl_2F \quad (3)$$

In all of the reactions of $PhHgCCl_2F$ which were studied, mercurial starting material containing *ca.* 20% diphenylmercury was used. The latter did not interfere in any way, being an inert diluent as far as the reactions studied were concerned. Analytical brominolysis served to determine the amount of this impurity in each batch of mercurial used.

Our studies have shown phenyl(fluorodichloromethyl)mercury to be an excellent source of fluorochlorocarbene. For example, when this mercurial was heated at reflux with 3 molar equiv of cyclohexene in benzene diluent for 48 hr, 7-fluoro-7-chloronorcarane was obtained in 86% yield as a mixture of the *syn* and *anti* isomers (eq 4). No 7,7-dichloronorcarane, the



(86%) (4)

product which would be obtained if elimination of phenylmercuric fluoride were a competing process, was obtained. The *syn* and *anti* isomers were partially resolved by gas–liquid partition chromatography (glpc), but no attempt was made to separate them. The progress of the reaction was monitored by thin layer chromatographic analysis[26] for starting mercurial.

In terms of our current ideas concerning dihalocarbene extrusion from phenyl(trihalomethyl)mercury compounds,[28] the exclusive formation of CFCl and phenylmercuric chloride in phenyl(fluorodichloromethyl)mercury thermolysis is not surprising. The greater nucleophilicity of Cl (*vs.* F), the weaker C–Cl bond (*vs.* C–F), and the greater stabilization by internal π bonding of CFCl (*vs.* CCl_2) all would operate to favor the extrusion process observed. Since in $PhHgCCl_2F$ it is phenylmercuric chloride which is eliminated, it is not surprising that its stability (hence its effective CFCl transfer reaction rate) is close to that of phenyl(trichloromethyl)mercury.[3]

Other olefins were converted into fluorochlorocyclopropanes using $PhHgCCl_2F$, and in most cases excellent product yields were obtained. In all reactions studied, a mixture of the two possible geometric isomers was formed. Table I shows the results which were obtained. All of these reactions were carried out in benzene solution at 80° for 48 hr. Trimethylvinylsilane is an olefin which is very unreactive toward dihalocarbenes generated by the haloform–base method;[29] yet it gave the expected fluorochlorocyclopropyltrimethylsilane in nearly quantitative yield on reaction with $PhHgCCl_2F$. Vinyl acetate and acrylonitrile are both base sensitive, hence not suited to cyclopropanation reactions in which basic reagents are used; in the present study they were converted into the fluorochlorocyclopropanes in good yield.

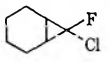
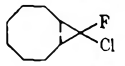
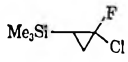
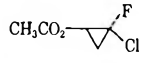
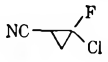
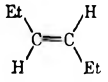
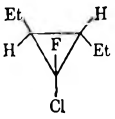
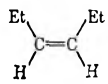
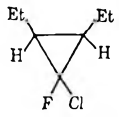
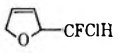
The reactions with *trans*- and *cis*-3-hexene provide information concerning the stereochemistry of the $PhHgCCl_2F$–olefin reaction. The formation of only one isomer in the case of *trans*-3-hexene and of two isomers with *cis*-3-hexene is exactly what would be expected if the reactions are stereospecific with respect to the configuration of substituents at the C=C bond. Also of interest was the stereoselectivity, *i.e.*, the *syn*/*anti* ratio in the case of *cis*-3-hexene. (Here "*syn*" denotes that structure in which the Cl substituent on the cyclopropane ring is in *syn* relationship to the two ethyl groups.) In this connection, the previous work of Moss and Gerstl[22] on the addition of CFCl to *cis*- and *trans*-2-butene is helpful. In making their structural assignments on the basis of ^{19}F nmr spectral data, these authors made the following points. (1) Since *cis* vicinal H–F coupling usually is observed to be greater than *trans* vicinal H–F coupling,[30] the isomer with the Cl *anti* with respect to the alkyl groups (*e.g.*, the *anti* isomer above) should have a fluorine resonance in its ^{19}F nmr spectrum that should be less broadened than those of the other two isomers (*i.e.*, of the *syn* isomer and of the isomer in which the alkyl groups are *trans* to one another) because of the absence of *cis* vicinal H–F coupling. Support for this argument was provided by Japanese workers,[18] who reported the vicinal H–F coupling in 7-fluoronorcarane to be larger when *cis* (18.0 Hz) than when *trans* (9.0 Hz). They also assigned the structures of the two isomers of 7-chloro-7-fluoronorcarane on this basis,

(29) D. Seyferth and H. Dertouzos, *J. Organometal. Chem.*, **11**, 263 (1968), and references cited therein.

(30) R. F. Merritt and F. A. Johnson, *J. Org. Chem.*, **31**, 1859 (1966).

TABLE I

PRODUCTS DERIVED FROM CFCl REACTIONS

Substrate	Product[a]	Yield,[b] %	$n^{25}D$[c]	Found (calcd), % Carbon	Hydrogen	Chlorine	Fluorine
		85	1.4591 (lit.[11] $n^{20}D$ 1.4603)				
		91	1.4707 (lit.[11] $n^{20}D$ 1.4712)	61.04 (61.17)	8.20 (7.99)	20.19 (20.08)	10.64 (10.76)
$Me_3SiCH{=}CH_2$		95	1.4194	43.33 (43.21)	7.58 (7.26)		
$CH_3CO_2CH{=}CH_2$		86	1.4113	39.69 (39.44)	3.95 (3.97)	23.28 (23.25)	12.70 (12.46)
$CH_2{=}CHCN$		40	1.4276	40.33 (40.14)	2.78 (2.53)		
		97	1.4071	55.83 (55.80)	8.10 (8.04)		
	 (mixed *syn* and *anti* isomers)	86	1.4129	55.59 (55.80)	8.07 (8.04)		
	 	8.4		43.96 (43.96)	4.59 (4.43)		
		75	1.4483	43.76 (43.96)	4.36 (4.43)		
Et_3SiH	$Et_3SiCFClH$	83	1.4351	45.59 (45.97)	8.65 (8.83)		
$Me_3SnSnMe_3$	$Me_3SnCFClSnMe_3$	36	1.5253	21.72 (21.32)	4.77 (4.60)	8.88 (9.00)	

[a] Mixed *syn–anti* isomers which were not separated. [b] In a reaction carried out in refluxing benzene for 48 hr. [c] Refractive indices of mixed *syn–anti* isomers for all olefins except *trans*-3-hexene.

with J^{cis}_{H-F} = 19.0 Hz and J^{trans}_{H-F} = 5.0 Hz. In Table II are given ^{19}F nmr data for the fluorochlorocyclopropanes derived from the *cis* and *trans* isomers of 2-butene and 3-hexene. It is apparent that the fluorine resonance of one isomer was indeed less broadened than those of the other two in the case of the products from each pair of olefin isomers. (2) Since cyclopropyl protons were known to be shielded by *cis* methyl groups and deshielded by *trans* methyl groups,[31] a similar shielding effect on the fluorine resonance of fluorocyclopropanes was expected; however, a more pronounced difference in these differential shielding effects was expected in the ^{19}F nmr spectra.[32] Thus the addition of a *cis* alkyl group and/or removal of a *trans* alkyl group should result in an upfield shift of the fluorine resonance. The data in Table II support this argument. On this basis then, we make the structural assignments for the isomers obtained from *cis*-3-hexene. The *syn/anti* ratio of the fluorochlorocyclopropanes from *cis*-3-hexene thus would be 1.2, and so, as in other cases of CFCl addition to olefins,[18,22] formation of the isomer in which the Cl is *syn* to the greater number of alkyl groups is preferred. In the case of *cis*-2-butene the *syn/anti* ratio in the product was *ca.* 3.1;[22] however, a significant steric effect must be introduced when the two methyl groups of *cis*-2-butene are replaced by two ethyl groups, and thus a decrease in this ratio on going to *cis*-3-hexene is not surprising.

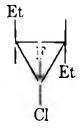
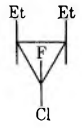
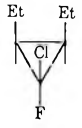
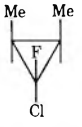
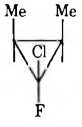
In the case of the 2,5-dihydrofuran–$PhHgCCl_2F$ reaction the C=C addition/C—H insertion ratio observed was about 9. For the 2,5-dihydrofuran–$PhHgCCl_2Br$ reaction this ratio was 0.85,[3] and in the 2,5-dihydrofuran–CF_2 reaction[10] the C=C addition product, 3-oxa-6,6-difluorobicyclo[3.1.0]hexane, was the only product formed. These results are as expected, since the selectivity of the dihalocarbenes in question decreases in the order CF_2 > CFCl > CCl_2 (ref 23 and references cited therein).

The long reaction time required in these $PhHgCCl_2F$–olefin reactions was a major disadvantage. In a previous study[33] we had shown that dichlorocarbene release from phenyl(trichloromethyl)mercury, which was equally slow in benzene at 80°, could be greatly accelerated by carrying out the olefin–mercurial reaction in 1,2-dimethoxyethane (DME) at reflux in the presence of 1 molar equiv of anhydrous sodium iodide. This "activation" proceeded *via* a change in mechanism: the iodide ion displaced the CCl_3^- ion from mercury in a fairly rapid reaction, and the latter then gave dichlorocarbene. Reaction times could be shortened from 48 hr to *ca.* 3 hr at 80–85°, and the *gem*-dichlorocyclopropane yields were, in general, quite good. This sodium

(31) R. A. Moss, *J. Org. Chem.*, **30**, 3261 (1965).
(32) J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 2791 (1966).
(33) D. Seyferth, J. Y.-P. Mui, M. E. Gordon, and J. M. Burlitch, *ibid.*, **89**, 959 (1967).

TABLE II

^{19}F NMR SPECTRA OF SOME *gem*-FLUOROCHLOROCYCLOPROPANES

Compd	Registry no.	Obsd resonance	$W_{1/2}$,[a] Hz	W_B,[a] Hz	Chemical shift, Hz[b]
	23359-72-0	Broad multiplet	38		4313[c]
	23348-94-9	Broad envelope	18		5506[c]
	23348-95-0	Broad envelope	41		3206[c]
	23348-96-1	Multiplet		42	8265[d]
	23359-73-1	Envelope	7	16	9334[d]
	23348-97-2	Triplet of multiplets		50	7164[d]

[a] $W_{1/2}$ = width at half height; W_B = width at base. [b] Chemical shift in hertz upfield from internal standard CCl_3F at 56.4 MHz solvent, CCl_4. [c] Frequency response = 5 Hz. [d] Frequency response = 1–2 Hz; data from ref 22.

iodide procedure had been applied to the generation of CF_2 from trimethyl(trifluoromethyl)tin with good advantage,[10] and we have found that it also is very useful in the generation of CFCl. When phenyl(fluorodichloromethyl)mercury and 1 equiv of sodium iodide were allowed to react in DME solution in the presence of an excess of cyclohexene at 85° for 5 hr, 7-fluoro-7-chloronorcarane (mixture of isomers) was obtained in 79% yield. An analogous reaction, carried out *at room temperature* for 48 hr, gave this product in 85% yield.

In the case of the $PhHgCCl_3$–NaI reagent, the intermediate CCl_3^- ion could be intercepted with vinyl acetate and acrylonitrile.[33] However, reaction of these olefins with the $PhHgCCl_2F$–NaI reagent in DME at 85° gave only the CFCl adducts, 2-chloro-2-fluorocyclopropyl acetate (70%) and 1-chloro-1-fluoro-2-cyanocyclopropane (33%), respectively. No CCl_2F^- adducts could be detected. These results are interpreted not as evidence against the intermediacy of CCl_2F^- in these reactions, but rather as confirmatory evidence relating to the lesser stability of this anion, relative to CCl_3^-. As Hine and coworkers[34] have pointed out, fluorine substitution tends to make the trihalomethyl anion less stable and to increase the stability of the dihalocarbene. Thus, of the two competing processes, CCl_2F^- addition to the C=C bonds or CCl_2F^- decomposition to CFCl + Cl^-, the latter seems to proceed at a significantly faster rate.

Other possible single-bond insertion reactions of CFCl were examined, and the results were in general indicative of a much diminished reactivity on going from CCl_2 to CFCl. Thus dichlorocarbene inserts into the C–H bond α to the oxygen of tetrahydrofuran in 67% yield.[3] In contrast, decomposition of $PhHgCCl_2F$ in the presence of tetrahydrofuran gave no isolable product. In similar fashion, $PhHgCCl_2F$-derived CFCl was inert toward isobutyltrimethylsilane, a compound into whose C–H bond β to the silicon atom CCl_2 inserts in high yield.[35] Successful insertions of CFCl into single bonds was accomplished in the case of triethylsilane and hexamethylditin (eq 5 and 6). Previous work had

$$PhHgCCl_2F + Et_3SiH \xrightarrow[80°]{C_6H_6} Et_3SiCFClH\ (83\%) + PhHgCl \quad (5)$$

$$PhHgCCl_2F + Me_3SnSnMe_3 \xrightarrow[80°]{C_6H_6} Me_3Sn{-}\underset{\displaystyle Cl}{\overset{\displaystyle F}{\overset{|}{\underset{|}{C}}}}{-}SnMe_3 + PhHgCl \quad (6)$$

36%

shown that dichlorocarbene inserts readily into silicon–hydrogen bonds[36] and into the Sn–Sn bond of hexa-

(34) (a) J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Amer. Chem. Soc.*, **79**, 1406 (1957); (b) J. Hine and S. J. Ehrenson, *ibid.*, **80**, 824 (1958).

(35) S. S. Washburne, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1968.

(36) D. Seyferth, J. M. Burlitch, H. Dertouzos, and H. D. Simmons, Jr., *J. Organometal. Chem.*, **7**, 405 (1967).

methylditin.[37] These reactions of CFCl with 2,5-dihydrofuran, triethylsilane, and hexamethylditin are the first examples of CFCl insertion into single bonds.

In summary, the thermolysis of phenyl(fluorodichloromethyl)mercury gives clearly superior yields of fluorochlorocyclopropanes compared with any other method of generating CFCl, and complications arising from basic reaction conditions, higher temperatures, and major competing side reactions are avoided. Phenylmercuric chloride is recovered from these reactions in nearly quantitative yield and good purity and may easily be recycled to preparation of more $PhHgCCl_2F$. Although the thermal reaction in benzene gives excellent yields of CFCl transfer products, the reaction time is rather long, and the $PhHgCCl_2F$–NaI reagent system is an attractive alternative, giving good yields in relatively short reaction times. This work has demonstrated the utility of phenyl(fluorodichloromethyl)mercury as a CFCl transfer agent and has shown that the mercurial route allows the development of hitherto inaccessible CFCl chemistry. The one drawback of this new procedure lies in the difficulty with which $PhHgCCl_2F$ is prepared even in modest yields, and current research is aimed at improving this procedure or at developing a better, alternate route.[37a]

Experimental Section

General Comments.—All reactions involving the preparation or the reactions of the mercurial reagent were carried out under an atmosphere of prepurified nitrogen. Infrared spectra were recorded on a Perkin-Elmer Infracord 337 or 237B grating spectrophotometer. Nmr spectra were obtained on a Varian Associates high-resolution spectrometer (^1H) or a Varian HA-60 instrument (^1H and ^{19}F). Proton chemical shifts are given in δ units downfield from internal tetramethylsilane and were measured in carbon tetrachloride solution unless otherwise specified. Thin layer chromatography (tlc) was performed on Eastman silica gel tlc sheet (K301R); the eluent was 20% benzene in cyclohexane. Development was accomplished by staining with iodine vapor followed by spraying with 10% Na_2S in 50% aqueous ethanol.

The following columns were used in gas chromatographic analysis and isolation: column 1, 8 ft × 12 mm glass packed with 20% General Electric Co. SE-30 silicone rubber gum on 80–100 mesh Johns Manville Chromosorb W; MIT isothermal glpc instrument; column 2, 7 ft × 8 mm glass column, otherwise same as column 1; column 3, 3 ft × 12 mm glass column, otherwise same as column 1; column 4, 12 ft × 0.25 in. aluminum column, same packing as column 1, F & M model 5754 gas chromatograph; column 5, 4 ft × 0.25 in. stainless steel column packed with 10% UC98W silicone rubber on Chromosorb W, F & M 5754. Thermal conductivity detectors were used in all cases.

Preparation of Phenyl(fluorodichloromethyl)mercury.—A 1-l., three-necked, creased flask equipped with a high-speed stirring assembly ("Stir-O-Vac," Labline Catalog No. 1280) and a nitrogen inlet tube was charged with 117 g (0.375 mol) of phenylmercuric chloride and *ca.* 1200 ml of dry diethyl ether. The mixture was cooled to −25° and then 250 g (2.43 mol) of fluorodichloromethane (Matheson Co.) was added. The latter had been dried by passing it as the gas mixed with nitrogen through a drying tower filled with 20% P_2O_5 on anhydrous calcium chloride and was condensed into a trap cooled to −30°. While the temperature was maintained at −25° (±5°), high-speed stirring was started; ~0.75 mol of potassium *t*-butoxide in the form of its *t*-butyl alcohol monosolvate[38] was added over a 20-min period. Stirring was continued at −20° for 45 min and then the mixture was poured slowly into 600 ml of distilled water. Filtration afforded impure PhHgCl (27.6 g, 24%). The organic phase was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. Recrystallization of the crude solids thus obtained from 1:2 chloroform–hexane gave 60.7 g of solid, mp 111–115° (softening at *ca.* 108°). This material was shown by bromine cleavage (see below) to contain $PhHgCCl_2F$ together with *ca.* 20% diphenylmercury as an impurity. Thus the yield of $PhHgCCl_2F$ was 35%. No conditions for recrystallization, column chromatography, or tlc could be found which would make possible the efficient separation of these two components.

This reaction was carried out several times with slight variations to attempt to improve upon the results described above. No substantial improvement resulted; the best $PhHgCCl_2F$ purity to be achieved was 85%.

Analysis of the $PhHgCCl_2F$–Ph_2Hg Mixture by Brominolysis.—A 50-ml, three-necked flask equipped with a magnetic stirring assembly, a 60-ml pressure-equalizing dropping funnel, and a Dry Ice–acetone cold finger topped with a nitrogen inlet tube was charged with 1.89 g of the mixture and 10 ml of dry benzene. Bromine, 12 ml of a 1 *M* solution in carbon tetrachloride, was added dropwise to the stirred solution over a 35-min period. The mixture was stirred for another hour and then 1.5 g of anhydrous $MgSO_4$ and 2.5 g of finely powdered $Na_2S_2O_3 \cdot 5H_2O$ were added. Stirring was continued until the bromine color had been discharged. The filtered organic layer was trap-to-trap distilled (0.1 mm, pot temperature to 100°). Glpc analysis of the distillate (column 2, 96°, 15 psi of helium, external standard method) showed the presence of 3.9 mmol of CCl_2FBr and 6.0 mmol of bromobenzene. If the $PhHgCCl_2F$ were 100% pure, a 1.89-g sample would be 5 mmol and bromination should give 5 mmol each of the two cleavage products. Thus R in PhHgR was as follows.

$$100\left(\frac{3.9 \text{ mmol}}{[3.9 + (6.0 - 5.0)] \text{ mmol}}\right) = 80\% \ CCl_2F$$

$$100\left(\frac{[6.0 - 5.0] \text{ mmol}}{[3.9 + (6.0 - 5.0)] \text{ mmol}}\right) = 20\% \ C_6H_5$$

Thus the mixture was 80% $PhHgCCl_2F$ and 20% Ph_2Hg.

Preparation of a Pure Sample of Phenyl(fluorodichloromethyl)mercury.—A 200-ml, three-necked flask equipped with a magnetic stirring assembly, a gas inlet tube, and a gas exit tube was charged with 28.4 g of 4:1 $PhHgCCl_2F$–Ph_2Hg mixture (60 mmol of $PhHgCCl_2F$) and 140 ml of dry benzene. Anhydrous HCl (Matheson Co.) was bubbled into the solution with vigorous stirring for 1 hr; a white solid precipitated immediately. The unconverted HCl in the mixture was purged with nitrogen. The precipitate (2.27 g), mp 230–270° dec (partial), was filtered and the filtrate was evaporated to dryness. The crude, benzene-soluble solids were chromatographed on a 27 × 3.5 cm silica gel column using 1:1 benzene–hexane as eluent. The white solid obtained was recrystallized from chloroform–hexane to give 17.7 g of white, silky needles, mp 146–149°. Another recrystallization gave an analytical sample, mp 149.5–151°, of fluorodichloromethylmercuric chloride, $CFCl_2HgCl$.

Anal. Calcd for CCl_3FHg: C, 3.55; Cl, 31.47; F, 5.62. Found: C, 3.79; Cl, 31.14; F, 5.23.

The $CFCl_2HgCl$ thus obtained (1.35 g, 4.0 mmol) was heated at reflux with 1.06 g (3.0 mmol) of diphenylmercury in 12 ml of dry benzene. Filtration removed 1.11 g of white solid, mp 255–260° (partial). Evaporation of the filtrate gave 1.4 g of white solid, the recrystallization of which from 1:2 chloroform–hexane (three times) yielded 0.51 g of $PhHgCCl_2F$: mp 98–100°; ir (Nujol) 1582 (w), 1026 (w), 1007 (m), 1002 (m), 794 (m), 748 (m), 735 (ms), 724 (m) and 696 cm^{-1} (m).

Anal. Calcd for $C_7H_5Cl_2FHg$: C, 22.15; H, 1.33; Cl, 18.68; F, 5.00. Found: C, 22.05; H, 1.23; Cl, 18.70; F, 4.48.

Reaction of Phenyl(fluorodichloromethyl)mercury with Cyclooctene.—To a 50-ml three-necked flask equipped with a magnetic stirring assembly and a reflux condenser topped with a nitrogen inlet tube were added 2.48 g of $PhHgCCl_2F$–Ph_2Hg mixture containing 5.2 mmol of $PhHgCCl_2F$, 1.66 g (15 mmol) of cyclooctene, and 10 ml of dry benzene. The reaction mixture was stirred and heated at reflux; the progress of the reaction was monitored by tlc. During the 48-hr reaction period phenylmercuric chloride

(37) D. Seyferth, F. M. Armbrecht, Jr., and B. Schneider, *J. Amer. Chem. Soc.*, **91**, 1954 (1969).

(37a) NOTE ADDED IN PROOF.—An improved procedure, the fluorination of $PhHgCCl_2Br$ with phenylmercuric fluoride, has been developed for the synthesis of $PhHgCCl_2F$ in the meantime: D. Seyferth, S. P. Hopper, and K. V. Darragh, *ibid.*, **91**, 6536 (1969).

(38) A. J. Speziale and K. W. Ratts, *ibid.*, **84**, 854 (1962).

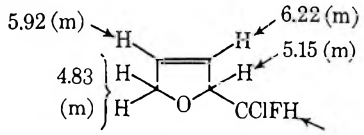
precipitated and after the completion of the reaction was filtered off in quantitative yield (1.63 g), mp 254–256°. The filtrate was trap-to-trap distilled at 0.1 mm (pot temperature to 60°). Glpc analysis of the distillate (column 2, 154°, 15 psi helium) showed the presence of 9-fluoro-9-chlorobicyclo[6.1.0]nonane in 91% yield. Overlapping peaks in the gas chromatogram indicated the presence of both the *syn* and the *anti* isomer. Pure samples of the mixed isomers were isolated by preparative glpc.

This procedure served in the reactions of $PhHgCCl_2F$ with the other olefins (*cf.* Table I), cyclohexene, vinyltrimethylsilane, vinyl acetate, acrylonitrile and the isomeric heptenes. In no cases were the individual *syn* and *anti* isomers separated. Their peaks in the gas chromatograms always overlapped. In all cases the isomer with the longer glpc retention time on a silicone oil column was present in slightly greater amount, *ca.* 1.1–1.2:1.

Reaction of $PhHgCCl_2F$ with 2,5-Dihydrofuran.—The procedure described above was used in the reaction of 11.85 g of $PhHgCCl_2F$–Ph_2Hg mixture containing 25 mmol of $PhHgCCl_2F$ with 74 mmol of 2,5-dihydrofuran in 50 ml of benzene at reflux for 48 hr. Filtration from phenylmercuric chloride and trap-to-trap distillation of the filtrate at 0.1 mm was followed by glpc analysis (column 2, 90°, 15 psi helium) of the distillate. Two higher boiling products were present. The product of shorter glpc retention time (I) was identified as 2-fluorochloromethyl-2,5-dihydrofuran (8.4% yield), and the other product was identified as the mixed *syn* and *anti* isomers (overlapping peaks) of 3-oxa-6-fluoro-6-chlorobicyclo[3.1.0]hexane (II, 75% yield). Pure samples were isolated by preparative glpc.

Product I gave the following data: ir (CCl_4) 3090 (w), 2980 (sh), 2944 (m), 2900 (sh), 2870 (vs), 2690 (vw), 1620 (w), 1480 (w), 1468 (w), 1368 (m), 1365 (m), 1325 (m), 1300 (w), 1278 (w), 1229 (m), 1185 (w), 1135 (sh), 1122 (s), 1085 (vs), 1041 (s), 1022 (sh), 963 (w), 950 (m), 918 (m), and 873 cm^{-1} (m); mass spectrum *m/e* (rel intensity) parent peak 69, mass ion 136 (ratio 136:138 = 3), 138 (<1), 136 (2), 107 (*ca.* 1), 99 (2), 81 (2), 79 (2.5), 78 (21), 77 (4.3), 73 (10), 70 (5.5), 69 (100, M − CClFH), 53 (9), 51 (10), 44 (9), 41 (25), 39 (18), 29 (5.5), and 27 (6.5).

The nmr spectrum is shown below.



6.05 (d of t, $J = 50$ Hz)

Product II gave the following data: ir (liquid film) 3065 (w), 2965 (s), 2935 (s), 2880 (vs), 1975 (w), 1481 (m), 1471 (m), 1424 (s), 1400 (s), 1342 (vs), 1281 (s), 1235 (s), 1195 (vs), 1125 (vs), 1042 (vs), 990 (s), 954 (m), 896 (vs), 867 (vs), 825 (m), 804 (m), 738 (vs), and 719 cm^{-1} (s).

Reaction of Phenyl(fluorodichloromethyl)mercury with Triethylsilane.—The reaction was carried out at 80° for 48 hr using the procedure described above with 2.48 g of $PhHgCCl_2F$–Ph_2Hg mixture containing 5.2 mmol of $PhHgCCl_2F$ and 1.59 g (14 mmol) of triethylsilane (Peninsular ChemResearch) in 10 ml of dry benzene. Phenylmercuric chloride was obtained in quantitative yield. Trap-to-trap distillation of the filtrate at 0.1 mm (pot temperature to 60°) was followed by glpc analysis (column 2, 145°, 15 psi of helium) of the distillate, which showed that triethyl(fluorochloromethyl)silane had been formed in 83% yield: ir (liquid film) 2965 (s), 2920 (s), 2885 (s), 1470 (sh), 1460 (m), 1415 (m), 1380 (w), 1303 (w), 1242 (m), 1005 (s, broad), 975 (sh), 782 (s), 735 (s, broad), 695 (s), and 607 cm^{-1} (m); nmr δ 0.94 (m, 15 H, Et_3Si) and 6.13 (d, 1 H, J = 45.5 Hz, CClFH).

Reaction of Phenyl(fluorodichloromethyl)mercury with Hexamethylditin.—The $PhHgCCl_2F$–Ph_2Hg mixture (4.76 g, containing 10 mmol of $PhHgCCl_2F$) and 6.42 g (20 mmol) of hexamethylditin (M & T Chemicals, Inc.) in 20 ml of dry benzene were heated at reflux under nitrogen for 48 hr. The precipitated solids (2.34 g, PhHgCl and metallic mercury) were filtered and the filtrate was trap-to-trap distilled at 0.0002 mm (pot temperature to 150°). Glpc analysis of the distillate (column 5, programmed at 60–170° at 4°/min) showed the following components to be present: bis(trimethyltin)fluorochloromethane (36%), bis(trimethyltin)dichloromethane (8%), unconverted hexamethylditin (10%), phenyltrimethyltin (4.5 mmol), trimethyltin chloride (3.9 mmol), and small amounts of other unidentified high-boiling compounds.

All by-products were identified by comparison of their glpc retention times and infrared spectra with those of authentic samples. The formation of phenyltrimethyltin and trimethyltin chloride could be explained by the process shown below.

$$Me_3SnSnMe_3 + PhHgCl \longrightarrow Me_3SnCl + [PhHgSnMe_3]$$

$$[PhHgSnMe_3] \searrow Hg + PhSnMe_3$$

Pure samples of $Me_3SnCClFSnMe_3$ were isolated by preparative glpc. This compound appeared to be somewhat unstable to the atmosphere and was best handled in an inert atmosphere: ir (CCl_4) 2980 (s), 2910 (s), 2355 (m), 2320 (sh), 1480 (sh), 1385 (m), 1192 (m), 923 (s) 714 (s), and 681 cm^{-1} (s); a liquid film spectrum showed bands also at 765 (s) and 740 cm^{-1} (sh).

Reaction of Phenyl(fluorodichloromethyl)mercury–Sodium Iodide with Cyclohexene.—A 50-ml, three-necked flask equipped with a magnetic stirring assembly, a 60-ml pressure-equalizing dropping funnel, and a reflux condenser topped with a nitrogen inlet tube was charged with 2.38 g of the $PhHgCCl_2F$–Ph_2Hg mixture containing 5.0 mmol of $PhHgCCl_2F$, 1.23 g (15 mmol) of cyclohexene, and 10 ml of DME (freshly distilled under nitrogen from lithium aluminum hydride). The dropping funnel was charged with a solution of 0.91 g (6 mmol) of sodium iodide [dried at 150° (0.02 mm) for 12 hr] in 10 ml of DME. The mercurial solution was heated to reflux and then the sodium iodide solution was added dropwise with stirring over a 15-min period. White solid began to precipitate immediately. The reaction mixture was stirred and heated for 5 hr, cooled, and filtered. The filtrate was trap-to-trap distilled at 0.05 mm (pot temperature to 80°). Glpc analysis of the filtrate (column 2, 121°, 15 psi of helium) showed the presence of the mixed *syn* and *anti* isomers of 7-fluoro-7-chloronorcarane in 79% yield.

The same reaction carried out at room temperature (*ca.* 25°) for 48 hr gave this product in 85% yield.

The procedure described above (*i.e.*, a reaction carried out at reflux) was used in the reaction of the $PhHgCCl_2F$–NaI reagent with vinyl acetate and acrylonitrile.

Registry No.—Phenyl(fluorodichloromethyl)mercury, 19326-35-3; fluorochlorocarbene, 1691-88-9; fluorodichloromethylmercuric chloride, 23348-91-6; 2-fluorochloromethyl-2,5-dihydrofuran, 23348-92-7; cyclooctene, 931-88-4; 2,5-dihydrofuran, 1708-29-8; triethylsilane, 617-86-7; hexamethylditin, 661-69-8; cyclohexene, 110-83-8.

Acknowledgment.—The authors are grateful to the Air Force Office of Scientific Research (SRC)-OAR for generous support of this work through U. S. Air Force Grant AFOSR-68-1350. This investigation was supported in part by U. S. Public Health Fellowship 5-F1-GM-23,497 (to K. V. D.).

Deoxymetalation Reactions. The Mechanism of Deoxystannylation[1,2]

DENNIS D. DAVIS AND CHARLES E. GRAY

Department of Chemistry, New Mexico State University, Las Cruces, New Mexico 88001

Received September 11, 1969

β-Triphenylstannyl and β-triphenylplumbyl alcohols prepared from the corresponding epoxides and the triphenylmetal–alkali metal derivatives readily undergo an acid-catalyzed deoxymetalation reaction in acetic acid–perchloric acid and methanol–perchloric acid mixtures. The reaction was followed manometrically and found to be first order in organometallic reagent and to show proportionality to the Hammett acidity function in both solvent systems. Additionally, dependence on water concentration was noted in acetic acid. By study of the acidity function, activation parameters, and stereochemistry and by comparison with similar reactions, a mechanism is proposed which involves a concerted elimination of water and a hydrated triphenylmetal cation.

In contrast to the well-studied deoxymercuration[3] reaction, deoxymetalation reactions involving group IV metals and metalloids have received little attention. Early observations by Whitmore, Sommer, and coworkers[4] indicated that substituted organosilanes of the general type $R_3SiCH_2CH(R')X$ (X = halogen or hydroxyl, R′ = H or alkyl) react rapidly with acid, base, and a variety of other reagents to generate the corresponding alkene and R_3SiX. Later studies by Sommer and Miller[5] have shown that the rate of deoxysilylation of 2-(trimethylsilyl)ethanol is proportional to the Hammett acidity function and that effects of substituents on the silicon correlate to the Taft equation with a ρ^* of -1.85. The similarly substituted organolead compound, 3-chloro-1-(triphenylplumbyl)propan-2-ol, reacts rapidly with HCl to yield the elimination product, allyl chloride.[6]

Although there may be some debate concerning the fine points of the deoxymercuration reaction, the generally accepted mechanism is similar to that proposed by Kreevoy and Kowitt,[3a] which involves a metal-bridged ionic intermediate. Because of the apparent overall similarity of the deoxymetalation reactions of the group IV elements and the deoxymercuration reaction, we have investigated the mechanism of deoxymetalation of group IV organometallic compounds with a hope toward further elucidating the nature of the intermediates and transition states involved in these reactions.

Results

The β-hydroxyalkyl triphenyl metal compounds are readily accessible through the reaction of triphenyl metal–alkali metal compounds with epoxides.[7] The alkali metal organometallic derivatives were prepared in a variety of ways depending upon the group IV element.[8] The epoxide opening occurs smoothly at room temperature in a tetrahydrofuran or ethylene glycol dimethyl ether solution in 1–2 hr. The final organometallic products are air- and water-stable crystalline solids; however, in either aqueous methanol or aqueous acetic acid solution containing a catalytic amount of perchloric acid the organotin and organolead compounds undergo a rapid elimination reaction to yield the alkene (95–100%) and a triphenyl metal salt (90–93%).

$$Ph_3MCR_2CR_2OH + HOAc + H^+ \xrightarrow{HOAc\text{–}H_2O} CR_2{=}CR_2 + Ph_3MOAc + H_2O + H^+ \quad (1)$$

$$Ph_3MCR_2CR_2OH + H^+ \xrightarrow{MeOH\text{–}H_2O} Ph_3MOH + CR_2{=}CR_2 + H^+ \quad (2)$$

The organometallic salts and alkenes were isolated and identified by comparison with known samples. The water produced was not identified directly, but is required by the stoichiometry and its formation was indirectly confirmed during the kinetic studies in acetic acid.

Kinetics.—The kinetics of the elimination reactions were followed by monitoring the evolution of the alkene manometrically. The solutions were previously saturated with the product alkene to prevent difficulties owing to solubility of the alkene in the solvent. Good pseudo-first-order kinetics were obtained in all reactions carried out as above. If the solutions were not saturated prior to the start of the run, deviations from linearity were particularly noticeable in the initial portions of the run and the expected volume of gas was not evolved. The overall rate in the nonsaturated solutions is not significantly different from that in the alkene-saturated solutions; thus there appears to be no effect on the rate owing to the presence of product alkene.

Dependence of Rate on Acidity.—At 25.0° in methanol containing 9–27 vol. % water and with perchloric and hydrochloric acid concentrations in the 0.003–0.2 *M*, range good pseudo-first-order kinetics were obtained. Acidity-function studies on the rate of elimination from 2-(triphenylstannyl)ethanol were carried out in 82% aqueous methanol. H_0 data is available for 91% aqueous methanol;[9] however, in our system the rates were too fast to measure at higher acid concentrations in this medium. H_0 data for HCl in 91 and 73% aqueous methanol are parallel functions,[9] and it is assumed

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) Portions of this work appeared as a communication: D. D. Davis and C. E. Gray, *J. Organometal. Chem.*, **18**, 1 (1969).

(3) (a) M. M. Kreevoy and F. R. Kowitt, *J. Amer. Chem. Soc.*, **82**, 739 (1960). (b) K. Ichikawa, K. Nishimura, and S. Takayama, *J. Org. Chem.*, **30**, 1593 (1965).

(4) (a) L. H. Sommer and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 485 (1946). (b) L. H. Sommer, G. M. Goldberg, E. Dorfman, and F. C. Whitmore, *ibid.*, **68**, 1083 (1946). (c) L. H. Sommer, D. L. Bailey, and F. C. Whitmore, *ibid.*, **70**, 2869 (1948). (d) J. Gold, L. H. Sommer, and F. C. Whitmore, *ibid.*, **70**, 2874, (1948).

(5) R. A. Miller, Ph.D. Dissertation, The Pennsylvania State University, 1957.

(6) L. C. Willemsens and G. J. M. van der Kerk, *J. Organometal. Chem.*, **4**, 34, (1965).

(7) H. Gilman and D. Wittenberg, *J. Amer. Chem. Soc.*, **80**, 2677 (1958); **80**, 5933 (1958).

(8) C. T. Tamborski, F. R. Ford, W. L. Lehn, G. J. Moore, and E. J. Soloski, *J. Org. Chem.*, **27**, 619 (1962); H. Gilman, O. L. Maris, and S. Y. Sim, *ibid.*, **27**, 4232 (1962).

(9) C. Eaborn, *J. Chem. Soc.*, 3148 (1953).

that, although the absolute values of H_0 for a given concentration of perchloric acid in 91 and 82% aqueous methanol will differ, the change in the water content will not affect the slope of a correlation line. The log k_1 value is linearly dependent on $-H_0$ with a slope of 0.935 ± 0.025 and is nonlinear with respect to acid concentration (Table I).

TABLE I
DEPENDENCE OF RATE ON ACIDITY FUNCTION[a]

$[HClO_4]$	H_0[b]	$k_1 \times 10^2$, sec
0.0983	1.87	0.602
0.210	1.43	1.42
0.307	1.18	2.77
0.371	1.05	3.46

[a] Conditions: 82% aqueous MeOH, 25.0°; $[Ph_3SnCH_2CH_2OH] = 0.045$. [b] H_0 measurement in 91% aqueous methanol.

The effect of water on the rate was studied in acetic acid–water mixtures containing a constant acid concentration and varying amounts of water.[10] As water concentration is increased from 0.6 to 3.8 M at a constant concentration of perchloric acid of 0.006 M, the rate is a function not only of H_0 but also of $[H_2O]$ (Table II). There is no observable reaction in the absence of added mineral acid.

TABLE II
H_0 AND H_2O EFFECTS IN HOAc–H_2O[a]

$[H_2O]$	H_0	$k_1 \times 10^2$ sec	$k_1/[H_2O]$
3.8	2.5	0.43	0.12
2.94	2.05	0.62	0.21
2.02	1.70	0.99	0.49
1.58	1.45	1.20	0.76
1.08	1.10	1.40	1.30
0.845	0.85	1.60	1.89
0.613	0.70	1.83	2.99

[a] Conditions: 25.0° $[HClO_4] = 0.006\ M$; $[Ph_3SnCH_2CH_2OH] = 0.045$.

The slope of a plot of log k_1 *vs.* $-H_0$ is 0.34 ± 0.14. However, if the effect of water is also to increase the rate by directly participating in the reaction as well as altering the acidity of the medium, then a plot of log $k_1/[H_2O]$ *vs.* $-H_0$ should be linear with unit slope. The actual slope of such a plot is 0.77 ± 0.13. Although there is considerable deviation from unit slope, the rate-accelerating effect of water is clear. Deviations of the slope from unity in low-dielectric media are commonly observed and lay open to question the overall validity of the acidity-function concept in such systems. Other concentration functions of the water, such as activity and molality, give lines of the same slope within experimental error. The inclusion of water as a reactant as suggested by the H_0 correlation is certainly not conclusive. However, further support for this idea is derived from the activation parameters (Table III).

Salt Effects.—The inclusion of water as a reactant in the elimination reaction suggests that some nucleophilic assistance at the metal ion is important. The effects of added salts were determined and are shown in Table IV.

(10) F. J. Ludwig and K. H. Adams, *J. Amer. Chem. Soc.*, **76**, 3853 (1954).

TABLE III
ACTIVATION PARAMETERS FOR $Ph_3SnCH_2CH_2OH$[a]

Temp, °C	$k_1 \times 10^2$, sec	
14.0	2.10	
19.8	3.46	
25.0	5.29	
		$\Delta H^{\pm} = 13.2$ kcal/mol
30.0	7.72	
		$\Delta S^{\pm} = -19.8$ eu
36.0	10.7	

[a] Conditions: 82% MeOH; $[HClO_4] = 0.09$.

TABLE IV
EFFECTS OF ADDED SALTS ON THE RATE OF ELIMINATION OF $Ph_3SnCH_2CH_2OH$[a]

Salt	[Salt]	$k_1 \times 10^2$, sec	k_{rel}
None	...	0.602	(1.0)
$NaClO_4$	0.25	0.925	1.53
NaI	0.25	0.753	1.25
NaBr	0.25	0.643	1.06
NaCl	0.25	0.593	0.99
NaF	0.25	No reacn	...

[a] Conditions: 91% MeOH, 25°; $[HClO_4] = 0.0982$.

Stereochemistry.—The stereochemistry of the acid-catalyzed elimination reaction in acetic acid–water mixtures was determined by using the 3-(triphenylstannyl)butan-2-ols (Table V). These particular compounds were chosen for study because the *threo* and *erythro* alcohols could be prepared from the reaction of triphenylstannylsodium with *cis*- and *trans*-2,3-butylene oxide, respectively.

The gas evolved from the reaction of *threo*-3-(triphenylstannyl)butan-2-ol (prepared from the reaction of triphenylstannylsodium and *cis*-2,3-butylene oxide) with 0.006 M perchloric acid in acetic acid–water was collected and analyzed by gas chromatography. *cis*-2-Butene was the only product found; no trace of the *trans* isomer was evident. Identical results were obtained in aqueous methanol solvent.

The *erythro*-3-(triphenylstannyl)butan-2-ol, prepared from *trans*-2,3-butylene oxide, was subjected to identical elimination conditions and yielded *trans*-2-butene as the only gaseous product.

Discussion

The deoxystannylation and deoxyplumbylation reactions are similar to deoxymercuration, with a few notable exceptions. Deoxymercuration[3a] in aqueous perchloric acid, deoxysilylation[5] in 50% methanol containing H_2SO_4, $HClO_4$, HNO_3, or HCl, and deoxystannylation in 73% aqueous methanol with perchloric acid all follow the Hammett acidity function with unit or nearly unit slopes, indicating a rapid prior protonation equilibrium. However, in acetic acid medium containing 0.6–3.2 M H_2O, the effect of added water cannot be accounted for by consideration of changes in the basicity of the medium only. Increasing the water content causes a decrease in the acidity of the medium, with a concomitant deceleration in rate. The rate of elimination, however, does not fall so fast as expected by the decrease in H_0. This necessitates the inclusion of water as a reactant whose increased concentration causes an increase in the rate. This is supported by the change in the Hammett slope from 0.34 to 0.77 when log $k_1/[H_2O]$ is used rather than log

TABLE V
RELATIVE RATES OF THE ACID-CATALYZED ELIMINATION REACTION

Compd	Registry no.	HOAc (3.2 M H_2O) k_ψ[a]	HOAc (3.2 M H_2O) k_{rel}	73% aqueous methanol k_ψ[b]	73% aqueous methanol k_{rel}
$Ph_3SiCH_2CH_2OH$		No reacn	...	No reacn	...
$Ph_3SiCH_2CH(CH_3)OH$		No reacn	...	No reacn	...
$Ph_3GeCH_2CH(CH_3)OH$	23604-55-9	No reacn	...	No reacn	...
$Ph_3SnCH_2CH_2OH$	23604-56-0	0.604 ± 0.035	(1.0)	0.35	(1.0)
$Ph_3SnCH_2CH(CH_3)OH$	23604-57-1	7.52 ± 0.57	12	0.51	1.4
$Ph_3SnCH(CH_3)CH(CH_3)OH$[c]	23601-91-4	10.8	18	2.3	6.6
$Ph_3SnCH_2C(CH_3)_2OH$	23604-58-2	>20	>33	4.4	12.4
$Ph_3PbCH_2CH_2OH$	1802-70-6	5.13 ± 0.77	8.5 (1.0)	0.77	2.2 (1.0)
$Ph_3PbCH_2CH(CH_3)OH$	23604-60-6	7.77 ± 0.47	13 (1.5)	1.9	5.4 (2.5)

[a] $k_\psi = k_1/[H^+]$; $[H^+] = 6 \times 10^{-3}$ M. [b] $k_\psi = k_1/[H^+]$; the acid concentration is within the range 6×10^{-3}–9×10^{-2} M and is essentially linearly related to H_0. [c] *Ca.* 75:25 mixture of *erythro* and *threo* isomers.

k_1. A similar dual role for water was noted by Eaborn[9] during a study of the acidity function–rate relationships for desilylation of *p*-methoxyphenyltrimethylsilane in aqueous methanol.

On the basis of acidity-function data alone this conclusion is at best tenuous. However, the entropy of activation for deoxystannylation is 19 eu more negative than that for deoxymercuration. Reactions proceeding with unimolecular decomposition of the protonated substrate usually exhibit entropies of activation near zero, while those proceeding with attack of water on the protonated substrate usually exhibit values which are large and negative.[11] Frost and Pearson estimate an entropy change of *ca.* −20 eu for the incorporation of a water molecule in the transition state.[12] See Table VI.

TABLE VI
ACTIVATION PARAMETERS FOR DEOXYMETALATION REACTIONS

Deoxymetalation of	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
2-Triphenylstannylethanol	13.2	−19.8
2-Ethoxyethylmercuric chloride	20	1.0
α-2-Methoxycyclohexylmercuric chloride	17.8	4.6
β-2-Methoxycyclohexylmercuric chloride	26.2	4.5

A reasonable proposition as to the function of the water in the reaction sequence is for nucleophilic assistance at the developing metal cation. The addition of salts to the medium, particularly those with nucleophilic anions, has little effect. Indeed, the salt effect appears to parallel the acidity of the conjugate acid of the anion: $HClO_4 > HI > HBr > HCl > HF$. It is not unreasonable that water should act as a more efficient nucleophile, since the triphenylmetal halides undergo extensive dissociation and complexation with water in aqueous systems.[13]

Stereochemistry.—The product obtained from the reaction of *cis*-2,3-butylene oxide with triphenylstannylsodium was a single compound to which we have assigned the *threo* configuration based upon the following facts.

A. Unsymmetrical epoxides such as propylene and isobutylene oxides are opened to give the metal-substituted alcohol in which the metal is located on the least substituted carbon. This mode of opening is that which is most commonly found for nucleophilic opening of unsymmetrical epoxides, proceeding with *trans* opening.[14]

B. We have noted similar nucleophilic activity in the reaction of triphenylstannylsodium with *sec*-butyl bromide, which proceeds with inversion of configuration.[15] Thus we assume that a nucleophilic, *trans* opening of *cis*-2,3-butylene oxide gives the *threo* product, and conversely.

When *threo*-3-(triphenylstannyl)butan-2-ol was treated with perchloric acid in acetic acid–water or methanol–water mixtures, 100% *cis*-2-butene was obtained, which indicates that the elimination also proceeds in a *trans* manner. Experiments involving the *erythro* isomer and a mixture of the *threo* and *erythro* isomers also showed complete stereospecificity in the opening and elimination reactions. This high degree of stereospecificity in the elimination reaction rules out the possible intervention of a carbonium ion whose lifetime is greater than the time required for rotation about the C–C single bond. On the basis of this stereochemical data, however, no conclusion can be made as to whether a bridged ion is involved, since the stereochemical outcome for both types of transition states is identical.

Substituent Effects.—The overall rate profile of the deoxystannylation reaction is similar to the order of the stability of the product alkenes and is compressed in comparison with the deoxymercuration reaction. However, the observed rate is also a function of the prior protonation equilibrium. As the functional group is changed from a primary to a tertiary alcohol, the base strength should be expected to change and a shift in the equilibrium occur. The observed order of basicity of the lower alcohols measured by Kolthoff[16] in acetic acid is 2-propanol > ethanol > methanol, which follows an inductive order. The equilibrium constants[16]

$$ROH + HS^+ \rightleftharpoons ROH_2^+ + S \qquad (3)$$

for the reaction of eq 3 are water, 68; 2-propanol, 17; ethanol, 15; and methanol, 8.8. Assuming the inductive order to hold in the triphenyltin-substituted alcohol series, the prior equilibrium constant increases in the same direction as the observed rate. However this increase is small, a factor of 2–5 at the most. As can be seen from Table VII, the relative rate spread for tin is much less than for mercury. Assuming that

(11) L. L. Schalegar and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 7.
(13) R. S. Tobias and M. Yasuda, *Can. J. Chem.*, **42**, 781 (1964).
(14) R. E. Parker and N. S. Isaac, *Chem. Rev.*, **59**, 737 (1959).
(15) D. D. Davis, Ph.D. Dissertation, University of California, Berkeley, 1966.
(16) I. M. Kolthoff and S. Bruckenstein, *J. Amer. Chem. Soc.*, **78**, 1 (1956).

TABLE VII
RELATIVE REACTIVITIES IN DEOXYMETALATIONS

	M = Ph_3Sn, X = OH 73% aq MeOH, 25°	M = Ph_3Sn, X = OH 95% aq HOAc, 25°	M = Ph_3Pb, X = OH 95% aq HOAc, 25°	M = HgCl, X = OEt 75% aq ETOH, 0°
MCH_2CH_2X	1	1	1	1
$MCH_2CH(CH_3)X$	1.4	12.4	1.5	14
$MCH(CH_3)CH(CH_3)X$	6.6	18	...	86
$MCH_2C(CH_3)_2X$	12.4	>33	...	1560

the relative substituent effects on the prior equilibrium are the same as those observed by Kolthoff, mercury appears to be much more sensitive to alkyl substitution than is tin or lead in the elimination reaction.

The effect of the leaving group appears to be Hg > Pb > Sn ≫ Ge, Si ≫ H, with relative rates of 5, 3, 1, 10^{-6}, and 10^{-11}, respectively. Quantitative data are not available because of the disparity of the reaction conditions; however, it is clear from Table V that the silicon and germanium compounds react much more slowly than comparable tin or lead analogs. Based upon Sommers data[5] for the deoxysilylation of 2-(trimethylsilyl)ethanol, we estimate that 2-(triphenylsilyl)ethanol deoxymetalates 10^{-6}–10^{-8} times slower than the triphenylstannyl ethanol. Kreevoy and Kowitt[3a] estimate that deoxymercuration is 10^{11} times faster than dehydration of alcohols. The great ease of deoxymetalation can be rationalized by consideration of the bond strengths of the leaving groups (kcal/mol): C–Hg, 27; C–Pb, 31; C–Sn, 54; C–Ge, 57; C–Si, 60; C–H, 96. This must account for a majority of the rate difference; however, both the ionization energy of the leaving group and the stability of cation in solution must also be considered. A precise quantitative explanation of the rate sequence for deoxymetalation reactions involving the group IV metals is lacking and is one of our current areas of investigation.

On the basis of the kinetics, stereochemistry, and the rate profile for the substituted compounds, we propose that the deoxymetalation reaction of organotin compounds, and probably the rest of the group IV organometallics, proceeds by Scheme I.

SCHEME I

$$Ph_3MCR_2CR_2OH + SH_2^+ \rightleftharpoons Ph_3MCR_2CR_2OH_2^+ + SH \quad (4)$$

$$Ph_3MCR_2CR_2OH_2^+ + H_2O \xrightarrow{\text{slow}} Ph_3M(OH_2)^+ + CR_2{=}CR_2 + H_2O \quad (5)$$

$$Ph_3M(OH_2)^+ + SH \rightleftharpoons Ph_3MOH + SH_2^+ \quad (6)$$

$$Ph_3M(OH_2)^+ + SH \rightleftharpoons Ph_3MS + H_3O^+ \quad (7)$$

A reasonable structure for the transition state involved in the rate-determining step would be similar to that commonly postulated for a bimolecular elimination reaction. Although the evidence presented does not rule out the intervention of a bridged-ion species, there is no compelling reason to propose such a structure.

Experimental Section[17]

2-(Triphenylsilyl)ethanol.—A solution of 0.0386 mol of triphenylsilyllithium[18] in tetrahydrofuran (THF) was cooled in an ice bath. Then 2.2 g (0.050 mol) of cold ethylene oxide was added slowly with stirring. The solution turned tan in color immediately. After the solution had been stirred for 0.5 hr, the work-up by hydroysis, extraction with ether, drying of the organic layer with sodium sulfate, and removal of the solvents gave an oil. With addition of 50 ml of heptane the oil solidified upon stirring. The solid was filtered, dried, and recrystallized three times from heptane to give 4.2 g (36%) of 2-(triphenylsilyl)-ethanol: mp 99–100° (lit.[18] mp 99–100°); nmr (CCl_4) δ 7.3 (complex m, Ph_3Si–), 3.7 (t, $SiCH_2$–), and 1.7 (complex m, $-CH_2OH$).

1-(Triphenylsilyl)propan-2-ol.—A solution of 0.0386 mol of triphenylsilyllithium in THF was cooled in an ice bath. Then 3.0 g (0.0517 mol) of propylene oxide was added with stirring. After the solution had been stirred for 0.5 hr at room temperature, the work-up as described before gave 4.3 g (35%) of 1-(triphenylsilyl)propan-2-ol: mp 86–86.5° after recrystallization three times from heptane (lit.[18] mp 86–88°); nmr (CCl_4) δ 7.3 (complex m, Ph_3Si–), 3.9 [complex m, $-CH_2CH(OH)$–], 1.62 (complex m, $SiCH_2$–), and 1.12 (d, $-CH_3$).

1-(Triphenylgermyl)propan-2-ol.—A solution of 13.76 g (0.0358 mol) of triphenylbromogermane in 50 ml of ethylene glycol dimethyl ether (GDME) was added to 75 ml of sodium naphthalene in GDME [prepared by addition of 3.45 g (0.15 g-atom) of sodium metal and 3.84 g (0.030 mol) of naphthalene to GDME]. Triphenylbromogermane was added slowly to maintain a green color at all times. After complete addition the green solution was stirred for 2 hr and then cooled in an ice bath. Then 8.3 g (0.143 mol) of propylene oxide in 25 ml of GDME was added slowly, the solution turning tan in color. After usual work-up and recrystallization three times from heptane, 6.85 g (52.7%) of 1-(triphenylgermyl)propan-2-ol was obtained: mp 72–73°; nmr (CCl_4) δ 7.3 (complex m, Ph_3Ge–), 4.0 [complex m, $-CH_2CH(OH)$–], 1.7 (complex m, $GeCH_2$–), and 1.2 (d, $-CH_3$).

Anal. Calcd for $C_{21}H_{22}GeO$: C, 69.48; H, 6.11. Found: C, 69.45; H, 6.05.

2-(Triphenylstannyl)ethanol.—A solution of 40.0 g (0.104 mol) of triphenyltin chloride in 100 ml of GDME was added to 100 ml of sodium naphthalene in GDME [prepared by addition of 6.0 g (0.26 g-atom) of sodium metal and 7.0 g (0.055 mol) of naphthalene to GDME]. Triphenyltin chloride was added slowly to maintain a green color at all times. After complete addition the solution was stirred for 2 hr and then cooled in an ice bath, and 10.0 g (0.227 mol) of ethylene oxide was added slowly. The resulting tan solution was stirred for 1.5 hr. After usual work-up and recrystallization three times from hepane, 27.45 g (67%) of 2-(triphenylstannyl)ethanol was obtained: mp 67–68° (lit.[19] mp 67–68°); nmr (CCl_4) δ 7.3 (complex m, Ph_3Sn–), 3.8 (t, $SnCH_2$–), and 1.7 (complex m, $-CH_2OH$).

1-(Triphenylstannyl)propan-2-ol.—This compound was pre-

(17) Reactions involving organometallic compounds were carried out in an atmosphere of dry, oxygen-free argon using three-neck flasks equipped with reflux condenser, self-equalizing addition funnel, mechanical stirrer, and an inlet for argon. No attempts were made to determine optimal conditions for preparation of the organometallic compounds.

Infrared spectra were recorded using the Beckman IR-8 and Perkin-Elmer 621 spectrophotometers. Nmr spectra were obtained with Varian Associates A-60A spectrometer using tetramethylsilane (TMS) as an internal standard in 10–20% solutions of carbon tetrachloride. Chemical shifts are reported in parts per million downfield from TMS.

The gas chromatographic analyses of the alkenes were performed by Gene Taylor, Department of Chemistry, New Mexico State University. The gas chromatograph (Aerograph A-90-P3) was equipped with a thermistor detector. The polyethylene chromatographic column measured 40 ft × 0.25 in. and was packed with saturated silver nitrate in 1,4-butanediol on 40–60 mesh Chromosorb. The following conditions were employed: helium flow rate, 200 ml/min; block temperature, 70°; injection port temperature, 25°; column temperature 12–15°. The materials were identified by comparing their retention times with those of authentic samples.

Melting points were taken with a Mel-Temp capillary melting point apparatus and are corrected.

Elemental analyses were performed by Crobaugh Laboratories, Cleveland, Ohio. Only compounds not previously reported were analyzed.

(18) H. Gilman, D. Aoki, and D. Wittenberg, *J. Amer. Chem. Soc.*, **81**, 1109 (1959).

(19) H. Gilman and C. Arntzen, *J. Org. Chem.*, **15**, 994 (1950).

pared in a similar manner as described above from 38.5 g (0.10 mol) of triphenyltin chloride, 4.6 g (0.20 g-atom) of sodium metal, 5.25 g (0.041 mol) of naphthalene, and 8.3 g (0.143 mol) of propylene oxide. After work-up and recrystallization from heptane, 25.40 g (62%) of 1-(triphenylstannyl)propan-2-ol was obtained: mp 83–84.5°; nmr (CCl_4) δ 7.3 (complex m, Ph_3Sn–), 4.1 [complex m, $-CH_2CH(OH)-$], 1.7 (complex m, $SnCH_2-$), and 1.1 (d, $-CH_3$).

Anal. Calcd for $C_{21}H_{22}OSn$: C, 61.65; H, 5.42. Found: C, 61.94; H, 5.34.

***threo*-3-(Triphenylstannyl)butan-2-ol.**—A solution of triphenyltin sodium was prepared in the usual manner from 38.5 g (0.10 mol) of triphenyltin chloride, 4.6 g (0.20 g-atom) of sodium metal, and 5.25 g (0.041 mol) of naphthalene in 125 ml of GDME. A solution of 7.2 g (0.10 mol) of *cis*-2,3-butylene oxide[20] in 25 ml of GDME was added slowly to the green solution of triphenyltin sodium. After addition the mixture was stirred for 6 hr, at which time a tan solution had developed. After work-up, 15.2 g (43.5%) of hexaphenylditin was recovered. The ether layer was evaporated and after two recrystallizations of the remaining solid from heptane, 9.76 g (23.2%) of *threo*-3-(triphenylstannyl)butan-2-ol was obtained: mp 88–89°; nmr (CCl_4) δ 7.3 (complex m, Ph_3Sn–), 3.91 [q, J = 6 cps, $-CH(OH)CH_3$], 1.9 [q, J = 7.5 cps, $SnCH(CH_3)-$], and 1.1 [d, J = 6 cps, $-CH(OH)CH_3$]; J = 3 cps for H_2–H_3.

Anal. Calcd for $C_{22}H_{24}OSn$: C, 62.45; H, 5.72. Found: C, 62.50; H, 5.53.

1-(Triphenylstannyl)-2-methylpropan-2-ol.—A solution of triphenyltin sodium was prepared in the usual manner from 38.5 g (0.10 mol) of triphenyltin chloride, 4.6 g (0.20 g-atom) of sodium metal, and 5.25 g (0.041 mol) of naphthalene in 125 ml of GDME. A solution of 7.2 g (0.10 mol) of isobutylene oxide in 25 ml of GDME was added slowly to the green solution of triphenyltin sodium. After addition the mixture was stirred for 18 hr, at which time a tan colored solution had developed. After work-up and recrystallization from heptane, 18.70 g (44.3%) of 1-(triphenylstannyl)-2-methylpropan-2-ol was obtained: mp 84–85°; nmr (CCl_4) δ 7.3 (complex m, Ph_3Sn–), 1.9 [s, $SnCH_2C(CH_3)_2PH$], and 1.3 [s, $-C(CH_3)_2OH$].

Anal. Calcd for $C_{22}H_{24}OSn$: C, 62.45; H, 5.72. Found: C, 62.62; H, 5.77.

2-(Triphenylplumbyl)ethanol.—A solution of 0.133 mol of triphenylplumbyllithium[21] was placed in an adding funnel and added to 8.8 g (0.20 mol) of ethylene oxide in 50 ml of GDME at −45°. After addition the solution was allowed to warm to room temperature. After the solution had been stirred for 1 hr, the contents of the flask were cooled to −45° and acetic acid was added dropwise until the solution was neutral to litmus paper. Cold water and diethyl ether were added, and the ether layer was separated, dried over sodium sulfate, and removed with the use of a rotary evaporator. The solid was recrystallized from heptane to yield 22.7 g (35.5%) of 2-(triphenylplumbyl)ethanol: mp 69–70° (lit.[21] mp 72°); nmr (CCl_4) δ 7.3 (complex m, Ph_3Pb–), 3.6 (t, $PbCH_2-$), and 1.7 (complex m, $-CH_2OH$).

1-(Triphenylplumbyl)propan-2-ol.—This compound was prepared in a similar manner as described above from 0.133 mol of triphenylplumbyllithium and 11.62 g (0.20 mol) of propylene oxide. After work-up and recrystallization from hexane, 29.05 g (44%) of 1-(triphenylplumbyl)propan-2-ol was obtained: mp 84–85° (lit.[21] mp 83–84°); nmr (CCl_4) δ 7.3 (complex m, Ph_3Pb–), 4.1 [complex m, $-CH_2CH(OH)-$], 1.7 (complex m, $PbCH_2-$), and 1.1 (d, $-CH_3$).

(20) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, **30**, 1271 (1965).

(21) L. C. Willemesens and G. J. M. van der Kerk, *J. Organometal. Chem.*, **4**, 34 (1965).

Kinetic Measurements.—The solvents used in the kinetic studies were carefully purified according to Weissberger's monograph on solvents.[22] Glacial acetic acid (Du Pont, reagent grade) was refluxed with potassium permanganate for 6 hr in order to oxidize any aldehydes present. The acid was then dried over and distilled from magnesium perchlorate at atmospheric pressure. Methanol (Baker analyzed reagent grade) was used as received. The amount of water in these solvents were determined by Karl Fisher titrations.[23] Perchloric acid (72%, Baker analyzed reagent grade) was used as supplied. The acid solutions used in the studies were prepared by adding the calculated amount of perchloric acid to the solvents used. Total acid concentration was determined by titrations according to Fritz's monograph on nonaqueous titrations.[24]

The alcohols were weighed into small 25-ml reaction flasks equipped with a side arm for connection to the gas-measuring buret and a rubber septum for injection of perchloric acid by use of a syringe. Then 10 ml of acetic acid–water or methanol–water was added by means of a calibrated pipet. The mixture was then placed in a 25.0° constant-temperature water bath, saturated with the appropriate alkene, and stirred for 10 min to establish thermal and gas–liquid equilibrium. The levels in the gas-measuring buret were adjusted to zero and the reaction was initiated by injecting 1 ml of perchloric acid of known concentration through the septum. The timer was started and volume readings were begun at once. The values were measured by moving the leveling bulb until the levels in the buret and the leveling bulb coincided. (For extremely fast reactions a tape recorder was used to record data. With this method reactions with half-lives between 5 sec and 2 hr could easily be followed.) Infinity volumes were determined by observing where the gas volume became constant, usually after 10 half-lives.

Product Analysis. A. Acetolysis of 2-(Triphenylstannyl)ethanol.—A sample of 0.2009 g (0.508 mmol) of 2-(triphenylstannyl)-ethanol was dissolved in 10 ml of glacial acetic acid at 25°, 1 ml of 0.066 *M* perchloric acid was added, and the solution was stirred for 2 hr. Ice–water and ether were added and the acid was neutralized by addition of sodium bicarbonate. The ether layer was separated and dried over sodium sulfate, then removed with a rotary evaporator to yield 0.188 g (90.5%) of triphenyltin acetate, mp 120–121° (lit.[25] mp 121–122°).

B. Methanolysis of 2-(Triphenylstannyl)ethanol.—A sample of 0.2009 g (0.508 mmol) of 2-(triphenylstannyl)ethanol was dissolved in 10 ml of 9 vol. % water in methanol, 1 ml of 0.992 *M* perchloric acid was added, and the solution was stirred for 2 hr. Ice–water and ether were added and the acid was neutralized by addition of sodium bicarbonate. The ether layer was separated and dried over sodium sulfate, then removed with a rotary evaporator to yield 0.172 g (92.5%) of triphenyltin hydroxide, mp 118–119° (lit.[25] mp 119°).

C. Acetolysis of *threo*-3-(Triphenylstannyl)butan-2-ol. Gas Product Analysis.—A sample of 0.200 g (0.473 mmol) of *threo*-3-(triphenylstannyl)butan-2-ol was dissolved in 10 ml of 18 vol. % water in methanol at 25°, 1 ml of 0.992 *M* perchloric acid was added, and the solution was stirred for 0.5 hr. The gas that evolved was analyzed by gas chromatography and found to be 100% *cis*-2-butene.

(22) A. Weissberger, E. S. Brokauer, J. A. Riddlick, and E. E. Toops, Jr., "Organic Solvents," 2nd ed, Interscience Publishers, New York, N. Y., 1955.

(23) H. A. Laitinen, "Chemical Analysis," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 421, and references cited therein.

(24) J. S. Fritz, "Acid-Base Titrations in Nonaqueous Solvents," G. Frederick Smith Chemical Co., Columbus, 1952.

(25) J. G. Noltes and G. J. M. van der Kerk, "Functionally Substituted Organotin Compounds," Institute for Organic Chemistry, T. N. O., Tin Research Institute (London), 1958.

Reactions of Organolithium Reagents with Siloxane Substrates

C. L. FRYE, R. M. SALINGER, F. W. G. FEARON,
J. M. KLOSOWSKI, AND T. DEYOUNG

Chemical Research Department, Dow Corning Corporation, Midland, Michigan 48640

Received October 2, 1969

A study of the reactions of organolithium reagents (RLi) with common siloxane substrates has led to the following findings (M = $Me_3SiO_{1/2}$ and D = $Me_2SiO_{2/2}$). (A) Diorganosiloxanes such as D_x are cleaved rapidly by RLi at ambient temperatures to yield lithium siloxanolates [*i.e.*, $R(Me_2SiO-)_xLi$], which are in turn completely consumed by additional RLi in an even faster series of alkylation reactions to yield the simple triorganosilanolate (*i.e.*, RMe_2SiOLi). Even when exceptionally reactive siloxane substrates such as D_3 are employed, the organolithium reagent exhibits exclusive preference for the derived siloxanolates; thus the combination of molar equivalents of BuLi and D_3 affords $BuMe_2SiOLi$ quantitatively, *none* of the presumed intermediate siloxanolate species (*e.g.*, $BuMe_2SiOMe_2SiOMe_2SiOLi$), and unreacted D_3 (*i.e.*, $^2/_3$ mol). Other cyclic and linear siloxanes react in a similar fashion. (B) Both neutral diorganosiloxanes and derived anionic siloxanolates are more reactive than Me_3SiCl toward RLi; hence, although reaction of BuLi with D_3 in the presence of Me_3SiCl did indeed afford the expected siloxanolate derivatives ($BuD_{1-3}SiMe_3$), *no* $BuSiMe_3$ was detected. (C) RMe_2SiOLi and RLi (R = Bu) are very unreactive with Me_3SiCl in the absence of ether. When ether is added to a hydrocarbon solution of these three reactants, RLi reacts much more rapidly than the silanolate. Siloxanolates, on the other hand, are more reactive than either of the above bases toward Me_3SiCl, reacting even in the absence of ethers. (D) Competition of various combinations of reactants for RLi has established the following order of relative reactivities: $D_3 > D_9 \cong MD_9M > D_4 >> MD_1M >>> MM$. Furthermore, the reactivity (relative to D_3) of MD_xM ($x \cong 10$–1000) increases with increasing values of x. This is because the relatively infrequent cleavages of MD_xM lead to increasingly larger amounts of RLi consumption by the resulting siloxanolate as the value of x increases. Thus this obviously ionic reaction exhibits certain characteristics of free-radical olefin polymerizations in that the concepts of *kinetic chain length* and *polymer chain length* become intimately related. (E) Displacement of methyl from $BuMe_2SiOLi$ by BuLi is rather facile, taking place in refluxing hexane to yield $Bu_2MeSiOLi$ and, upon longer treatment, Bu_3SiOLi. A similar displacement on a neutral substrate, MDM, was also observed and rationalized. (F) Although $Me_3SiOSiMe_3$ was not cleaved by lengthy reflux with BuLi, the more complicated trimethylsiloxy derivative $Si(OSiMe_3)_4$ did react. In this case initial slow attack on the peripheral triorganosilicon produces a siloxanolate which subsequently undergoes several rapid alkylations; thus $Si(OSiMe_3)_4$, reacts with BuLi to give $BuSiMe_3$ and $LiOSi(O\overset{*}{S}iMe_3)_3$, whereupon the latter species undergoes rapid alkylation to yield $Bu_3\overset{*}{S}iOLi$ and $3Me_3SiOLi$. (G) Several interesting metallation reactions were also observed. The most facile of these was the metalation of $Me_3SiOSiMe_2CH_2SiMe_3$ at the methylene site by *n*-BuLi in the absence of any of the common donor solvents. (H) Lithium triorganosilanolates react cleanly in a selectively stepwise fashion with suitable alkoxysilane substrates. Several examples are provided.

Although organometallic agents have been widely employed for the synthesis of carbon–silicon linkages in organosilicon chemistry,[1] their reactions with siloxane functionality have received relatively little attention.[2] Kipping and Hackford showed many years ago[2b] that the reaction of Grignard reagents with silsesquioxanes afforded triorganosilanols upon work-up. Similarly, Sauer[2c] prepared Me_3SiOH from the reaction of MeMgX with $(Me_2SiO)_x$. The above reaction generally required rather forcing conditions, *i.e.*, excess Grignard reagent and high temperatures (near 200°). Although organolithium reagents are much more reactive than are Grignard reagents toward siloxane substrates, the literature contains only a few scattered examples of their use. It was determined by Gilman and coworkers[2d] that the most electrophilic silicon of an unsymmetrical hexaorganodisiloxane underwent preferential alkylation. Seyferth[2e] demonstrated that, although unreactive in ether, MeLi did react quite readily with $Me_3SiOSiMe_3$ in the presence of tetrahydrofuran. Although this constituted a convenient route to Me_3SiOLi, the reaction of ethereal MeLi with dimethylsiloxane substrates was shown[2f] by Ruidisch and Schmidt to be an even better route, since it made more efficient use of the organolithium reagent (*i.e.*, no loss of Me_4Si).

We became interested in elucidating the chemistry of organolithium reagents with siloxane substrates, motivated at least in part by the knowledge that lithium bases are useful as catalysts for the highly selective polymerization of cyclotrisiloxanes[3] leading to novel nonequilibrium polymers.

Reactions of RLi with Dimethylsiloxy Substrates.—The reaction of 3 equiv of BuLi with hexamethylcyclotrisiloxane (*i.e.*, D_3, where D represents $Me_2SiO_{2/2}$) was found to proceed rapidly and exothermally in hydrocarbon media to yield $BuMe_2SiOLi$ (*i.e.*, BuD_1Li) (eq 1), paralleling the earlier work[2f] with ethereal MeLi.

$$3BuLi + (Me_2SiO)_3 \xrightarrow[\text{toluene}]{\text{hexane}} 3BuMe_2SiOLi \qquad (1)$$

In an attempt to prepare the linear trimeric siloxanolate species BuD_3Li, only 1 equiv of BuLi was added to D_3; much to our surprise an essentially quantitative conversion into the simple triorganosilanolate, BuD_1Li, resulted, accompanied by 66% of the unreacted starting trimer (eq 2). Completely analogous results were obtained in the reaction of BuLi with D_4. It is apparent that the neutral cyclosiloxane substrate undergoes a ring-opening alkylation in a rate-determining step followed by

$$BuLi + D_3 \xrightarrow[\text{toluene}]{\text{hexane}} BuMe_2SiOLi + {}^2/_3D_3 \qquad (2)$$

(1) C. Eaborn, "Organosilicon Compounds," Butterworth and Co. Ltd., London, 1960, pp 10–33.

(2) (a) Reference 1, pp 268–270; (b) F. S. Kipping and J. Hackford, *J. Chem. Soc.*, **99**, 138 (1911); (c) R. O. Sauer, *J. Amer. Chem. Soc.*, **66**, 1707 (1944); (d) H. Gilman, H. N. Benedict, and H. Hartzfeld, *J. Org. Chem.*, **19**, 419 (1954); (e) D. Seyferth and D. L. Alleston, *Inorg. Chem.*, **2**, 418 (1963); (f) I. Ruidisch and M. Schmidt, *Angew. Chem.*, **75**, 575 (1963).

(3) C. L. Lee, C. L. Frye, and O. K. Johannson, *Polymer Preprints*, **10** (2), 1361 (1969). (b) E. E. Bostick, U. S. Patent 3,337,496 (1967).

a very fast series of alkylations on the resulting linear siloxanolates (eq 3a–3c). The above rate relationships

$$\mathrm{BuLi} + \mathrm{D_3} \xrightarrow{k_1} \mathrm{BuD_3Li} \qquad (3a)$$

$$\mathrm{BuLi} + \mathrm{BuD_3Li} \xrightarrow{k_2} \mathrm{BuD_2Li} + \mathrm{BuD_1Li} \qquad (3b)$$

$$\mathrm{BuLi} + \mathrm{BuD_2Li} \xrightarrow{k_3} 2\mathrm{BuD_1Li} \qquad (3c)$$

$$k_1 \ll k_2 \text{ or } k_3$$

are reminiscent of those observed by Selin[4] (eq 4). It should be noted, however, that the Selin work in-

$$\mathrm{Me_3SiONa} + (\mathrm{Ph_2SiO})_4 \xrightarrow{k_1} \mathrm{Me_3SiO}\left[\mathrm{Ph_2SiO}\right]_4\mathrm{Na} \xrightarrow[k_2]{3\mathrm{Me_3SiONa}} \mathrm{Ph_2}\ 4\mathrm{Me_3SiOSiONa} \qquad (4)$$

$$k_1 \ll k_2$$

volved base-catalyzed siloxane redistribution, whereas in the above lithium systems *no* siloxane redistribution *per se* occurs. Thus the resulting silanolate, BuD_1Li, did not react with the remaining D_3 under the conditions employed (neither at room temperature nor in refluxing hexane). The reaction products in the present work were derivatized for subsequent isolation and analysis by hydrolyzing with dilute acid to give the silanols or by trimethylsilylating with ethereal Me_3SiCl. *Ether is necessary because the lithium triorganosilanolates will not react with Me_3SiCl in hydrocarbon media. Furthermore, even BuLi is very unreactive toward Me_3SiCl in the absence of donor solvents.*

The presumed siloxanolate intermediates, BuD_xLi, were trapped by adding BuLi to a mixture of D_3 with Me_3SiCl. Essentially the same product mixtures were obtained regardless of whether ether was present during or added subsequently to the BuLi addition. In either case, the major product was the simple triorganosilanolate derivative $BuMe_2SiOSiMe_3$ (*i.e.*, BuD_1SiMe_3) accompanied by much smaller amounts of BuD_3SiMe_3 (the trisiloxanolate derivative) and BuD_2SiMe_3 (the disiloxanolate derivative), and substantial amounts of unreacted D_3. Little or no $BuSiMe_3$ was formed, underscoring the low reactivity of BuLi toward Me_3SiCl (relative to its high reactivity toward D_3 and the resulting siloxanolates). The fact that BuD_3SiMe_3 and BuD_2SiMe_3 were formed prior to the addition of the ether shows the lithium siloxanolates to be highly reactive bases toward Me_3SiCl in marked contrast to BuLi or BuD_1Li. The relative reactivity of these last two species was determined. As shown below, the addition of 6BuLi (hexane solution) to a toluene solution of D_3 yields a solution containing $3BuD_1Li$ and 3BuLi. This was followed by the addition of $3Me_2SiCl$, which did not react (as evidenced by glpc monitoring) even when the solution was heated at reflux. The addition of a modest amount of ether caused the prompt and exclusive consumption of Me_3SiCl by the BuLi to form $3BuSiMe_3$. Subsequent addition of another $3Me_3SiCl$ produced the expected BuD_1SiMe_3. Thus, under these conditions, BuLi was clearly much more reactive than was BuD_1Li (eq 5). It was of some interest to

$$\mathrm{D_3} + 6\mathrm{BuLi} \xrightarrow[\text{hexane}]{\text{toluene}} 3\mathrm{BuD_1Li} + 3\mathrm{BuLi} \xrightarrow{3\mathrm{Me_3SiCl}} \text{no reaction} \xrightarrow{\text{ether}} \mathrm{BuD_1SiMe_3} \xrightarrow[3\,\mathrm{Me_3SiCl}]{} \mathrm{BuD_1Li} + 3\mathrm{BuSiMe_3} \qquad (5)$$

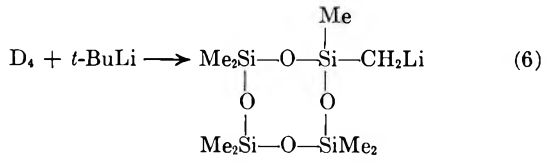
compete the relatively sluggish D_4 with Me_3SiCl for BuLi in the presence of added ether. Under these conditions, D_4 reacted sufficiently rapidly to compete very effectively for the organolithium reagent, the major product being BuD_1SiMe_3 accompanied by relatively small amounts of $BuSiMe_3$ and $BuD_{2-4}SiMe_3$, and unreacted D_4. The fact that relatively little $BuSiMe_3$ was formed indicates that, even in ether, Me_3SiCl is less reactive than D_4 toward BuLi. Ether evidently accelerates the reactivity of D_4, as well as that of Me_3SiCl, toward BuLi. Increasing the Me_3SiCl to D_4 ratio beyond the above 1:1 value did, of course, produce larger amounts of $BuD_{2-4}SiMe_3$ and $BuSiMe_3$ and correspondingly decreased amounts of BuD_1SiMe_3.

Competition of various combinations of dimethylsiloxane reactants for BuLi revealed the following qualitative order of relative reactivities (M represents $Me_3SiO_{1/2}$): $D_3 > D_9 \cong MD_9M > D_4 >> MD_1M >>> MM$. In this series, D_3 is so much more reactive than D_4 that the addition of 1 equiv of BuLi to a solution containing 1 molar equiv of these two cyclics results in completely selective consumption of the trimer. At the other end of the series, hexamethyldisiloxane is so unreactive that it undergoes no reaction even when heated for several days at reflux with BuLi in hexane solution. The reactivity (relative to D_3) of the linear siloxanes, MD_xM (x = 10–1000), *appears* to become greater with increasing chain length. We will discuss this phenomenon more fully at a later point (*vide infra*).

Other organolithium reagents react in more or less the same fashion with D_3 and related materials. The product distribution was not much affected by the presence of ether in those instances wherein ethereal organolithium reagents were employed (*i.e.*, MeLi and PhLi). Because of its increased steric requirements, it had been anticipated that *t*-BuLi might not be very reactive toward cyclosiloxanes. On the contrary, *t*-BuLi reacted exothermally with D_3 and the use of 3*t*-BuLi per D_3 resulted in essentially quantitative conversion into *t*-$BuMe_2SiOLi$. Experiments in which only 1*t*-BuLi per D_3 was added revealed that the siloxanolate alkylation reaction was not as rapid relative to ring opening as in the earlier *n*-BuLi examples. Thus, even in the absence of Me_3SiCl as a trapping agent, the expected product *t*-BuD_1Li (and unreacted D_3) was accompanied by substantial amounts of *t*-BuD_2Li and *t*-BuD_3Li. It is certainly to be expected that steric crowding should decrease the relative rates of siloxanolate alkylations, and especially the one involving *t*-BuLi and the disiloxanolate *t*-BuD_2Li, since in this case juxtaposition of bulky *t*-butyl groups on immediately adjacent silicon sites is necessarily involved. This rationale accords well with the observation that the above reaction

(4) T. G. Selin, Abstracts, Third International Symposium on Organometallic Chemistry, Munich, 1967, p 362.

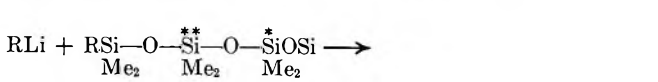
yielded mostly *t*-BuD_1Li and *t*-BuD_2Li but very little *t*-BuD_3Li. Very similar results were obtained from the reaction of *t*-BuLi with D_4; *i.e.*, in addition to unreacted D_4, one obtains substantial amounts of *t*-BuD_1Li and *t*-BuD_2Bi but almost no *t*-BuD_3Li or *t*-BuD_4Li. This reaction was further complicated by a competing D_4 metallation reaction leading to the formation of an unusually unreactive organometallic species (eq 6).



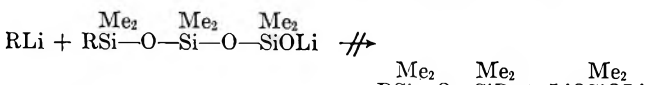
(6)

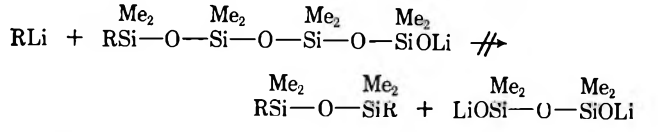
This species was characterized after a 24-hr reaction period as its Me_3SiCl derivative; it is remarkable that this organolithium persisted for so long in the presence of appreciable amounts of dimethylsiloxy material.

No attempt has been made thus far in this paper to rationalize the marked increase of reactivity of siloxanes toward organolithium reagents upon siloxanolate formation. One might have predicted the opposite effect, anticipating that the formal negative charge of the siloxanolate would discourage attack by the nucleophilic organometallic species. Apparently, this is more than offset by other factors. The heightened reactivity of the siloxanolates is presumably related to the tendency of dipolar materials to associate in nonpolar media; *i.e.*, the charged siloxanolate species presumably are more able to associate with, or gain entry to, the organolithium micelles, thereby facilitating reaction. It has not yet been unequivocally determined which particular silicon site in a given siloxanolate undergoes preferential alkylation. Our present observations are not inconsistent with a scheme involving preferential attack on the end silicon (eq 7). Certainly, this is necessarily true in the reaction of RLi with the disiloxanolate, although it should be recognized that in the case of higher siloxanolates, attack at other silicon sites could lead to the same products. One mode of attack singularly absent throughout this work is that involving siloxane cleavage to yield a hexaorganodisiloxane; *i.e.*, processes of the following type do not appear to occur readily on siloxanolate substrates.

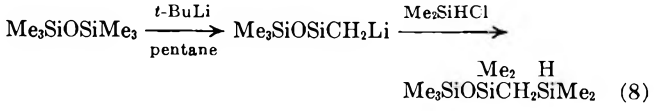


(7)





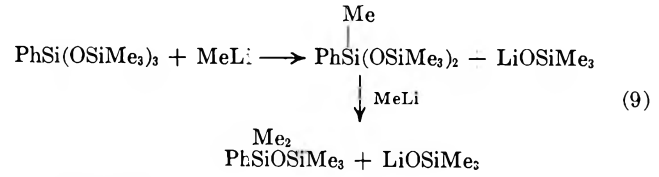
Reactions with Other Siloxanes.—Although attention has been directed mainly at various dimethylsiloxane substrates, several other types have also been examined. Other diorganosiloxanes such as $(PhMeSiO)_x$ and $[F_3CCH_2CH_2(Me)SiO]_x$ react with organolithium reagents more or less analogously to $(Me_2SiO)_x$. As noted previously herein, hexaalkyldisiloxanes are not cleaved by BuLi in hydrocarbon media nor by ethereal MeLi. As anticipated, *t*-BuLi also did not cleave $Me_3SiOSiMe_3$; however, it did unexpectedly afford the metallated derivative $Me_3SiOSiMe_2CH_2Li$ in good yield under unprecedentedly mild conditions, *i.e.*, at room temperature and in the absence of a donor solvent.[5] To establish unequivocally that the above derivative had not undergone rearrangement to the isomeric disilmethylene species, the Me_2SiHCl derivative was prepared (eq 8). The nmr spectrum of this



(8)

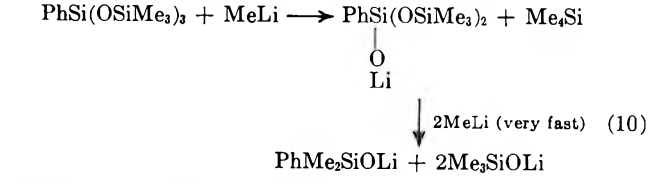
product revealed the expected CH_2 doublet arising from coupling with the immediately adjacent SiH moiety, thus confirming the assignment.

Trimethylsiloxylated substrates, in addition to those already cited, which have been reacted with organolithium reagents include $PhSi(OSiMe_3)_3$ and $Si(OSiMe_3)_4$. The first of these two substrates undergoes two types of reaction. One involves alkylation of the most electrophilic silicon center, *i.e.*, the Ph–Si site (eq 9).



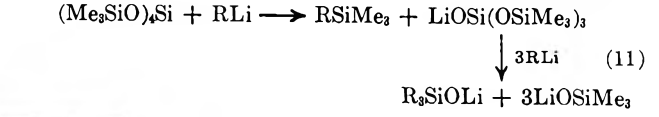
(9)

$PhMeSi(OSiMe_3)_2$ was shown to be *ca.* 5.5 times as reactive as $PhSi(OSiMe_3)_3$, presumably as a consequence of decreased steric hindrance about the central silicon site. A competing process involves initial alkylation at one of the peripheral Me_3Si sites, generating a tetraorganosilane and a siloxanolate which then undergoes two very rapid subsequent alkylations to yield the expected silanolates (eq 10). In addition to identifying



(10)

Me_4Si in the ether distillate, treatment of the reaction product with Me_2SiHCl yielded the expected derivative, $PhMe_2SiOSiHMe_2$ (as well as $Me_3SiOSiHMe_2$). The resulting glpc peak area ratio of $1PhMe_2SiOSiMe_2H/2.8PhMe_2SiOSiMe_3$ shows the reaction involving alkylation of a peripheral Me_3SiO- group to be an important factor. The compound $Si(OSiMe_3)_4$ appears to undergo exclusively this latter mode of reaction, *i.e.*, initial attack on a peripheral Me_3SiO- unit followed by successive rapid alkylation of the resulting siloxanolate (eq 11). The species $RSiMe_3$ was the *only* volatile species



(11)

(5) Metalations of this and related substrates in tetramethylethylenediamine were reported: G. A. Gornowicz and R. West, *J. Amer. Chem. Soc.*, **90**, 4478 (1968).

observed as the reaction proceeded. It is interesting to note that these tris- and tetrakistrimethylsiloxy compounds do not appear to undergo any detectable alkyl exchange of the type observed with the bistrimethylsiloxy derivative, MDM (*vide infra*). Perhaps the additional steric requirements of the bulky Me_3SiO– substituent preclude the formation of the suggested type of organolithium–siloxane intermediate.

Competition of D_3 *vs.* Alkoxysilane Substrates for Organolithium Reagents.—The relative reactivity of alkoxysilane substrates toward BuLi has also been briefly examined: D_3 was allowed to compete for BuLi *vs.* Me_3SiOMe, $Me_2Si(OMe)_2$, and $MeSi(OMe)_3$; Me_3SiOMe was wholly unreactive in hydrocarbon media toward both BuLi and $BuMe_2SiOLi$. Very similar results were obtained using ethereal MeLi (eq 12).

$$\mathrm{RLi} + \mathrm{D_3} + \mathrm{Me_3SiOMe} \longrightarrow 2/3\mathrm{D_3} + \mathrm{Me_3SiOMe} + \mathrm{RD_1Li} \longrightarrow \text{no reaction (}i.e.\text{, } Me_2RSiOSiMe_3 \text{ and LiOMe were } not \text{ formed)} \quad (12)$$

However, the more functional alkoxysilanes, $Me_2Si(OMe)_2$ and $MeSi(OMe)_3$, reacted with BuLi at rates comparable with that of D_3. Thus, while some of the BuLi was intercepted by $Me_2Si(OMe)_2$ to give $BuMe_2SiOMe$ (B), most of it reacted with D_3 to give $BuMe_2SiOLi$, which then attacked $Me_2Si(OMe)_2$ to give $BuMe_2SiOSiMe_2OMe$ (A); glpc peak area comparison showed *ca.* a 2:1 ratio of A to B (eq 13). An

$$\mathrm{BuLi} + \mathrm{D_3} + \mathrm{Me_2Si(OMe)_2} \longrightarrow \sim 3/4\,\mathrm{D_3} + \mathrm{BuMe_2SiOSi(Me)OMe\ (A)} + \mathrm{BuMe_2SiOMe\ (B)} \quad (13)$$
$$\mathrm{A/B} \cong 2{:}1$$

analogous competition reaction employing $MeSi(OMe)_3$ produced similar results. Part of the BuLi reacted directly with the $MeSi(OMe)_3$ to give $BuMeSi(OMe)_2$ (and a little $Bu_2MeSiOMe$), but a substantial portion of the BuLi was consumed by the D_3 to yield BuD_1Li, which then coupled with the di- and trimethoxysilanes in the system to give $BuMe_2SiOSiMe(OMe)_2$ (a major product) and $BuMe_2SiOSiBuMeOMe$.

The implications of the above competition reactions were tested by treating individual alkoxysilanes with $BuMe_2SiOLi$ (Scheme I).

It is interesting that lithium silanolates (and presumably the siloxanolates) attack alkoxysilanes such as $MeSi(OMe)_3$ and $Me_2Si(OMe)_2$ employing conditions under which siloxanes as reactive as D_3 are unaffected.

Reactivity of D_3 Relative to Longer Chain Polydimethylsiloxanes.—Because of the increased reactivity of lithium siloxanolates toward BuLi, it was anticipated that hydroxy end blocked polydimethylsiloxanes (HOD_zH) would be more reactive than the analogous trimethylsiloxy end blocked materials (MD_zM). Our initial attempts to demonstrate this were, however, rather confusing. Thus the hydroxy end blocked polymer ($HOD_{270}H$) was indeed much more reactive toward BuLi than was D_3 in hydrocarbon solution. However, a comparable MD_zM material was also much more reactive than D_3 when these two substrates were allowed to compete for BuLi in hydrocarbon solution. Suspecting silanol impurities in the MD_zM, we treated it with $(Me_3Si)_2NH$ in order to trimethylsiloxylate any such silanolic site. Subsequent competition with D_3 for BuLi did indeed then show a reactivity reversal, but *not because of our endblocking effort; i.e.*, this latter competition for BuLi was run in the presence of ether, and we were eventually able to demonstrate a rather profound solvent effect on the relative reactivities of siloxane substrates toward BuLi. In hydrocarbon media, polydimethylsiloxanes of sufficient length react much faster with BuLi than does D_3, regardless of the nature of the end-blocking moiety. In reaction media containing moderate amounts of donor solvents such as Et_2O, these same long-chain siloxanes react much more slowly with BuLi than does D_3. One should *not* conclude that linear siloxanes are less reactive in ether media; quite the opposite is true, *i.e.*, *all* of these siloxanes react faster in the presence of ether, but the reactivity of D_3 is increased to a much greater extent. These differences are possibly related to the ability of linear siloxanes to solvate intramolecularly the reactive sites in the absence of donor solvents; *i.e.*, a siloxane moiety, a few units removed from the site of attack, may be able to assume a position in which its oxygen can somehow coordinate with the BuLi as it cleaves a neighboring siloxane bond. Such coordination would be exceedingly unlikely in a rather rigid cyclic structure such as D_3. This advantage is removed when ether is added, and the greater reactivity inherent in the strained D_3 is then manifested.

One might still wonder why the hydroxy and Me_3SiO end blocked materials were of comparable reactivity. This is just another illustration of the relative unimportance of end group functionality at sufficiently high degree of polymerization (DP). The reaction of BuLi with neutral linear siloxanes, although relatively slow, becomes increasingly competitive with the siloxanolate reaction as the DP of the substrate is increased. When the chain is long enough, the nature of the end group becomes completely irrelevant to the rate of BuLi consumption. Below this limit, it also is to be

SCHEME I

$Me_3SiOMe + BuMe_2SiOLi \xrightarrow[\text{room temperature}]{\text{hexane–toluene}}$ no reaction after 4 days

$Me_2Si(OMe)_2 + BuMe_2SiOLi \xrightarrow[\text{toluene}]{\text{hexane–}} BuMe_2SiOSiMe_2OMe$ (after 10 min at room temperature)

$\xrightarrow{\text{added } 1\,BuMe_2SiOLi}$ no additional reaction after 1 day at 70°

$MeSi(OMe)_3 + BuMe_2SiOLi \xrightarrow[\text{toluene}]{\text{hexane–}} BuMe_2SiOSiMe(OMe)_2$ (formed *very* rapidly at room temperature)

$\xrightarrow{1\,BuMe_2SiOLi} (BuMe_2SiO)_2SiMeOMe$ (after 4 days at room temperature)

$\xrightarrow{1\,BuMe_2SiOLi} (BuMe_2SiO)_3SiMe$ (did not form even after several days at reflux)

expected that a linear series, MD_xM, should consume BuLi at rates proportional to their molecular weights.

Confirmation is provided by the following tabulation (Table I), which shows the results of treating a series of D_3–MD_xM solutions (hydrocarbon) with enough BuLi to react with exactly 50% of the available D units (the average DP for these fluids ranges from *ca.* 15 for the 10-cSt fluid to *ca.* 1300 for the 60,000-cSt fluid). It is evident that the relative reactivity of the MD_xM not only is increasing substantially with increasing molecular weight, but that it is also leveling out, as indeed it should when the chain length becomes so long that the ends are again irrelevant.

TABLE I

MD_xM, viscosity at 77° F, cSt	Unreacted D_3, %
10	24
100	48
1,000	60
12,500	72
60,000	75

These results are consistent with a reaction scheme involving rupture of a siloxane bond in a relatively very slow initial step followed by a series of very fast subsequent alkylations (eq 14).

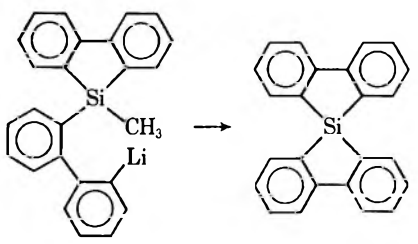
$$MD_xM + RLi \xrightarrow{\text{slow}} MD_{x/2}R + LiD_{x/2}M$$
$$\downarrow (x/2 - 1)RLi \quad (14)$$
$$(x/2 - 1)RDLi + LiM$$

For purposes of illustration, we have arbitrarily ruptured the chain right in the middle. Now it is apparent that as x (the polymer DP) increases, the amount of RLi consumed per initial rupture should also increase. If this picture is correct, then this obviously ionic reaction exhibits kinetics reminiscent of free-radical olefin polymerizations in which the ordinarily independent concepts of *polymer* chain length and *kinetic* chain length become closely related.

Displacement of Methyl from Silicon by Organolithium Reagents.—As noted above, D_4 is much less reactive toward BuLi than is D_3; consequently, reflux conditions were generally employed to shorten the reaction time. It was observed that under these conditions the principal product of the BuLi–D_4 reaction (*i.e.*, BuD_1Li) was accompanied by small amounts of an additional product, which was eventually identified as $Bu_2MeSiOLi$ (characterized *via* hydrolysis as the silanol or *via* trapping with Me_3SiCl as $Bu_2MeSiOSiMe_3$). The reaction of D_4 with *n*-BuLi is sufficiently slow that the main product, $BuMe_2SiOLi$, is exposed for a longer time to BuLi, and under these conditions (reflux temperature *ca.* 70°) the following competitive reaction apparently occurs (eq 15).

$$BuLi + BuMe_2SiOLi \longrightarrow MeLi + Bu_2MeSiOLi \quad (15)$$

The suggested sequence of events was confirmed by treating D_3 with 6 equiv of BuLi, which rapidly results in a hydrocarbon solution containing $3BuMe_2SiOLi$ and 3BuLi. Upon heating at reflux for 1 day, most of the silanolate was converted into $Bu_2MeSiOLi$. The formation of MeLi was established *via* trapping with $PhMe_2SiCl$, which afforded the anticipated $PhMe_3Si$. In a similar run employing 9BuLi, 1-week reflux resulted in almost complete conversion into Bu_3SiOLi. Displacement of the methyl substituent from silicon by organometallic species has been observed previously only in certain cyclization reactions where entropy considerations were presumably very favorable, *e.g.*,[6] eq 16. The driving force in the present



+ MeLi (16)

example is possibly the formation of the more stable methyl carbanion.[7] Since similar results were obtained in ether, the insolubility of MeLi in hydrocarbon media is not a relevant factor.

In addition to the above methyl displacement from the anionic siloxanolate species, we also observed an interesting methyl displacement from a neutral siloxane substrate. Methyl displacement of this type has no precedent and can apparently be observed only under certain favorable conditions, as noted more fully below. Having determined that $Me_3SiOSiMe_3$ did not react to any detectable extent upon refluxing for several days with BuLi in a hydrocarbon solvent, it was of interest to examine the reactivity of $Me_3SiOSi(Me_2)OSiMe_3$ (MDM) toward BuLi. Although this substrate is much less susceptible than D_4 to siloxane cleavage by BuLi in hydrocarbon media, it does slowly undergo the following siloxane cleavage reaction (eq 17).

$$Me_3SiO\overset{Me_2}{Si}OSiMe_3 + BuLi \xrightarrow[\text{temperature}]{\text{room}} Me_3SiOLi + BuMe_2SiOSiMe_3 \quad (17)$$
(*i.e.*, BuD_1M)

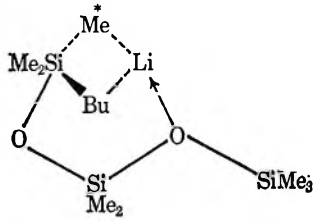
Under these conditions, however, *most* of the MDM substrate is consumed by the following novel alkyl exchange process (eq 18).

$$Me_3SiO\overset{Me_2}{Si}OSiMe_3 + BuLi \longrightarrow BuMe_2SiO\overset{Me_2}{Si}OSiMe_3 + MeLi \quad (18)$$
(*i.e.*, BuD_2M)

The product, BuD_2M, was unequivocally identified by spectral methods and independent synthesis; the presence of MeLi was confirmed by appropriate derivatization (*i.e.*, $PhMe_2SiCl \rightarrow PhMe_3Si$). Examination of the product mixture by vapor phase chromatography also revealed the gradual formation of a pair of dibutylated linear trimers believed to be $Bu_2MeSiOSiMe_2OSiMe_3$ and $BuMe_2SiOSiMe_2OSiMe_2Bu$; the structure of the latter member of this pair was confirmed by independent synthesis. These unusual exchange reactions are believed to be facilitated by anchimeric assistance

(6) H. Gilman and R. D. Gorsich, *J. Amer. Chem. Soc.*, **80**, 3243 (1958).
(7) R. M. Salinger and R. E. Dessy, *Tetrahedron Lett.*, 729 (1963).

of a strategically situated siloxane oxygen moiety as shown schematically (I). It was anticipated that



I

similar exchanges on the next higher homolog, MD_2M, would be precluded by a facile competing siloxane cleavage reaction, since in this case the leaving group (asterisked) in I could be the siloxy moiety, Me_3SiO–. Although this type of siloxane cleavage did indeed occur, the alkyl exchange reaction *was* competitive, as evidenced by the presence of substantial amounts of BuD_3M in the reaction product. In the presence of increasing amounts of ether, siloxane cleavage of MDM predominated over alkyl exchange, as shown by the indicated relative yields of BuD_2M and BuD_1M (eq 19).

$$\text{BuLi} + \text{MDM} \longrightarrow \underset{\text{(alkyl exchange)}}{\text{BuD}_2\text{M}} + \underset{\text{(SiOSi cleavage)}}{\text{BuD}_1\text{M}} \qquad (19)$$

No ether	5·5	1
1 ether/1BuLi	0·9	1
10 ether/1BuLi	0·4	1

This trend is consistent with the above scheme involving anchimeric assistance; *i.e.*, the organolithium reagent would presumably be coordinated by ether in preference to MDM, and there would then be much less tendency for the organolithium to be held in such a way as to favor alkyl exchange over siloxane cleavage.

The possibility that BuD_2M might have arisen from some combination of siloxane cleavage, butylation of silanolate, and siloxane–silanolate redistribution was also considered; *i.e.*, the following sequence could conceivably have produced BuD_2M (eq 20a–20c).

$$\text{BuLi} + \text{MDM} \longrightarrow \text{BuD}_1\text{M} + \text{LiOSiMe}_3 \qquad (20a)$$

$$\text{BuLi} + \text{LiOSiMe}_3 \longrightarrow \text{BuMe}_2\text{SiOLi} + \text{MeLi} \qquad (20b)$$

$$\text{BuMe}_2\text{SiOLi} + \text{MDM} \not\longrightarrow \underset{\text{(}i.e.\text{, BuD}_2\text{M)}}{\text{BuMe}_2\text{SiO}\overset{\text{Me}_2}{\text{SiOSiMe}_3}} + \text{Me}_3\text{SiOLi} \qquad (20c)$$

This possibility was disposed of, however, by demonstrating in a separate experiment that $BuMe_2SiOLi$ underwent no detectable reaction with MDM after 1 week at reflux.

From a consideration of the above schematic (I), it seemed not unreasonable to expect a similar facile alkyl exchange to occur on the closely related substrate $Me_3SiCH_2SiMe_2OSiMe_3$. However, much to our surprise, this compound underwent extremely facile metalation at the methylene site (eq 21).

$$\text{Me}_3\text{SiCH}_2\text{SiMe}_2\text{OSiMe}_3 + n\text{-BuLi} \xrightarrow{\text{hexane}} \underset{\text{Li}}{\text{Me}_3\text{SiCHSiMe}_2\text{OSiMe}_3} \xrightarrow[\text{ether}]{\text{Me}_3\text{SiCl}} (\text{Me}_3\text{Si})_2\text{CHSiMe}_2\text{OSiMe}_3 \qquad (21)$$

Capping the metalated species with Me_3SiCl afforded the expected derivative, which showed the expected nmr proton ratio ($SiCH_3$, 33; Si_3CH, 1).

Experimental Section

General.—Reactions were performed under dry nitrogen atmosphere and the organometallic reagents were transferred *via* syringe techniques. Organolithium reagents were purchased from commercial sources and used as received; the butyllithium was 1.6 *M* in hexane, the *t*-BuLi was 1.24 *M* in pentane, and the MeLi was 1.67 *M* in ether. The siloxane substrates were commercially available and were shown to be reasonably pure by glpc prior to use.

The organolithium–siloxane reactions were followed by periodic removal of aliquots *via* syringe, which were then subjected to glpc analysis. Although these aliquots were sometimes examined directly, they were usually first treated with water (to convert ≡SiOLi into ≡SiOH) or ethereal R_3SiCl (to convert ≡SiOLi into ≡$SiOSiR_3$). The glpc analysis generally involved the use of internal standards. In the absence of suitable standards, the fractions in question were isolated by distillation or preparative glpc and characterized by appropriate elemental and spectral analysis. Not every observation described in the above discussion of our results has been detailed in the following examples, which have been selected mainly to illustrate the methods employed.

Reactions of BuLi with D_3. A. 1BuLi/1D_3.—Butyllithium (31 ml, 0.050 mol) in hexane was added to a toluene solution (50% by weight) of D_3 (11.1 g, 0.050 mol), resulting in an exothermic reaction. Analysis by glpc indicated that *ca.* 1/3 of the D_3 had been consumed. The reaction mixture was then heated at reflux for a period of 2 hr, whereupon glpc analysis revealed no additional consumption of D_3. Trimethylchlorosilane (6.3 ml, 0.050 mol) was then added along with a small quantity (15 ml) of ether. Subsequent experience showed that this was not enough ether to cause rapid reaction with Me_3SiCl. After refluxing for several hours, reaction of the Me_3SiCl was substantially complete. The reaction mixture was then filtered and distilled to yield 6.3 g (65% yield) of $BuMe_2SiOSiMe_3$: bp 80° (45 mm); nmr τ 9.95 ($SiMe_3$), 9.97 ($SiMe_2$), 9.3–9.7 ($SiCH_2$), 9.10 (CCH_3), and 8.45–8.85 (CCH_2). The proper intensity ratio of 9 (H_{Bu}):15 (H_{MeSi}) was observed.

Anal. Calcd for $C_9H_{24}Si_2O$: C, 52.9; H, 11.83; Si, 27.46. Found: C, 53.1; H, 11.85; Si, 26.51.

B. 3BuLi/1D_3.—Butyllithium (93 ml, 0.15 mol) in hexane was added (exothermic) to a toluene solution (50% by weight) of D_3 (11.1 g, 0.05 mol); immediately subsequent glpc analysis indicated complete consumption of D_3. When the reaction mixture cooled to room temperature, 50 ml of water was added; separation of the resulting organic layer followed by distillation afforded 16.2 g (82% yield) of $BuMe_2SiOH$, bp 85° (50 mm). The presence of silanol functionality was confirmed by a strong infrared absorption at 3 μ. The nmr spectrum was also consistent with the assigned structure, having absorptions at τ 4.89 (SiOH), 8.6–9.4 (SiBu), and 9.95–9.97 (SiMe), with a proton ratio of 0.9 (H_{OH}):8.9 (H_{Bu}):6 (H_{Me}) (theory 1:9:6). The compound was not obtained analytically pure.

1BuLi/1D_3/1Me_3SiCl.—The addition of butyllithium (0.050 mol) to a solution of D_3 (0.050 mol) and Me_3SiCl (0.050 mol) in toluene (13 ml) produced an exotherm; glpc analysis of a hydrolyzed aliquot showed that *ca.* 50% of the D_3 had been consumed, a large peak attributable to $BuMe_2SiOH$ (*no* $BuMe_2SiOSiMe_3$, since BuD_1Li does not couple readily with Me_3SiCl in the absence of ether), and a moderate-sized peak attributable to BuD_3SiMe_3. A small amount of ether (25 ml) was then added and the reaction mixture was refluxed for several hours, during which time periodic glpc analysis revealed the appearance and gradual increase of $BuMe_2SiOSiMe_3$; no further change in the D_3 or BuD_3SiMe_3 peaks was noted. The glpc peak area ratios for the pertinent species in the final reaction mixture were *ca.* 8D_3:7BuD_1SiMe_3:1BuD_2Me_3:4BuD_3SiMe_3. Distillation afforded *ca.* a 20% yield of BuD_3SiMe_3: bp 147° (50 mm); nmr τ 8.65–9.91 (Si-*n*-Bu) and 9.93–9.95 (SiMe), with a proton ratio of 9.3 (H_{Bu}):267 (H_{Me}) (theory 9:27).

Anal. Calcd for $C_{13}H_{36}Si_4O_3$: C, 44.3; H, 10.31; S, 31.82; mol wt, 352. Found: C, 44.7; H, 10.26; Si, 31.25; mol wt, 337 (vapor phase osmometry).

Very similar results were obtained when ether was present *during* the addition of the BuLi to the D_3–MeSiCl solution. It was also observed that by increasing the proportion of Me_3SiCl, a larger fraction of the BuD_3Li was converted into BuD_3SiMe_3, as evidenced by glpc analysis. In all cases, the amount of BuD_2SiMe_3 formed was much smaller than that of BuD_3SiMe_3. This suggests that BuD_2Li may be much less reactive than BuD_3Li toward Me_3SiCl. The addition of BuLi to D_4–Me_3SiCl solutions containing ether yielded similar results in that the BuD_1SiMe_3 was the major product. However, the $BuD_{2-4}SiMe_3$ peaks, while definitely of minor proportions, differed somewhat from the above D_3 reaction in that they were all of approximately the same size; *i.e.*, the BuD_3SiMe to BuD_2SiMe_3 glpc peak area ratio was *ca.* 1 rather than *ca.* 4 as in the above example. This may suggest that BuD_4Li undergoes preferential attack on the penultimate D site. Alternatively, this variation in product ratios may merely be an artifact of variations in reaction procedure; *i.e.*, the effective instantaneous Me_3SiCl to BuLi ratio presumably will determine the extent to which the various intermediate siloxanolates are trapped or cleaved.

Reaction of Alkyllithium Compounds with D_4. A. D_4 + *n*-BuLi.—A solution of *n*-BuLi in hexane (31 ml, 0.050 mol) was added dropwise to a solution of D_4 (14.8 g, 0.050 mol) in toluene (10 ml). A mildly exothermic reaction occurred which consumed 25% of the original D_4 within 15 min. After 2 hr the mixture was treated with Me_3SiCl (0.060 mol) in ether (25 ml) to give $BuMe_2SiOSiMe_3$, bp 81° (50 mm), yield 8.85 g (87%).

B. D_4 + *t*-BuLi.—A solution of *t*-BuLi (0.050 mol) in pentane was added to a solution of D_4 (14.8 g, 0.050 mol) in toluene. After 24 hr at ambient temperature, the reaction mixture was treated with a solution of Me_3SiCl (0.060 mol) in ether (25 ml). After the vigorous reaction had subsided, the mixture was found (by glpc) to contain three major products, two of which were identified as *t*-$BuMe_2SiOSiMe_3$ and *t*-$Bu(Me_2SiO)_2SiMe_3$ by glpc (using internal standards) and by their mass spectra. The mixture was filtered and the filtrate was fractionally distilled to obtain a portion considerably enriched in the unidentified material, which was then isolated by preparative glpc ($n^{20}D$ 1.4270) and identified as II on the basis of the following analytical data.

$$\begin{array}{c} Me_3SiCH_2MeSiOSiMe_2 \\ O \quad O \\ Me_2SiOSiMe_2 \\ \text{II} \end{array}$$

(A) The mass spectrum gave a molecular weight of 368 (theory 368), a loss of a Me group at *m/e* 353, and a loss of Me_4Si from the *m/e* 353 peak at *m/e* 265.

(B) The infrared spectrum showed absorptions at 835 (Me_3Si) and 1355 cm^{-1} ($-SiCH_2-$).

(C) The nmr spectrum showed absorptions at τ 9.92–9.97 (SiMe) and 10.19 ($SiCH_2$) with a proton ratio of 29.8 (H_{SiMe}): 2.2 (H_{SiCH_2}) (theory 30:2).

When a similar reaction mixture was treated with deuterium oxide instead of Me_3SiCl, the recovered $(Me_2SiO)_4$ was shown by mass spectroscopy to contain appreciable amounts of the expected monodeuterio derivative.

Alkyl Exchange Reactions. A. Silanolate Substrate.—Butyllithium (0.200 mol) was added to D_3 (7.4 g, 0.033 mol) dissolved in an equal weight of toluene. The reaction mixture was heated at reflux after the initial exothermic reaction subsided. After 2 hr the formation of a white precipitate (presumably MeLi) was noted. Small samples of the reaction mixture were taken at intervals and hydrolyzed by the addition of a little water; glpc analysis of these hydrolyzed aliquots showed the presence of a peak assigned to $Bu_2MeSiOH$ which grew at the expense of the $BuMe_2SiOH$ peak. After the mixture had been refluxed overnight, glpc analysis of a hydrolyzed aliquot showed the presence of mainly $Bu_2MeSiOH$ and minor amounts of $BuMe_2SiOH$ and Bu_3SiOH. The assignment of these two new peaks was confirmed by internal standards, employing authentic $Bu_2MeSiOH$ and Bu_3SiOH prepared by the hydrolysis of the monochlorosilanes obtained from the reaction of BuLi with $MeSiCl_3$ and $SiCl_4$, respectively. To confirm the presence of MeLi in the above reaction product, $PhMe_2SiCl$ (0.200 mol) and ether (50 ml) were added. The reaction mixture was then stirred for 30 min, washed with water, and distilled to afford $PhSiMe_3$ (63% yield), which was identified by glpc analysis using an authentic sample as internal standard. The use of larger amounts of BuLi and longer reflux times resulted in the gradual consumption of $Bu_2MeSiOLi$ and the formation of Bu_3SiOLi.

B. A Neutral Siloxane Substrate, MDM.—A mixture of 11.8 g (0.050 mol) of MDM and 31 ml (0.050 mol) of *n*-BuLi in hexane was stirred for 48 hr at ambient temperature. The mixture, which contained some precipitated solids, was treated with a solution of $PhMe_2SiCl$ (9.4 g, 0.055 mol) in ether (15 ml). When the exothermic reaction was complete, the following major components were identified in the reaction mixture by tandem glpc–mass spectroscopic analysis: MDM, *n*-$BuMe_2SiOSiMe_3$, $PhSiMe_3$, *n*-$Bu(Me_2SiO)_3SiMe_3$, $PhMe_2SiOSiMe_3$, and *n*-$Bu(Me_2SiO)_3$-*n*-Bu.

Metalation of $Me_3SiOSiMe_3$ by *t*-BuLi.—A solution of *t*-BuLi in pentane (175 ml, 0.2 mol) was added to $Me_3SiOSiMe_3$ (100.6 g, 0.6 mol). The solution was stirred for 96 hr and then derivatized with Me_3SiCl (21.7 g, 0.2 mol) in the presence of ether (100 ml), filtered, and distilled to give $Me_3SiCH_2Me_2SiOSiMe_3$: yield 35 g (85.5%); bp 72–72.5° (15 mm); $n^{25}D$ 1.4110; nmr τ 9.93–9.97 (–SiMe) and 10.2 ($SiCH_2$) with a proton ratio of 24.3 (H_{SiMe}):1.7 (H_{SiCH_2}) (theory 24.0:2.0).

Anal. Calcd for $C_9H_{28}Si_3O$: C, 46.2; H, 11.1; Si, 35.9; mol wt, 234. Found: C, 46.2; H, 11.04; Si, 35.0; mol wt, 234.

A similar reaction mixture was derivatized with ethereal (100 ml) HMe_2SiCl (189 g, 0.2 mol) to give $HMe_2SiCH_2Me_2SiOSiMe_3$: yield 29.2 g (66%); bp 85–86° (55 mm); $n^{25}D$ 1.4215; nmr τ 6.03 (SiH), 9.90–9.94 (SiMe), and 10.16 (doublet, J_{CH_2-SiH} = 3.5 cps, $SiCH_2$) with a proton ratio of 0.9 (H_{SiH}): 21.3 (H_{SiMe}):1.8 (H_{SiCH_2}) (theory 1:21:2).

Anal. Calcd for $C_8H_{24}Si_3O$: C, 43.6; H, 10.8; mol wt, 220. Found: C, 44.0; H, 10.8; mol wt, 220 (mass spectrum).

***n*-BuLi Metalation of $Me_3SiCH_2Me_2SiOSiMe_3$.**—A solution of *n*-BuLi in hexane (32 ml, 0.05 mol) was added to $Me_3SiCH_2Me_2SiOSiMe_3$ (11.7 g, 0.05 mol). The solution was refluxed for 72 hr before Me_3SiCl (5.4 g, 0.05 mol) and THF (25 ml) were added to give a mixture of products containing one major component (53% by glpc) which was isolated by preparative glpc and identified as $(Me_3Si)_2CHMe_2SiOSiMe_3$: nmr τ 9.84–9.97 (SiMe) and 10.63 (SiCH) with a proton ratio of 33 (H_{SiMe}):1 (H_{SiCH}) (theory 33:1).

Anal. Calcd for $C_{12}H_{34}Si_4O$: mol wt, 306. Found: mol wt, 306 (mass spectrum).

Registry No.—$BuMe_2SiOSiMe_3$, 23667-12-1; $BuMe_2SiOH$, 23667-13-2; $Me_3SiCH_2MeSiOSiMe_2Me_2SiOSiMe_2$, 23667-14-3; $Me_3SiCH_2Me_2SiOSiMe_3$, 6231-63-6; $HMe_2SiCH_2Me_2SiOSiMe_3$, 23667-16-5; $(Me_3Si)_2CHMe_2SiOSiMe$, 23754-35-0.

Diels–Alder Reactions of 5-Substituted Naphthacenes

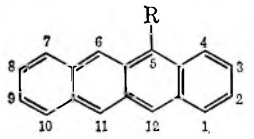
JOHN S. MEEK AND FRED M. DEWEY[1]

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received September 22, 1969

Diels–Alder reactions of 5-naphthacenealdehyde and 5-bromo-, 5-cyano-, and 5,12-diacetoxynaphthacene occur more readily at the 6,11 than at the 5,12 positions. The maleic anhydride adducts were thermally more stable than those of tetracyanoethylene, and the ethylene adduct of 5,12-diacetoxynaphthacene was quite stable. 5-Naphthacenealdehyde and allyl alcohol condensed at the 5,12 positions owing to acetal formation preceding an intramolecular Diels–Alder reaction. Photooxidation of 5,12-diacetoxynaphthacene occurred at its 6,11 positions to give the corresponding diacetoxyquinone.

Placing a substituent in the 5 position of naphthacene (1) results in a compound possessing two diene sys-



1

tems capable of reacting competitively with dienophiles. Condensation of such a compound with ethylene or tetracyanoethylene can lead theoretically to two different adducts, with maleic anhydride to four, and with allyl alcohol to eight. However, the Diels–Alder reaction is frequently quite selective and one or two adducts will predominate to the apparent exclusion of the others.

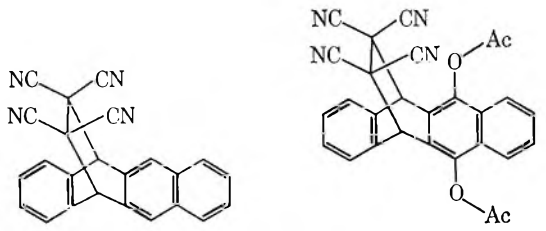
In the condensation of a 5-substituted naphthacene the substituted ring has the site of attack sterically hindered and addition to the unsubstituted ring should be favored. Substituents which increase the electron density of the ring should promote reaction with that ring and perhaps counterbalance the steric hindrance. In a few cases the substituted ring might be the preferred location of addition, but suitable compounds have not yet been tested.

Anthracene has been reported to condense with maleic anhydride five times more rapidly than does 9-bromoanthracene and over one-hundred times more quickly than 9-cyanoanthracene in dioxane at 130°.[2]

From these data one would predict that the 6,11 positions should be about five times more reactive than the 5,12 positions in 5-bromonaphthacene and that a Diels–Alder reaction with 5-cyanonaphthacene should go almost exclusively at the 6,11 positions. Although rate data for 9-anthraldehyde and 9,10-diacetoxyanthracene were not available, one would predict that 5,12-diacetoxy- and 5-naphthacenealdehyde would be more reactive at the 6,11 positions.

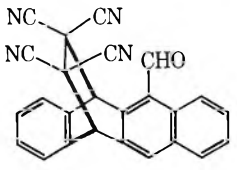
Tetracyanoethylene (TCNE), being a symmetrical and highly reactive dienophile, was chosen for this investigation in order to avoid the formation of vicinal–nonvicinal and *syn–anti* isomers. Isomers arising from addition of the dienophile across the 5,12 and 6,11 positions of the naphthacene skeleton are the only ones possible. Unfortunately, the TCNE adducts were found to be thermally unstable, and only three of the five adducts which were prepared could be sufficiently characterized to permit an assignment of structure. For instance, TCNE and 5-cyanonaphthacene gave a product which crystallized from a solution of tetrahydrofuran at −15° as colorless crystals, but these turned orange in less than a day while being dried *in vacuo* at room temperature. The TCNE adducts when heated, either in solution for recrystallization or as a solid in a melting-point tube, quickly produced the color of the starting 5-substituted naphthacene, which indicated that the Diels–Alder reaction was easily reversed. This thermal instability was surprising, since the ethylene, acrylonitrile, allyl alcohol, and methyl acrylate adducts of naphthacene have been found to be quite stable and the nitrile adducts could be separated in glpc at 200°.[3]

TCNE was condensed with naphthacene, 5,12-diacetoxynaphthacene, and 5-naphthacenealdehyde at room temperature to give the colorless adducts, **2**–**4**.



2

3



4

The adducts of the latter two dienes were characterized by inspection of their infrared spectra. A single carbonyl absorption at 5.64 μ was observed in the spectrum of **3** indicating the presence of an enolic acetate.[4] The spectrum of **4** showed a carbonyl absorption at 5.95 μ, characteristic of an aromatic formyl group.[4] The carbonyl absorption of 9,10-dihydro-9,10-ethano-9-anthraldehyde appears at 5.80 μ,[5,6a] whereas 1-naphthaldehyde shows an absorption at 5.97 μ.[6b] Therefore, adducts **3** and **4** resulted from additions of TCNE in the unsubstituted ring of the naphthacene derivative.

(1) National Science Foundation Predoctoral Fellow, 1963–1965.

(2) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem. Int. Ed. Engl.*, **1**, 268 (1962).

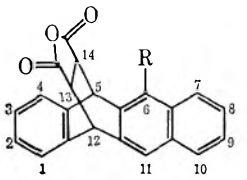
(3) J. S. Meek, F. M. Dewey, and M. W. Hanna, *J. Org. Chem.*, **32**, 69 (1967).

(4) A. K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, pp 43, 44.

(5) W. R. Benson, Ph.D. Thesis, University of Colorado, 1958.

(6) (a) "Sadtler Standard Spectra," Midget ed, Sadtler Research Laboratories, Philadelphia, Pa., 1959, Spectrum No. 3489; (b) Spectrum No. 8444.

Decomposition resulted when the TCNE adducts of 5-cyano- and 5-bromonaphthacene were recrystallized, and the structure of the adducts was not established. The corresponding maleic anhydride adducts (**5** and **6**) were found to be thermally more stable.

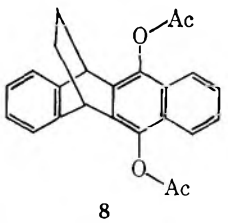


5, R = CN
6, R = Br
7, R = CHO

The infrared spectrum of **5** showed a single nitrile absorption at 5.51 μ, indicative of an aromatic nitrile,[7] thereby establishing its structure as that resulting from addition of the dienophile in the unsubstituted ring. The structure of **6** was assigned from its pmr spectrum. Resonances were observed at τ 6.44 (2 H), assigned to the bridge hydrogens on C-13 and C-14, 5.59 (1 H), assigned to the hydrogen on C-12, 5.11 (1 H), assigned to the hydrogen on C-5, and 2.4 (9 H), assigned to aromatic hydrogens. The downfield shift observed for the C-5 hydrogen is that expected for a proton *peri* to a bromine atom. Thus the formation of **6** also resulted from addition of the dienophile in the unsubstituted ring of the naphthacene derivative. It was not determined whether the maleic anhydride adducts of 5-bromo-, 5-cyano-, and 5-naphthacenealdehyde were the *syn* or the *anti* adducts.

The aldehyde–maleic anhydride adduct was assigned structure **7**, since it showed an aromatic aldehyde carbonyl stretch at 5.96 μ in addition to anhydride carbonyl frequencies at 5.40 and 5.63 μ. Only in the crudest material was there a hint of absorption at 5.80 μ, where the ethylene adduct of 9-anthraldehyde has its aliphatic carbonyl frequency.[6a]

Ethylene was condensed with 5,12-diacetoxynaphthacene, and a stable adduct (**8**) was obtained. The adduct showed a single carbonyl absorption at 5.69 μ characteristic of enolic esters.[4] As further proof that the ethano bridge was situated on the unsubstituted ring compound, **8** was hydrolyzed and on air oxidation gave a quinone. An attempt to prepare this quinone from 5,12-ethano-5,12-dihydronaphthacene gave a mixture of carbonyl compounds, but reduction and acetylation of this mixture gave rise to some **8**.

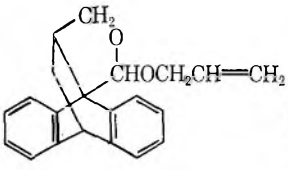


8

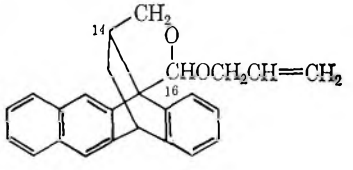
It is noteworthy that adducts **3**–**8** all resulted from addition of the dienophile in the unsubstituted ring of the naphthacene derivative with virtually the total exclusion of addition in the substituted ring. Since the electronic effects of diene substituents have been found to be greater with the more electrophilic tetracyanoethylene than with maleic anhydride,[8] addition in the substituted ring is more likely to occur using maleic anhydride as a dienophile. Also to be considered are the steric repulsions between diene substituents and dienophile substituents, which would undoubtedly be less important with a disubstituted dienophile than with a tetrasubstituted one.

This discovery that a substituent in the 5 position of naphthacene caused adduct formation to occur at the unsubstituted 6,11 positions cast doubt on the structure assigned the maleic anhydride adduct of 5,12-diphenylnaphthacene and that of the 6,13-diphenylpentacene–maleic anhydride adduct. Communication with Allen led to his reexamination of these adducts and established the fact that the Diels–Alder reaction had occurred at the unsubstituted 6,11 positions of the naphthacene and the unsubstituted 5,14 positions of the pentacene and not at the positions bearing the phenyl groups, as was previously suggested.[9]

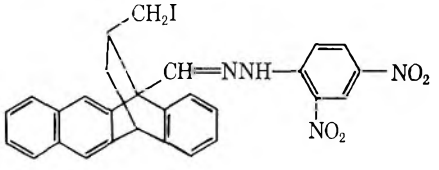
Allyl alcohol and 9-anthraldehyde react to give compound **9**.[10] Thus it was felt that allyl alcohol and



9



10



11

5-naphthacenealdehyde would give **10**. This product would arise from hemiacetal or acetal formation occurring more rapidly than an intermolecular Diels–Alder reaction at the 6,11 positions. Once hemiacetal or acetal formation occurred, a very rapid intramolecular Diels–Alder reaction would occur at the 5,12 positions and lead to **10**.

The reaction actually gave two white products (**10a** and **10b**) whose analyses corresponded to **10**. Since the products were white, neither could have been the acetal of the starting aldehyde. Cleavage of **10a** and **10b** with hydriodic acid gave in each case the same halogen-containing aldehyde, which was converted into **11** for analysis. The aldehyde carbonyl absorption was at 5.80 μ, and a CH aldehyde absorption was found at 3.68 μ. The carbonyl frequency is that expected for a bridgehead aldehyde rather than that of an aromatic aldehyde and showed that the Diels–Alder reaction had occurred at the 5,12 positions. Hence **10a** and **10b** were epimeric at either C-16 or C-14. Since both gave the same aldehyde, the difference in stereochemistry had to be at C-16.

An attempt to make a photooxide of 5,12-diacetoxynaphthacene was made to see if radical addition would

(7) J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 264.

(8) C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).
(9) C. F. H. Allen, *Can. J. Chem.*, **45**, 1201 (1967).
(10) J. S. Meek and J. R. Dann, *J. Org. Chem.*, **21**, 968 (1956).

take place at the same site as the Diels–Alder reaction. Oxidation occurred to give 6,11-diacetoxynaphthacene-5,12-quinone.

Experimental Section

13,13,14,14-Tetracyano-5,12-dihydro-5,12-ethanonaphthacene (2).—A mixture of 0.85 g (3.7 mmol) of naphthacene, 0.50 g (3.9 mmol) of tetracyanoethylene, and 30 ml of tetrahydrofuran was stirred at room temperature for 10 min until the solid had dissolved to give a dark orange solution. The solution was allowed to stand for 21 hr and no further change in color was observed. The solvent was evaporated and the solid was collected and washed several times with a few milliliters of benzene to remove the excess tetracyanoethylene. The off-white solid (2) weighed 1.33 g (100%) and melted at 278–286° dec. Two recrystallizations from acetonitrile at −15° raised the melting point to 294–297° dec.

Anal. Calcd for $C_{24}H_{12}N_4$: C, 80.88; H, 3.39; N, 15.72. Found: C, 80.68; H, 3.28; N, 15.56.

The infrared spectrum of **2** showed a nitrile absorption at 4.45 μ. Rapid decomposition of **2** occurred when it was warmed above room temperature in solution or in its crystalline state.

6,11-Diacetoxy-13,13,14,14-tetracyano-5,12-dihydro-5,12-ethanonaphthacene (3).—Naphthacene-5,12-quinone was prepared in 80% yield by oxidizing naphthacene with sodium chlorate and vanadium pentoxide.[11] After recrystallization from acetic acid the quinone melted at 277–280°.

5,12-Diacetoxynaphthacene was prepared from naphthacene-5,12-quinone in 53% yield using the method of Fieser.[12] Recrystallization from acetic acid gave orange needles which melted at 279–286°. A mixture of 0.33 g (0.96 mmol) of 5,12-diacetoxynaphthacene, 0.14 g (1.1 mmol) of tetracyanoethylene, and 20 ml of tetrahydrofuran was stirred at room temperature. After 5 min the solid had completely dissolved to give a yellow-orange solution. After the solution stood for 15 hr with no apparent change in color, the solvent was evaporated, leaving a pale yellow solid. Recrystallization of the crude product from acetone–ethanol gave 0.36 g (80%) of almost colorless crystals of **3**, mp 267.5–270.0°. Recrystallizations from acetone at room temperature and then at −15° raised the melting point to 270–271° dec.

Anal. Calcd for $C_{28}H_{16}N_4O_4$: C, 71.18; H, 3.41; N, 11.86. Found: C, 71.10; H, 3.45; N, 12.06.

13,13,14,14-Tetracyano-5,12-dihydro-5,12-ethano-6-naphthacenealdehyde (4).—5-Naphthacenealdehyde was prepared in 60% yield from naphthacene and N-methylformanilide in *o*-dichlorobenzene.[13] After recrystallization from benzene the product melted at 147–150° (dark crimson crystals). A mixture of 0.50 g (2.0 mmol) of 5-formylnaphthacene, 0.26 g (2.0 mmol) of tetracyanoethylene, and 20 ml of tetrahydrofuran was stirred under nitrogen at room temperature for 21 hr. The solvent was evaporated and the resulting dark green solid was washed several times with a few milliliters of benzene to remove tetracyanoethylene. The tan solid weighed 0.63 g (84%) and melted at 190–275° dec. This product decomposed rapidly even when it was warmed gently. It was dissolved in acetonitrile by warming the solution slightly above room temperature and was allowed to crystallize at 0°. A second recrystallization gave the analytical sample. The melting point, determined by inserting a capillary containing the sample into an oil bath already at 260°, was 270–274° dec.

Anal. Calcd for $C_{25}H_{12}N_4O$: C, 78.11; H, 3.15. Found: C, 78.30; H, 3.17.

5,13,13,14,14-Pentacyano-5,12-dihydro-5,12-ethanonaphthacene.—5-Naphthacenealdoxime[13] was prepared in 100% yield from 5-naphthacenealdehyde and hydroxylamine hydrochloride in pyridine. The rust-red solid melted at 174–181°.

5-Cyanonaphthacene was prepared in 95% yield by dehydrating naphthacene-5-formoxime with acetic anhydride.[13] Recrystallization from benzene gave crimson crystals melting at 188–194°. A mixture of 0.40 g (1.6 mmol) of 5-cyanonaphthacene, 0.21 g (1.6 mmol) of tetracyanoethylene, and 20 ml of tetrahydrofuran was stirred at room temperature for 18 hr. The solvent was evaporated and the pink solid which resulted was washed with 10 ml of cold benzene. The product weighed 0.60 g (100%) and melted at 259–283° dec. Attempts to recrystallize this product in hot solvents led to colored solutions whose darkening hue indicated a reverse Diels–Alder reaction. When tetrahydrofuran was used as the solvent and allowed to stand for 3 days in a cold room at −15°, colorless crystals were deposited, mp 279–282° dec. (The sample was inserted in an oil bath preheated to 260° and immediately turned red.) An attempt to dry the crystals under vacuum at room temperature resulted in their turning orange in less than 20 hr, and an analysis was not satisfactory.

The infrared spectrum of the crude product showed a nitrile absorption at 4.50 μ with a shoulder at 4.45 μ.

Preparation of 5-Bromonaphthacene.—Reference is made to 5-bromonaphthacene in the literature,[13] but no method of preparation is given nor are any physical properties included.

The bromination of 2.0 g (8.8 mmol) of naphthacene with 2.0 g (8.9 mmol) of cupric bromide in refluxing carbon tetrachloride was patterned after the preparation of 9-bromoanthracene.[14] The crude product was passed through a short column (2.0 × 12 cm) of alumina. The resulting bright red solid weighed 1.2 g (92% based on cupric bromide), mp 125–140°. After two recrystallizations from benzene the sample melted at 153–156° (0.52 g, 40%): mol wt (calcd for $C_{18}H_{11}Br$) 307; mass spectrum (70 eV) *m/e* rel intensity 308 (18), 306 (16), 227 (13), 91 (18), 78 (10), 58 (29), and 43 (100).

Addition of Tetracyanoethylene to 5-Bromonaphthacene.—A mixture of 0.35 g (1.1 mmol) of 5-bromonaphthacene, 0.15 g (1.2 mmol) of tetracyanoethylene, and 15 ml of tetrahydrofuran was stirred at room temperature for 1 hr. The bright red color of 5-bromonaphthacene faded gradually to give a bright yellow solution. The solvent was removed using a rotary evaporator and left a yellow oil. The product was precipitated by dissolving the oil in a few milliliters of tetrahydrofuran and adding 25 ml of petroleum ether. The resulting pale yellow solid was collected, yield 0.50 g (100%), mp 238–241° dec. Recrystallization from tetrahydrofuran at −15° raised the melting point to 270–272° dec. Further attempts at recrystallization resulted in rapid decomposition.

6-Cyano-5,12-dihydro-5,12-ethanonaphthacene-13,14-dicarboxylic Acid Anhydride (5).—A mixture of 0.45 g (1.8 mmol) of 5-cyanonaphthacene, 0.40 g (4.1 mmol) of maleic anhydride, and 10 ml of *p*-xylene was refluxed for 11.5 hr. The reaction mixture was cooled and the resulting tan solid was collected by filtration. Concentration of the filtrate and treatment with 20 ml of petroleum ether yielded additional solid material. The combined solid (5) weighed 0.45 g and melted at 263–269° dec. Recrystallizations from acetonitrile and ethyl acetate raised the melting point to 308–311° dec. (The capillary tube was inserted in the oil bath at 290°.)

Anal. Calcd for $C_{23}H_{13}NO_3$: C, 78.62; H, 3.73. Found: C, 78.45; H, 3.70.

The infrared spectra of the analytical sample and the crude product showed a single nitrile absorption at 4.51 μ, characteristic of aromatic nitriles.[4] 9-Cyano-9,10-dihydro-9,10-ethanoanthracene shows a nitrile absorption at 4.44 μ.[5]

6-Bromo-5,12-dihydro-5,12-ethanonaphthacene-13,14-dicarboxylic Acid Anhydride (6).—A mixture of 0.40 g (1.3 mmol) of 5-bromonaphthacene, 0.50 g (5.1 mmol) of maleic anhydride, and 10 ml of *p*-xylene was refluxed (135°) for 0.5 hr. The xylene was evaporated under a jet of air and the resulting tan crystals were collected on a filter and washed with 10 ml of ethanol, yield 0.50 g (95%), mp 242–282°. Two recrystallizations from benzene–petroleum ether mixtures gave 0.15 g (28%) of colorless crystals of **6**, mp 301–304° dec. One additional recrystallization raised the melting point to 306–309° dec.

Anal. Calcd for $C_{22}H_{13}BrO_3$: C, 65.20; H, 3.23. Found: C, 65.47; H, 3.43.

The nmr spectrum of **6** was run in *sym*-tetrachloroethane at 100° on a Varian A-60 spectrophotometer.

6-Formyl-5,12-dihydro-5,12-ethanonaphthacene-13,14-dicarboxylic Acid Anhydride (7).—A mixture of 0.34 g (1.3 mmol) of 5-naphthacenealdehyde, 0.40 g (4.1 mmol) of maleic anhydride, and 12 ml of benzene was refluxed for 22 hr. Upon cooling a tan solid separated from the red-brown solution. After the solid was collected, the filtrate was concentrated and the additional solid which separated was combined with the first crop, yield 0.39 g (83%), mp 263–268°. This product was recrystallized from acetonitrile–tetrahydrofuran at −15°, and a mixture of

(11) H. W. Underwood, Jr. and W. L. Walsh, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 553.

(12) L. F. Fieser, *J. Amer. Chem. Soc.*, **53**, 2329 (1931).

(13) M. Martynoff, *Compt. Rend.*, **238**, 249 (1954).

(14) D. C. Nonhebel, *Org. Syn.*, **43**, 15 (1963).

tetrahydrofuran and petroleum ether (bp 60–70°) (Skellysolve B) at −15° to give the analytical sample of **7**, mp 317–320° dec. (The sample was inserted in the oil bath at 290°.)

Anal. Calcd for $C_{23}H_{14}O_4$: C, 77.96; H, 3.98. Found: C, 77.78; H, 4.07.

This adduct appeared to be thermally more stable than **4**.

6,11-Diacetoxy-5,12-dihydro-5,12-ethanonaphthacene (8).—A mixture of 2.0 g (5.8 mmol) of 5,12-diacetoxynaphthacene, 0.1 g of hydroquinone, and 100 ml of benzene was placed in a glass liner which was in turn placed in a 0.5-l. stainless steel bomb. The bomb was charged with 200 psi of ethylene and the apparatus was heated at 188–194° with shaking for 22 hr, during which time the pressure rose to 800 psi. The solution was removed from the liner and the solvent was evaporated. The resulting oil gradually solidified to a tan solid. The yield of crude **8** was 2.23 g, mp 189–213°. The product was recrystallized twice from benzene–petroleum ether, once from methanol, and four times from ethyl acetate–petroleum ether to give the analytical sample, mp 219.5–222.0°.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.17; H, 5.33.

Alkaline Hydrolysis of 8.—A mixture of 0.36 g (1.0 mmol) of **8**, 10 ml of 20% sodium hydroxide solution, and 30 ml of ethanol was warmed on a steam bath for 30 min. The color of the solution became blood red immediately. The solution was cooled and carefully neutralized with 30% sulfuric acid. The ethanol was evaporated on a rotary evaporator, and the resulting solid was washed into a separatory funnel and extracted with ether–benzene. As the extract was shaken, it gradually turned bright yellow owing to air oxidation of the hydroquinone to 5,12-dihydro-5,12-ethano-6,11-naphthacenequinone. After the ether was evaporated on a steam bath, the remaining solution was filtered, and to it was added an equal volume of petroleum ether. Crystallization was initiated by partial evaporation of the solvent with a slow stream of air. Bright yellow crystals formed, yield 0.20 g (67%), mp 200–210°. The product was recrystallized twice from ethyl acetate–petroleum ether and three times from ethanol to give the analytical sample, mp 206–209°.

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90, H, 4.93. Found: C, 84.15; H, 5.20.

The infrared spectrum had a carbonyl absorption at 6.05 μ and strong absorptions at 8.30, 11.35, 13.02, and 13.35 μ.

A solution of 0.65 g of 5,12-dihydro-5,12-ethanonaphthacene[3] in 10 ml of acetic acid was heated to 50°, and 1.5 ml of 30% hydrogen peroxide was added. As the temperature was raised to 80°, the color of the solution gradually became bright yellow. After 1 hr an additional 0.5 ml of hydrogen peroxide was added, and heating was continued at 80–84° for a total of 10 hr. The solvent was evaporated to give 0.76 of a bright yellow solid which melted at 146–169°. Three recrystallizations from ethyl acetate raised the melting point to 172–174°. The elemental analysis was unsatisfactory for the anticipated quinone.

A solution of 0.26 g of this oxidation product in 15 ml of benzene was hydrogenated over palladium on charcoal (10%) for 1 hr in a modified Brown hydrogenation apparatus. The hydrogen atmosphere was replaced with nitrogen and the mixture was heated with 0.4 g of anhydrous sodium acetate and 13 ml of acetic anhydride for 15 hr. After standing for 2 days the catalyst was removed by filtration, and the solution was concentrated and allowed to crystallize. The resulting yellow crystals weighed 0.10 g and were shown to be starting material by an undepressed mixture melting point. Concentration of the mother liquor resulted in the crystallization of a small amount of **8**, mp 205–215°. It was identified from its infrared spectrum.

Further work-up of the mother liquors gave a small amount of another acetate melting at 253–259°. Its infrared spectrum was markedly different from the spectrum of **8**. Too little sample was isolated to permit its structure to be determined.

Condensation of Allyl Alcohol and 5-Naphthacenealdehyde.—A mixture of 1.20 g (4.7 mmol) of 5-naphthacenealdehyde, 12 ml of allyl alcohol, and 0.1 g of hydroquinone was heated in a sealed tube at 154° for 12 hr. The resulting brown oil was chromatographed on alumina. The majority of the product (1.16 g), which was eluted with benzene, was an almost colorless oil. Crystallization occurred from cold petroleum ether to give a white solid, which was then recrystallized from the same solvent to give 0.20 g of colorless crystals, mp 168–176°. Several recrystallizations from petroleum ether and then from tetrahydrofuran–petroleum ether gave pure **10a**, mp 176–178°.

Anal. Calcd for $C_{25}H_{22}O_2$: C, 84.71; H, 6.25. Found: C, 84.42; H, 6.46.

The mother liquor from **10a** was rechromatographed on alumina. Comparison of the infrared spectra of the fractions indicated the presence of *ca.* 0.3 g of **10b** in the first few fractions. Repeated recrystallizations from petroleum ether gave the analytical sample, mp 112.7–115.7°.

Anal. Calcd for $C_{25}H_{22}O_2$: C, 84.71, H, 6.25. Found: C, 84.50; H, 6.09.

The infrared spectra of these two compounds showed an absence of a carbonyl group, but did show bands indicative of a vinyl group. The spectrum of **10a** showed major bands at 9.30, 9.90, 10.75, 11.00, 11.46, 13.30, and 13.40 μ; **10b** showed absorptions at 9.25, 9.96, 10.90, 11.20, 13.30, and 13.40 μ.

Cleavage of 10a and 10b with Hydrogen Iodide.—To a hot solution of 52 mg of **10b** in 6 ml of acetic acid was added 2 ml of hydrogen iodide (47–50%). The reaction mixture was heated under nitrogen for 1.5 hr at 120°. After cooling it was poured into 100 ml of cold water. The resulting white precipitate weighed 0.050 g (83%) and melted at 84–100°. It gave a positive Beilstein test. Attempts to recrystallize this product from benzene resulted in decomposition. The cleavage product was dissolved in a few milliliters of alcohol, and a solution of 2,4-dinitrophenylhydrazine in ethanolic sulfuric acid was added. After a few minutes a yellow solid precipitated yield 0.05 g (70%), mp 155–170°. Recrystallizations from ethyl acetate–petroleum ether and ethyl acetate–pentane at 0° gave the analytical sample of **11**, mp 178–179° dec. The violet color of iodine vapor was evolved on melting.

Anal. Calcd for $C_{23}H_{21}IN_4O_4$: C, 55.64; H, 3.50. Found: C, 55.37; H, 3.29.

Using the same procedure, 0.10 g of **10a** was cleaved, giving 0.11 g (92%) of the aldehyde, mp 90–100°. The crude 2,4-dinitrophenylhydrazine derivative melted at 161–169° dec and gave a positive Beilstein test. The aldehydes and the derivative had the same infrared spectra as the samples obtained from **10a**.

Photooxidation of 5,12-Diacetoxynaphthacene.—A solution of 0.46 g (1.3 mmol) of 5,12-diacetoxynaphthacene in 125 ml of acetone was allowed to stand in the sunlight in a stoppered flask for 1 month. Evaporation of the solvent left a gummy, yellow solid. This was dissolved in ethanol, treated with charcoal, and filtered. Crystallization yielded 0.14 g (28%) of fine, yellow needles, mp 220–225°. The infrared spectrum showed carbonyl absorptions at 5.70 and 5.99 μ. The product was 5,12-diacetoxy-6,11-naphthacenequinone, which is reported to begin to soften at 215° and melt at 220–235°.[15]

Registry No.—**2**, 23790-72-9; **3**, 23790-71-8; **4**, 23790-73-0; **5**, 23843-58-5; **6**, 23790-76-3; **7**, 23843-59-6; **8**, 23843-60-9; **10**, 23790-77-4; **11**, 23843-62-1; 6,13,13,14,14-pentacyano-5,12-dihydro-5,12-ethanonaphthalene, 23790-74-1; 5-bromonaphthacene, 23790-75-2; 5,12-dihydro-5,12-ethano-6,11-naphthacenequinone, 23843-61-0.

(15) S. Gabriel and E. Leupold, *Chem. Ber.*, **31**, 1281 (1898).

Conformational Preferences in Diastereomers. V. Hydrogen-Bonding Systems

CHARLES A. KINGSBURY

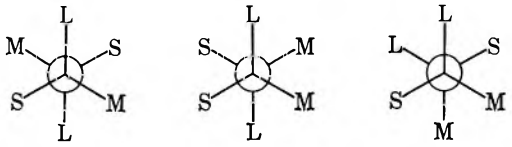
Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received April 15, 1968

In several alkyl-substituted phenylethanediols and in two propanediols, the increase in size of the alkyl substituent results in generally increasing coupling constants in the *erythro* isomers. In the *threo* isomers, diminishing coupling constants are observed. Diastereomers with *t*-butyl substituents are again anomalous. The *erythro* isomers generally have lower coupling constants than the *threo* isomer in carbon tetrachloride. In hydrogen-bonding solvents such as dimethyl sulfoxide or pyridine, the coupling constants are much larger for the *erythro* isomers and smaller for the *threo* isomers than those in carbon tetrachloride. The effect of dilution was also to increase coupling constants for the *erythro* isomers and to diminish coupling constants for the *threo* isomers. These effects are in contrast with the observations in a rigid system, 3-methyl-1,2-cyclohexanediol. In the open-chain system, infrared data showed that the solvent effects were associated with reduction of intermolecular hydrogen bonding. In one set of isomers at very low concentration, time-averaging runs disclosed coupling constants rather similar to those determined at high concentrations. The results are interpreted in terms of changes from polymeric and dimeric to monomeric diols.

Previous work in nonhydrogen-bonding systems[1-8] has shown that the *erythro*-s isomer of an *erythro*-s–*threo*-s pair of diastereomers usually has the larger vicinal coupling constant, J (the suffix s indicates that the definition of *erythro* is based on the size of groups).[9] Thus, as Chart I shows, the preferred *trans* arrangement

CHART I



of the large group, L, and *trans* medium groups, M, imposes a *trans* relationship on the small groups (hydrogen), resulting in a large vicinal coupling constant.[10,11] The *threo*-s isomers are usually conformationally mixed to a greater extent than the *erythro*-s isomers.[12] In some types of *threo*-s diastereomers[7] a trend toward lower J values has been observed upon increasing the size of the groups involved, suggesting the growing importance of conformer *threo*-s_1, in which the large groups are again *trans*. In other types of *threo* diastereomers quite large J values are observed.[3,5,6] Thus *threo*-s_2 is quite highly populated even though the large groups are *gauche*. The conformer *threo*-s_2 exhibits two sets of *gauche* interactions between sizable groups, whereas *threo*-s_1 shows three such interactions.[12] The former behavior is often, though not exclusively, associated with the presence of alkyl groups. The latter type frequently occurs with "soft" substituents such as aryl or carboxyl. However, the reason for the difference in behavior is not completely understood as yet.

The above behavior is not to be expected in systems in which substantial attractive interactions exist between two or more groups.[5,13-19] The present study is concerned with such an attractive interaction, intramolecular hydrogen bonding. *A priori*, three types of behavior might be anticipated depending on the strength of the hydrogen bond.

(A) In weak or nonhydrogen-bonding systems, the conformation is determined primarily by nonbonded interactions between the larger groups (as in Chart I). Little effect of concentration or of solvent is expected, although some groups such as hydroxyl may prefer a more open conformation to facilitate hydrogen bonding with solvent.[20]

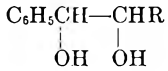
(B) In moderately strong hydrogen-bonding systems, the hydrogen bond may override the nonbonded interactions between the large groups, resulting in quite a different conformation than those shown in Chart I. However, the effect of solvent should be large, since some types of solvents may break up the intramolecular hydrogen bond, resulting in conformations similar to those in Chart I.

(C) In strong intramolecular hydrogen-bonding systems, the conformation is dominated by the hydrogen bond. However, little effect of concentration or of

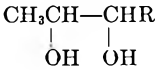
(1) F. Anet, *J. Amer. Chem. Soc.*, **84**, 747 (1962).
(2) A. Bothner-By and C. Naar-Colin, *ibid.*, **84**, 743 (1962).
(3) J. Ralston and K. Yates, *ibid.*, **91**, 1469 (1969).
(4) R. C. Fahey, *ibid.*, **88**, 4681 (1966); M. Dewar and R. C. Fahey, *ibid.*, **85**, 3645 (1963).
(5) M. E. Munk, M. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968).
(6) M. C. Cabaleiro and M. D. Johnson, *J. Chem. Soc., B*, 565 (1967).
(7) C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, **31**, 1000 (1966).
(8) See also (a) M. Buza and E. I. Snyder, *J. Amer. Chem. Soc.*, **88**, 1161 (1966); (b) R. J. Jablonski and E. I. Snyder, *ibid.*, **90**, 2316 (1968); (c) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965); (d) S. Brownstein, *Can. J. Chem.*, **39**, 1677 (1961).
(9) H. E. Zimmerman and W. Chang, *J. Amer. Chem. Soc.*, **81**, 3634 (1959).
(10) (a) M. Karplus, *ibid.*, **85**, 2870 (1963); (b) A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 195 (1965).
(11) E. Garbisch, Jr. and M. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968).
(12) See J. L. Mateos and D. J. Cram, *ibid.*, **81**, 2756 (1959); D. Y. Curtin, *Record Chem. Progr.*, **15**, 111 (1954); H. Felkin, *Bull. Soc. Chim. Fr.*, 1050 (1956); M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).
(13) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961), and related papers. This work emphasizes the fact that dihedral angles may be other than 60°. While we recognize the fact that the molecules in question have varying dihedral angles, as well as bond angles and bond lengths to some extent, to achieve the most comfortable arrangement, we will, as before, picture dihedral angles as 60° for convenience.
(14) M. Stiles, R. Winkler, Y. Chang, and L. Traynor, *J. Amer. Chem. Soc.*, **86**, 3337 (1964).
(15) L. Erickson, *ibid.*, **87**, 1867 (1965).
(16) J. W. Huffman and R. P. Elliott, *J. Org. Chem.*, **30**, 365 (1965).
(17) C. G. Overberger and T. Kurtz, *ibid.*, **31**, 288 (1966).
(18) J. Canceill, J. Basselier, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1906 (1963).
(19) See also W. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **90**, 1318 (1968).
(20) L. M. Jackman and N. S. Bowman [*ibid.*, **88**, 5565 (1966)] have also considered the effect of intermolecular hydrogen bonding on conformation.

solvent is anticipated, since a hydrogen bond of high stability would not be easily disturbed.[14,21]

The compounds of this study are the vicinal diols **1** and **2**, which are believed to be examples of case B above.



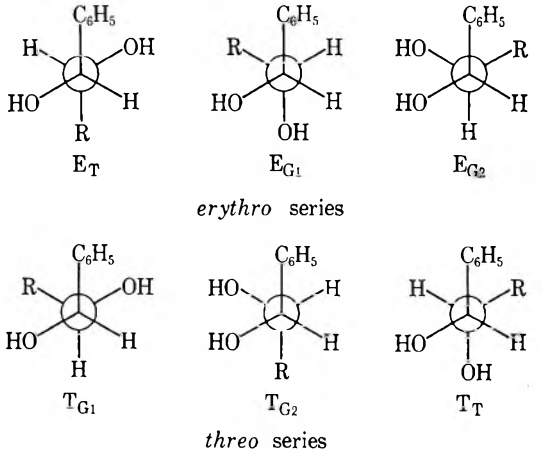
1



2

The coupling-constant data are listed in Table I. These data will be discussed with reference to the conformers shown in Chart II.

CHART II

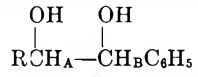


The data in Table I show that the *erythro* diastereomers generally have lower J values than the *threo* isomers, somewhat similar to other studies of hydrogen-bonding systems.[5,14,16,18] The *erythro t*-butyl compound **6** (and also probably *threo*-**6** and -**9**) is out of line in comparison with other *erythro* isomers. This fairly common phenomenon[8,22] is thought to be due to a different mode of relieving nonbonded interactions than internal rotation.[23] Bond-angle deformations involving the methyl groups of the *t*-butyl function or of the *t*-butyl group itself are thought to be important. For **3**–**5**, increasing the size of the R group in the *erythro* isomers generally results in increasing J values, indicative of the growing importance of conformer E_T (J_{AB} = 10–13 Hz).[10,11] A similar change for the *threo* isomers involved decreasing J values, showing the importance of T_{G1} and/or T_{G2} ($J_{AB} \cong 3$ Hz), most likely the latter conformer, since the largest groups may again be *trans*.

In order that maximum and minimum coupling constants may be roughly approximated, a rigid system was investigated. Three of the four isomers of 3-methyl-1,2-cyclohexanediol were obtained and the nmr data for the suggested structures are given in Chart III.[24]

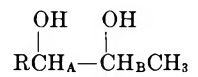
TABLE I

NMR COUPLING CONSTANTS[a] IN SYSTEMS 1 AND 2



1

Compd	R	Isomer	J_{AB} (CCl$_4$),[b] Hz 10%[c]	5%	2.5%	1.3%	J_{AB}[c,d] (DMSO)
3	CH_3	*erythro*[f]	Insol	3.8	4.0	4.0	5.3
		threo	7.8	7.7	7.6	7.5	6.4
4	C_2H_5	*erythro*	3.8	3.9	4.2	4.4	5.7
		threo	7.6	7.3	7.1	6.9	6.1
5	*i*-C_3H_7	*erythro*[f]	Insol	5.6	5.7	5.8[g]	7.5
		threo	7.1	6.8	6.5	6.4	6.2
6	*t*-C_4H_9	*erythro*		5.2[h]	5.5	5.8	6.7
		threo	2.6[h]		2.6	2.6[g]	2.6
7	$CH_2C_6H_5$[i]	*threo*		6.5	6.2	6.0[g]	4.7



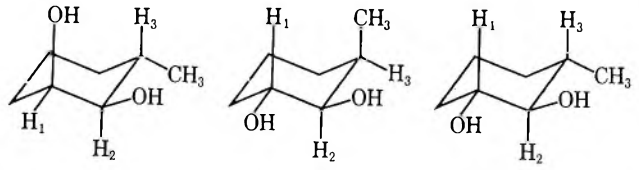
2

8	*i*-C_3H_7	*erythro*		3.4	3.6	3.7	6.0
		threo	6.4	6.4	6.1	5.9	5.3
9	*t*-C_4H_9	*erythro*	2.6	2.8	3.0	3.3	4.0
		threo	2.1	2.0	2.0	1.9	1.8

[a] Data was taken from expanded spectra on a Varian A-60D instrument *vs.* tetramethylsilane as internal standard. A trace of trifluoroacetic acid was added to promote rapid exchange. [b] These coupling-constant data have duplicated the spectrum at selected concentrations using computer simulation techniques. [c] Concentration 10%. [d] For system **2**, the solutions were composed of 75% CCl_4 and 25% DMSO to avoid trouble from spinning side bands. [e] 10% sample by weight per unit solvent volume. [f] Slightly heated for solubility reasons. [g] Approximate value; an expanded spectrum was not possible. [h] Approximate concentration. [i] The *erythro* value is *ca.* 4.2 Hz. as observed from a solution of mixed diastereomers.

For the *cis*-diol **10** and the *trans*-diol **12**, the major couplings were verified by spin decoupling and the spectra were simulated by computer techniques using the approximate chemical shifts for H_3 derived from spin-decoupling data. The data in Chart III accurately

CHART III



10 $J_{1,2} = 2.5$ Hz, $J_{2,3} = 9.2$ Hz

11 $J_{1,2} = 8.4$ Hz, $J_{2,3} = 4.8$ Hz

12 $J_{1,2} = 9.1$ Hz, $J_{2,3} = 9.1$ Hz

duplicated the splitting pattern for H_2, but difficulty was encountered with the H_1 pattern, probably owing to the extensive coupling (real and virtual) with several other ring protons. The *cis* isomer **10** shows a vicinal

(21) (a) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); (b) O. L. Chapman, R. W. King, and W. Welstead, Jr., *ibid.*, **86**, 4968 (1964); (c) I. Kolthoff, M. Chantooni, Jr., and S. Bhowmik, *ibid.*, **90**, 23 (1968); (d) N. Bauld and Y. Rim, *J. Org. Chem.*, **33**, 1303 (1968).

(22) D. C. Best and C. A. Kingsbury, *ibid.*, **33**, 3252 (1968).

(23) D. C. Best, G. Underwood and C. Kingsbury, *Chem. Commun., Part D*, 627 (1969).

(24) The comparison of a cyclohexane system such as **10** or **12**, included at the behest of the referee, to an open-chain system such as **8** is not necessarily valid. The variation of dihedral angles to achieve the most "comfortable" arrangement differs. The infrared $\Delta\nu$ of the *cis*-diol **10** (45 cm^{-1}) is larger than that of the *trans*-diol **12** (35 cm^{-1}): R. W. Wright and R. Marehessault, *Can. J. Chem.*, **46**, 2567 (1968). Further, *cis*-diols are reported to form acetonides, unlike *trans*-diols: J. Boeseken and J. van Giffen, *Rec. Trav. Chim. Pays-Bas*, **39**, 183 (1920). The dihedral angle between the *cis* axial–equatorial hydroxyl groups is thought to have become compressed,[11] and the dihedral angle between *trans* equatorial–equatorial hydroxyls has become widened, possibly to relieve across ring nonbonded interactions. Quite the opposite trend in the $\Delta\nu$ factors is observed for *erythro*-**8** (comparable with **10**) and *threo*-**8** (see the ensuing discussion). Any similarity in J values may be coincidental. See also H. Feltkamp and N. C. Franklin, *Tetrahedron*, **21**, 1541 (1965).

coupling constant[24,25] reasonably close to that observed for the most closely analogous open-chain compound, *erythro*-**8**. On the other hand, **12** shows a somewhat larger $J_{1,2}$ value than that observed for *threo*-**8** (or any of the other *threo* compounds), indicating that the open-chain compounds are more conformationally mixed owing to competition between T_T and T_{G^2} conformers. Compound **11** is also not conformationally pure. Although the infrared $\Delta\nu$ factors for **11** and **12** are similar (*ca.* 35 cm^{-1}), the apparent intensity of the intramolecularly bonded hydroxyl absorption for **11** is only *ca.* 60% that of **12**. The infrared data, coupled with rather low $J_{1,2}$ and rather high $J_{2,3}$ values, show that the conformer of **11** with equatorial methyl and diaxial hydroxyl groups is substantially populated. However, the dominant conformation of **11** (Chart III) prefers equatorial hydroxyl functions at the expense of placing the methyl group axial.

Unlike the open-chain compounds, **10** and **12** were insensitive to the solvent change from deuteriochloroform to pyridine. Compounds **10** and **12** were also insensitive to a twofold dilution in carbon tetrachloride.

The effect of concentration on the coupling constants of the open-chain materials is given in Table I. For the *erythro* isomers, the effect of dilution is generally a trend toward higher J values. For the *threo* isomers the trend is the opposite. Although the changes were rather small in some cases, repetition always gave similar results. The effect of adding a second hydrogen-bonding material, such as ephedrine, to a constant concentration of *erythro*-**3** or -**9** was diminishing J values. Upon adding ephedrine to *threo*-**5**, increasing J values were observed.

The effect of moving from carbon tetrachloride to the intensely hydrogen-bonding solvent dimethyl sulfoxide (DMSO) is also shown in Table I. In the latter solvent, intermolecular hydrogen bonding between diols and much of the intramolecular hydrogen bonding, if any, is thought to be eliminated.[21] In DMSO, the *erythro* isomers usually show larger J values than in carbon tetrachloride. Again the *threo* isomers usually show smaller J values for the same solvent change. For **3**, a more complete study of the effect of solvent[26] is given in Table II. Moving from nonpolar solvents to progressively more strongly hydrogen-bonding solvents involves an increase in J_{AB} for *erythro*-**3** and a decrease for the *threo* isomer. The coupling constants observed in chloroform solution are substantially different from those in carbon tetrachloride, consistent with the weak hydrogen-bonding properties of the former. In contrast, a model nonhydrogen-bonding compound having the same carbon skeleton, 1,2-dibromo-1-phenylpropane,[3] showed little or no change in J_{AB} (10.2 Hz) for the *erythro* isomer and a slight increase from the original J_{AB} (5.4 Hz) for the *threo* isomer for the same solvent variation.[2]

TABLE II

VICINAL COUPLING CONSTANTS AS A FUNCTION OF SOLVENT[a] FOR **3**

	CCl_4	$CDCl_3$	CH_3OH	CH_3COCH_3	Pyridine[b]	CH_3SOCH_3
erythro	3.8[c]	4.1	5.1	4.7	5.0	5.4
threo	7.8	7.4	7.0	7.0	6.9	6.4

[a] Concentration 10% except as indicated. [b] Concentration 5% in pyridine. [c] Concentration 5%.

Infrared data were obtained for systems **1** and **2** for the same range of concentrations in carbon tetrachloride utilized for the nmr studies. Qualitatively, the results are similar to the studies of Kuhn and others.[27-34] For the *threo* isomers, three absorptions were noted (**7**, however, was anomalous): (A) sharp peak at *ca.* 3620 cm^{-1}, very likely the free hydroxyl absorption; (B) somewhat broader peak of similar apparent intensity at 3560–3585 cm^{-1}, probably the intramolecularly bound hydroxyl; (C) a broad absorption at *ca.* 3400 cm^{-1}, probably the polymeric hydroxyl absorption. In the 10% solutions the polymeric absorption was strongly dominant. Dilution eliminated much of the polymeric absorption, but at 1.3% (the minimum concentration at which most nmr spectra could be run) it was still a sizable peak. It is noteworthy that the size of the polymeric absorption peak was less for **5** and **6** than for **3** and **4**, probably the effect of steric hindrance to external association.

For the *erythro* isomers **1**, an infrared peak was observed at *ca.* 3630 cm^{-1} upon which a shoulder was evident, in addition to the concentration-dependent peak at *ca.* 3400 cm^{-1}. The shoulder was very likely due to the intramolecular hydrogen-bonded hydroxyl.[30] For system 2, however, separated free and intramolecularly bonded hydroxyl peaks were evident (*e.g.*, $\Delta\nu$ is 45 cm^{-1} for *erythro*-**9** compared with 60 cm^{-1} for *threo*-**9**). The effect of dilution for all *erythro* isomers was generally similar to the *threo* isomers described above. In all cases, the intramolecular hydrogen bond is less stable for the *erythro* than for the *threo* isomers (as judged from the lower $\Delta\nu$).[5,13,14] As others have pointed out,[5,13,29,31] distortion of the dihedral angles to relieve the R–phenyl interaction increases the hydroxyl–hydroxyl distance in the *erythro* isomers, thus weakening the hydrogen bond.

It is difficult to assess what role, if any, hydroxyl–phenyl hydrogen bonding plays. The $\Delta\nu$ factor ascribed to hydroxyl–π interaction[29] is roughly similar to the $\Delta\nu$ observed for hydroxyl–hydroxyl bonding; therefore, the above infrared results could as easily be the effect of the former type of interaction. However, the nmr data are difficult to explain in any rational manner in terms of conformations dominated by hydroxyl–π bonding. In competition between bonding to a nonbonded pair on oxygen as opposed to the delocalized electrons of a π system, the former would seem more probable (bond energy *ca.* 4 kcal, in the ideal case) than the latter (interaction energy *ca.* 1 kcal). Never-

(25) These J values are reasonably close to those given for similar cyclohexane systems: R. A. B. Bannard, *Can. J. Chem.*, **44**, 775 (1966); F. A. L. Anet, *ibid.*, **41**, 2331 (1963).

(26) See however, E. I. Snyder, *J. Amer. Chem. Soc.*, **85**, 2624 (1963); K. Deb and R. J. Abraham, *J. Mol. Spectrosc.*, **23**, 393 (1967); also ref 2 concerning solvent effects.

(27) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954); **80**, 5950 (1958).

(28) A. Cole and P. R. Jeffries, *J. Chem. Soc.*, 4391 (1956).

(29) J. Sicher and J. Farkas, *Collect. Czech. Chem. Commun.*, **20**, 1391 (1955); J. Sicher, M. Cherest, Y. Gault, and H. Felkin, *ibid.*, **28**, 72 (1963).

(30) W. Mosher and N. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).

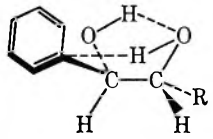
(31) N. Mori, S. Omura and Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **38**, 2199 (1965); **38**, 1630 (1965).

(32) H. Buc, *Ann. Chim.*, **8**, 409 (1963); 431 (1963).

(33) H. Agahigian, J. Moraveck, and H. Gauthier, *Can. J. Chem.*, **41**, 194 (1963).

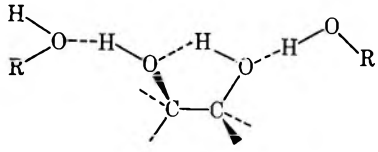
(34) See, however, R. Piccolini and S. Winstein, *Tetrahedron Lett.*, No. 13, 4 (1959).

theless, the hydroxyl–π interaction may be of some importance in the *erythro* isomers in which the hydroxyl–hydroxyl bond is weakened by other factors. A further complication is possible simultaneous hydroxyl–hydroxyl and hydroxyl–phenyl bonds, as illustrated below.[35]

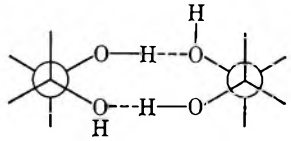


In any case, the effect of dilution on the nmr J values (Table I) is related to diminishing amounts of intermolecular association, as determined from the infrared spectra. However, in one case it was possible to determine the nmr spectra of a pair of isomers under conditions in which intermolecular association was small. Under time-averaging conditions[36] (concentration 0.1% in carbon tetrachloride), *erythro*-**5** exhibited a J value of 5.8 Hz and *threo*-**5** a value of 6.4 Hz, rather similar to the data in Table I taken at higher concentrations.

Concerning the nmr data, a group of related questions remain to be answered. First, why are the conformations populated by the isomers **5** similar under conditions favoring intermolecular association compared with intramolecular association? Second, of the changes which do occur on dilution or solvent change, why are increasing J values observed for the *erythro* isomers, and decreasing J values for the *threo* isomers? To partially rationalize these questions, it should be pointed out that the polymeric hydroxyl groups at high concentrations may in fact involve many intramolecularly bonded and therefore *gauche* hydroxyl groups.



A second possibility, which helps to account for the *erythro* as well as the *threo* data, consists of dimeric molecules. Dimers have been implicated in the association pattern of simple alcohols. The difunctional molecules of this study should exhibit the same phenomenon to a greater extent.[37] Thus the dimer and the intramolecularly hydrogen bonded monomer would both



require conformations T_T and T_{G^2} for the *threo* isomers and E_{G^1} and/or E_{G^2} for the *erythro* isomers.[38,39]

(35) D. Horton, J. Hughes, and J. Thomson, *J. Org. Chem.*, **33**, 728 (1968).

(36) The 100-MHz accumulation runs, as well as the 100-MHz spectra of **10–12**, were ably determined by R. W. King, Iowa State University.

(37) (a) E. D. Becker, *J. Chem. Phys.*, **31**, 269 (1959); (b) J. C. Davis, Jr., K. S. Pitzer, and C. Rao, *J. Phys. Chem.*, **64**, 1744 (1960); (c) G. Dana, J. Chuche, and M.-R. Monot [*Bull. Soc. Chim. Fr.*, 3308 (1967)], in an elegant study, postulated dimeric association of certain related glycols.

(38) H. Matsuura and T. Miyazawa [*Bull. Chem. Soc. Jap.*, **40**, 85 (1967)] have presented other lines of evidence for *gauche* hydroxyls (in the liquid state) of ethanediol.

Concerning the effect of dilution,[37c] it is suggested that the *threo* conformer T_T is relatively more important in the dimeric and polymeric forms owing to minimum steric hindrance to external association.[27] Going to the intramolecularly bonded monomer, T_{G^2} becomes somewhat more important, since in this conformer the largest groups may again be *trans*. The increase in J values for the *erythro* isomers is more difficult to explain. Possibly the nonhydrogen-bonded conformer E_T becomes somewhat more important on dilution, since the intramolecular bond in E_{G^1} and/or E_{G^2} is none too stable.

The much larger effect of moving to highly polar solvents such as DMSO is superficially similar to the effects of dilution. For the *threo* isomers, hydroxyl–hydroxyl hydrogen bonding is largely replaced by bonding to DMSO. There is no particular necessity for conformer T_T in DMSO, and the other conformers become increasingly populated, resulting in a lower coupling constant. For the *erythro* isomers E_T is formed at the expense of E_{G^1} and/or E_{G^2} and a larger J value results.

Experimental Section

Compounds *erythro*- and *threo*-**3** were prepared by acid-catalyzed opening of the epoxide. The substrate, 1-phenyl-2,3-epoxypropane (10.7 g, 0.08 mol), in 20 ml of ether was stirred overnight with 0.5 ml of perchloric acid in 100 ml of water. The ether layer was separated, and the aqueous layer was extracted with 50 ml of ether. The combined ether layers were extracted with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent left an oil that could not be crystallized. The oil was chromatographed on a 60 × 2 cm column of silica gel, using increasing amounts of ether in hexane as eluent. Most fractions were oils with discouraging nmr spectra. One fraction (pure ether as eluent) partially crystallized on long standing. The solid was recrystallized from ether–pentane by the triangle scheme and afforded *erythro*-**3**, yield 1.8 g, mp 88.0–89.0° (lit.[40] mp 92°), and *threo*-**3**, yield 0.2 g, mp 52.2–53.2° (lit.[14,40] mp 52°). A total of 0.5 g less pure *threo* isomer was obtained.

Compound *threo*-**4** was prepared by the method of Zincke.[41] The oily product was distilled over a short-pass still head, bp 125–129° (0.5 mm). The nmr spectra indicated no extraneous peaks.

Compound *erythro*-**4** was prepared by the method of Bonner and Raunio[42] from iodine, silver acetate, and 1-phenyl-1-butene, hereafter called procedure A. The product showed a melting point of 42–44° (lit.[40] mp 41°).

Compound *threo*-**5** was prepared by a variant of procedure A as described below, mp 73.6–74.2° (lit.[40] mp 81°). The nmr spectrum disclosed no impurities.

Compound *erythro*-**5** was prepared by a variant of procedure A. The intermediate ester was cleaved with dilute sodium hydroxide in water, yielding a nonhydroxylic oil, probably an epoxide. This material was stirred with 0.3 ml of formic acid in 10 ml of water overnight. The crude product was extracted with ether and dried over magnesium sulfate, and the solvent was evaporated. The product crystallized on long standing and was recrystallized twice from ether–hexane, mp 103.2–103.9° (lit.[40] mp 108°). No impurities were evident in the nmr spectrum.

Compound *threo*-**6** was prepared similarly to *erythro*-**5** described above. The reaction in this case was markedly nonstereospecific, with a mixture of epoxides being formed from either pure *cis*- or mostly *trans*-3,3-dimethyl-1-phenyl-1-butene. The cleavage of the mixture of epoxides, however, yielded predominantly a single diol **6** plus much ketonic material. The diol **6** was re-

(39) Conformers T_{G^1} and E_{G^1} are unlikely in **5** and **8** owing to severe 1,3 interactions (see ref 22).

(40) M. Tiffeneau, J. Levy, and P. Weill, *Bull. Soc. Chim. Fr.*, **49**, 1606 (1931).

(41) T. Zincke and K. Zahn, *Chem. Ber.*, **43**, 849 (1910).

(42) W. A. Bonner and T. Raunio, *J. Org. Chem.*, **31**, 291 (1966).

crystallized as before, mp 93–94°. Similar results to the above were obtained beginning with mostly *trans* olefin. Only traces of the second diol were evident. Owing to the similarities in infrared hydrogen bonding spectra and similar nmr dilution shifts with the above *threo* materials, this material, mp 94°, is assigned the *threo* configuration.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.20; H, 9.30. Found: C, 74.08; H, 9.36.

Compound *erythro*-**6** was finally prepared by oxidizing the *cis* olefin with potassium permanganate according to the procedure of Bonner and Raunio,[42] mp 80.1–80.6°.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.20; H, 9.30. Found: C, 73.98; H, 9.44.

Compound *threo*-**7** was prepared by procedure A, mp 62–64° (lit.[42] mp 64°).

Compound *threo*-**8** was prepared by the procedure of Lucas and coworkers.[43,44] To *cis*-4-methyl-2-pentene (26 g 0.31 mol) stirred in 150 ml of water, 100 ml of acetic acid, and 2 ml of sulfuric acid was added N-bromosuccinimide (71 g, 0.4 mol). The reaction mixture was stirred overnight and then extracted several times with ether. The ether layers were extracted with an equal volume of water, dilute sodium carbonate, and water, and dried over magnesium sulfate. The solvent was evaporated and the remaining oil was distilled over a Vigreux column at 17 mm. The fractions collected from 74–82° (27.1 g) were the mixed bromohydrins.

The bromohydrin (33.5 g, 0.185 mol) was stirred in 150 ml of water, and a solution of 8 g of sodium hydroxide in 30 ml of water was added dropwise. The final solution was gently heated. Upon cooling the solution was extracted with ether as before and dried, solvent was evaporated, and the epoxide was distilled through a 30-cm Podbielniak column, yield 9.2 g (50%), bp 98–103°.

The epoxide (2.3 g, 0.021 mol) was placed in 15 ml of acetic acid, 40 ml of water, and 0.5 ml of perchloric acid and stirred at room temperature for *ca.* 16 hr. The solution was saturated with ammonium chloride and extracted many times with ether. The ether layers were extracted with an ammonium chloride solution and dried over magnesium sulfate, and the solvent was evaporated. The residue was recrystallized from ether–hexane, mp 55.3–56.4° (lit.[45] mp 59.7°).

Compound *erythro*-**8** was prepared similarly from the commercial *trans* olefin, mp 51.5–52.5° (lit.[45] mp 49.6°).

Compound *threo*-**9** was prepared similarly, mp 81.1–82.0° (lit.[45] mp 78.5°).

Compound *erythro*-**9** was prepared similarly, mp 73.8–74.6°.

Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.19. Found: C, 63.72; H, 12.06.

The 3-methyl-*trans*-1,2-cyclohexanediols were prepared by the procedure of Adkins and Roebuck.[46] The solid isomer **11** was recrystallized twice from methylene chloride–carbon tetrachloride, mp 95.5–97.0° (lit.[46] mp 96°). The remaining oil was distilled over a short pass head, bp 104–113° (*ca.* 4 mm). However, the nmr spectrum indicated extensive contamination. The *trans*-diol **12** was obtained by preparative vpc on a 5 ft × 0.375 in. 10% LAC 446 acid-washed Chromosorb W column. At a column temperature of 190° and a flow rate of 50 ml/min, the retention time was 8.2 min. The nmr spectrum still indicated slight impurity.

The 3-methyl-*cis*-1,2-cyclohexanediol (**10**) was prepared by the permanganate oxidation method of Bonner and Raunio,[42] mp 82–83° (lit.[47] mp 81–82°).

The nmr data were obtained on a Varian A-60D instrument *vs.* tetramethylsilane as internal standard. A trace of trifluoroacetic acid was added to promote rapid exchange. The coupling constants were taken by averaging the data from three to five 500-sec 100-Hz sweeps in either direction at each concentration (precision ±0.1 Hz). The spectrum of each compound was run at least twice using fresh solutions. The trends in J values were always as indicated in Table I, although the absolute values varied slightly from run to run (±0.2 Hz). The time-average spectra of **5** were obtained with a Varian HA-100 instrument at concentration of 0.1% (50-fold accumulation). It was impossible to go to lower concentrations without adding macro quantities of trifluoroacetic acid to catalyze exchange. The above spectra were simulated at one concentration using the LAOCOON III program with a Calcomp plotter trace of the spectrum. The simulations were run until the plot was superimposed with the original. However, the observed line separations were very close to the actual coupling constants, with the exception of **11**.

The infrared data were obtained on a Perkin–Elmer Model 237 instrument and standardized against known polystyrene absorptions. The solvents used were reagent grade in each case; however, carbon tetrachloride was dried over Linde Molecular Seive 4A before use. The infrared data is considered good to ±5 cm^{-1}.

Registry No.—*erythro*-**3**, 1075-04-3; *threo*-**3**, 1075-05-4; *erythro*-**4**, 19774-62-0; *threo*-**4**, 19774-63-1; *erythro*-**5**, 19776-13-7; *threo*-**5**, 19776-14-8; *erythro*-**6**, 23570-91-4; *threo*-**6**, 23646-54-0; *threo*-**7**, 5565-57-1; *erythro*-**8**, 6702-10-9; *threo*-**8**, 6464-40-0; *erythro*-**9**, 23646-57-3; *threo*-**9**, 23646-58-4.

Acknowledgment.—Initial support by the NSF was appreciated. Dr. M. E. Munk is thanked for a preprint of his interesting related work. Professor R. W. King is especially thanked for his efforts in obtaining the 100-MHz spectra.

(43) H. J. Lucas, M. Schlatter, and R. Jones, *J. Amer. Chem. Soc.*, **63**, 22 (1941).

(44) C. E. Wilson and H. J. Lucas, *ibid.*, **58**, 2396 (1936).

(45) M. L. Sassiver and J. English, *ibid.*, **82**, 4891 (1960).

(46) H. Adkins and A. K. Roebuck, *ibid.*, **70**, 4041 (1948).

(47) M. Mousseron, G. Manon, and C. Combes, *Bull. Soc. Chim. Fr.*, 396 (1949).

Substituent Effects on the Orientation of Diels–Alder Reactions. I[1,2]

CIRILL SCHMIDT

Department of Chemistry, University of Prince Edward Island, Malpeque Campus, Charlottetown, Prince Edward Island, Canada

Received August 8, 1969

A novel attempt was initiated to investigate the transition state of the diene synthesis by studying the structures and ratios of adducts formed from 1,4 unsymmetrically disubstituted dienes with 2,6-disubstituted benzoquinones. The competitive *ortho*[3]-directing influence of acetoxy and methyl groups was studied by treating 1-acetoxy-1,3-pentadiene with 2,6-dimethylbenzoquinone in a Diels–Alder reaction. The structures of the two adducts formed (**4** and **5**) were elucidated and their ratio was determined. The acetoxy group was found to be four times more powerful as an *ortho* director than a methyl group. A similar study with methyl sorbate and the same quinone revealed that the relative *ortho*-directing influence of a carbomethoxy group compared with methyl is even more pronounced, since only one of the two possible adducts (**6**) was isolated. The readily available intermediate **10** is a potential precursor for the synthesis of highly oxygenated decanortriterpenes of the quassin type.[4]

Despite intensive efforts devoted to its study, the mechanism of the Diels–Alder reaction warrants further attention. While the concerted nature of the reaction is well established, it is believed that the two σ bonds do not form completely simultaneously.[5–7] The characteristic Diels–Alder orientation rules[8] have been regarded as manifestations of the unequal σ-bond formation in the transition state. The suggested mechanisms postulating the existence of discrete intermediates, however, do not account for all the observations concerning Diels–Alder reactions.[5,6]

The majority of the additions studied involved the reaction of dienes carrying only one substituent at the terminal positions and an α,β-unsaturated carbonyl dienophile.[5,9,10] Owing to the special steric and electronic nature of hydrogen, it would be more informative to study the additions of 1,4 unsymmetrically disubstituted butadienes to 2,6-disubstituted benzoquinones (eq 1, 2).

The determination of the structures and the ratio of the two possible adducts in a number of critically chosen cases should provide a deeper insight into the transition state of Diels–Alder reactions.

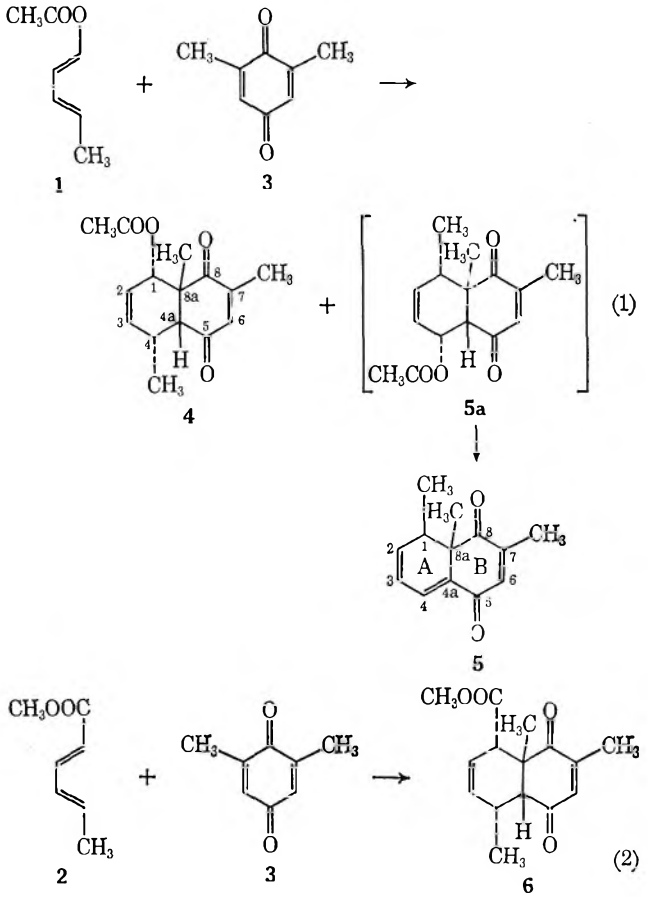
Such an experimental design should have the following advantages compared with the known examples.

(A) The electronic moiety at the four carbon atoms involved in the formation of the two σ bonds can be efficiently varied.

(B) The relative *ortho*-directing influence of the two terminal substituents[11] (other than H) can be studied by allowing competition within the same diene for the *ortho* or *meta*[3] positions in the adduct.

(C) Selecting a 2,6-disubstituted benzoquinone in lieu of an α,β-unsaturated carbonyl compound will allow a more representative study of the role of the substituent itself in the dienophile. The unsymmetrical electric field in the substituted quinone is entirely due to the substituent, whereas in the α,β-unsaturated carbonyl dienophile the presence of only one electron-withdrawing group overwhelms the influence of the substituent.

In the present study the electron-donating properties of an acetoxy group in diene **1** are exposed to the



(1) Presented in part at the 52nd C.I.C. Conference, Montreal, Canada, May 28, 1969.

(2) This work was carried out entirely on the premises of St. Dunstan's University, Charlottetown, Prince Edward Island, Canada.

(3) The terms *ortho* and *meta* refer to the relative positions of the angular methyl group to the two substituents contained in the cyclohexene ring of the Diels–Alder adduct (see eq 1).

(4) Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos, and C. Podešva, *Tetrahedron*, **18**, 1433 (1962).

(5) A. S. Onishchenko, "Diene Synthesis," Israel Program for Scientific Translations, Jerusalem, 1964.

(6) J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).

(7) A. Wassermann, "Diels–Alder Reactions," Elsevier Publishing Corp., New York, N. Y., 1965.

(8) (a) Addition of a 1-substituted butadiene to an unsymmetric dienophile results in a high *ortho*/*meta* isomer ratio. (b) Addition of a 2-substituted butadiene to the same dienophile leads to a high *para*/*meta* isomer ratio. (c) The structure of the predominant adduct of 1,2- or 1,3-disubstituted dienes corresponds to that predicted for a 1-substituted diene (see ref 5, 6).

(9) A. A. Petrov and N. P. Sopov, *Zh. Obshch. Khim.*, **27**, 1795 (1957).

(10) A. A. Petrov and V. Lyndvig, *ibid.*, **25**, 739 (1955).

(11) The directing influence of a terminal group outweighs that of any other substituent in the diene (ref 8c). It is therefore advisable to concentrate on 1,4-disubstituted butadienes.

mechanistic challenge of the nearly neutral methyl group, which is endowed only with hyperconjugative electron donation (eq 1).

The second diene 2 allows comparison of the electron-withdrawing carbomethoxy group with a methyl group in the same manner (eq 2).

Diels–Alder reactions of these two dienes are studied with the same dienophile—2,6 dimethylbenzoquinone (**3**).

The steric requirements of the three groups involved are as close to each other as such a selection permits.

Results

Diels–Alder Reaction of 1-Acetoxy-1,3-pentadiene (1) with 2,6-Dimethylbenzoquinone (3).—The novel 1-acetoxy-1,3-pentadiene was readily prepared from 2-penten-1-al using acetic anhydride and potassium acetate in 89% yield.[12] Since the homogeneous product reacts with the quinone without any difficulty, diene **1** is assumed to possess the *trans,trans* configuration.

The reaction of the acetoxydiene **1** and xyloquinone **3** in benzene at 150° led to an 85% yield of **4** and **5** in a ratio of 4:1. An attempt to convert **4** into **5** under the same reaction conditions proved to be unsuccessful, indicating a difference in orientation[13] of the two products.

The structure of the minor product **5** follows from its manner of formation. The molecular weight of the product at *m/e* 202 represents the loss of acetic acid from the primary Diels–Alder product **5a** (mol wt, 262), which, however, could not be observed. The elimination of acetic acid at this relatively low temperature can be explained by the 1,3 positions of the acetoxy and keto group.

The uv spectrum of the bright yellow product indicates a novel conjugated system. The low intensity of the highest peak at 342 mμ (ε 7000) might be explained by the nonlinear conjugation of the butadiene system in ring A with the enedione system of ring B. The nmr and ir of product **5** are in agreement with the assigned structure.

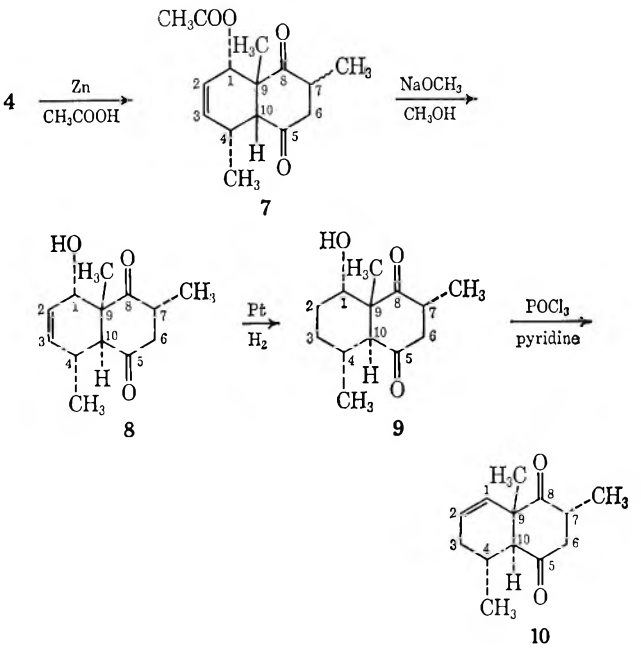
Since position 1 in compound **5** is vinylogously α to the 5-keto group, it can be assumed that the 1-methyl group is in the more stable quasiequatorial position.

The structure of **4** was elucidated by chemical means (Scheme I). The spectroscopic properties, mass spectroscopic molecular weights, and elemental analyses of the crystalline compounds **4**–**10** were in agreement with the proposed structures.

The diketo alcohol **9** was recovered unchanged when its methanol solution was heated in the presence of dilute sulfuric acid. The only other possible structure, **11**, possessing the alternative orientation, is therefore excluded. A β-hydroxy ketone under these conditions should have led to an α,β-unsaturated ketone. This elimination was inhibited by the presence of the angular methyl group in **9** at C-9.

The fact that **9** was recovered after the above-mentioned treatment allows the tentative assignment of its stereochemistry as portrayed. The ring junction is assumed to be *trans*, and the 7-methyl group is regarded to be equatorial in order to avoid 1,3-diaxial interaction with the angular methyl group. The 4-methyl and 1-hydroxy groups can be assigned *trans* to the angular methyl group as a consequence of the *endo*,-*cis*-addition principle of Diels–Alder reactions.

Scheme I



It is possible that during the acidic treatment of **9**, a retro aldol reaction took place; this however, must have been reversible, regenerating the original compound.

In order to obtain more positive proof, the diketo alcohol was converted into the unsaturated ketone **10** by treatment with phosphorus oxychloride in pyridine. Compound **10** was recovered unchanged after refluxing its methanol solution in the presence of sodium methylate. The fact that the β,γ-unsaturated ketone did not isomerize to the α,β isomer confirms the position of the angular methyl group. The lack of change allows the stereochemical assignment in **10** as drawn. The additional bonus of structure **10** is that it could serve as a precursor for the synthesis of quassin and other decanortriterpenes,[4] representing rings A and B with the correct stereochemistry and manageable functionality.

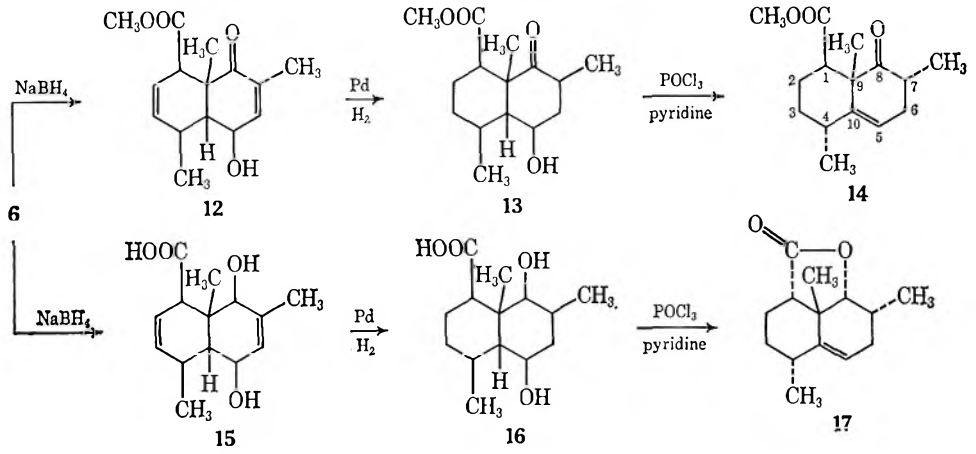
Diels–Alder Reaction of Methyl Sorbate (2) with 2,6-Dimethylbenzoquinone (3).—The reaction of 2,6-dimethylbenzoquinone with methyl sorbate was carried out by heating the benzene solution of the two compounds in a sealed tube for 35 hr at 150°. Only one product, **6**, was isolated from the reaction mixture corresponding to an 80% yield based on the amount of reacted quinone. Attempts were unsuccessful to detect the adduct with the alternative orientation. Adduct **6** had the correct mass, elemental analysis, and spectroscopic properties in agreement with the proposed structure, elucidated by chemical means as outlined in Scheme II.

Reduction with sodium borohydride led to a mixture of **12** and **15**, which was hydrogenated without separation in the presence of palladium on charcoal, giving **13** and **16**. The latter two components were then subjected to phosphorous oxychloride and pyridine, leading to **14** and **17**, which could be readily separated by

(12) A similar procedure was used for the preparation of 1-acetoxybutadiene: B. Y. Blanc, *Helv. Chim. Acta*, **44**, 1 (1961).

(13) Orientation is defined as the influence of a substituent in the diene or dienophile on the relative positions of substituents in the Diels–Alder adduct.

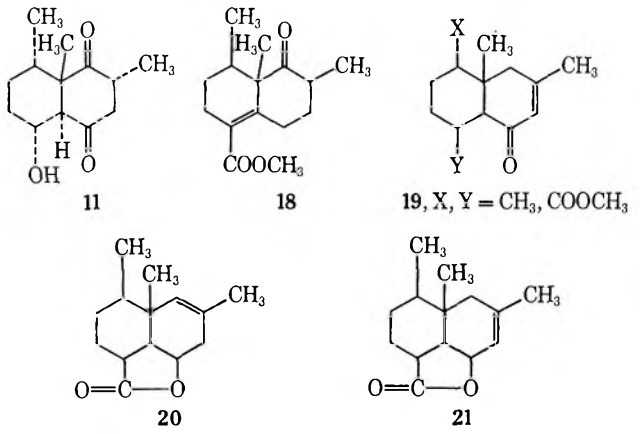
SCHEME II



preparative thick layer chromatography. The total yield of the latter two compounds corresponded to 70% based on **6**. The ratio of **14** to **17** was 2:1.

The unsaturated keto ester **14** had the correct mass and spectroscopic properties. Compound **14** was recovered unchanged after treatment with sodium methylate in methyl alcohol or after similar acidic treatment at 60° for 6 hr.

The fact that **14** remained unchanged and did not isomerize to a uv-active compound proves that the structure of the adduct is **6**, since a similar series of reactions with the alternatively oriented compound should have produced **18** instead of **14**.



It is also clear that in **6** the less hindered 5-keto group was reduced to a hydroxyl group, giving **12**, since the reduction of the more hindered keto group followed by hydrogenation and elimination should have produced **19**, contrary to the chemical and spectroscopic data.

An examination of the spectroscopic properties of the crystalline **17** adduces evidence for the assignment of the orientation in **6**. The lactone (mol wt, 220) shows only end absorption in the uv. The nmr of **17** contained a singlet for the angular methyl group and two doublets for the other two methyl groups.

These data prove that the orientation of adduct **16** was as represented. Had it been the opposite, the structure of the lactone could have been only **20** or **21**, contrary to the fact that the nmr spectrum of compound **17** does not indicate a methyl group situated on a double bond. It is therefore concluded that **6** has the structure shown.

The stereochemistry of **14** was assigned as follows. The angular methyl group should be *trans* to the 4-methyl group as a consequence of the *endo,cis*-addition principle. The carbomethoxy and 7-methyl groups are assumed to be in the equatorial position, since the compound was recovered unchanged after attempts of isomerization.

The γ-lactone **17** should have the angular methyl group *trans* to the 4-methyl group for the same reasons as in **14**. Inspection of a Dreiding model shows that the γ-lactone must be *trans* to the angular methyl group. The 7-methyl group is assumed to be in the more stable equatorial position.

Discussion

The present orientation study demonstrates for the first time that the *ortho*-directive influence of either an electron-donating group (acetoxy) or an electron-withdrawing group (carbomethoxy) is more powerful than that of a methyl group as defined in the present experimental design.

This indicates that polarity considerations should not be given high priority in the investigation of the transition state of the diene synthesis.

The results cannot be attributed to steric reasons, since the three groups are of similar sizes at least in the vicinity of the reaction sites—the terminal positions of dienes.

The internal electronic competition of a carbomethoxy group against a methyl led only to the *ortho* isomer, whereas the directive influence of an acetoxy group against its methyl counterpart led to a 4:1 *ortho–meta* mixture. From this it appears that the carbomethoxy group is a more powerful *ortho*-orienting group than the acetoxy group.

The results therefore indicate the following order of *ortho*-orienting influence, as defined by eq 1 and 2.

$$COOCH_3 > OCOCH_3 > CH_3$$

The recently published[14–17] perturbational MO calculations concerning the orientation problem of Diels–Alder reactions could be applied to the examples of the present paper.

(14) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968).
(15) L. Salem, *J. Amer. Chem. Soc.*, **90**, 543, 553 (1968).
(16) W. C. Herndon and L. H. Hall, *Theor. Chim. Acta*, **7**, 4 (1967).
(17) J. Klopman, *J. Amer. Chem. Soc.*, **90**, 223 (1968).

It is hoped that accumulation of further orientation studies will lead to a better understanding of the mechanism and extend the synthetic utility of the reaction.

Experimental Section[18]

1-Acetoxy-1,3-pentadiene (1).—A 60-g sample of 2-penten-1-al prepared according to the procedure of Grunager and Greco[19] was refluxed with 180 ml of acetic anhydride in the presence of 60 g of anhydrous potassium acetate for 6 hr. An efficient mechanical stirrer was used to agitate the rather viscous solution. The mixture was then cooled to 50° and poured on ice. The solution was extracted three times with benzene. The combined benzene extracts were stirred mechanically with a 10% solution of sodium bicarbonate while cooling with ice water. Some solid sodium bicarbonate was also added every 10 min to maintain the solution alkaline. After 2 hr the pH of the water solution remained permanently alkaline. This treatment completely removed the excessive acetic anhydride and acetic acid from the solution. The benzene phase was then separated, washed with saline solution in the presence of ice, and dried with magnesium sulfate. Most of the benzene was removed by atmospheric distillation. The residue was then fractionated at 100 mm. After the collection of 1–3 ml of forefraction, the product was distilled at 100–105° (100 mm), yielding 79 g (89%) of diene acetate. The product appeared to be homogeneous when analyzed using vpc on several columns: mass spectrum (70 eV) *m/e* (rel intensity) 126 (76, parent peak), 98 (9.5), and 83 (100); ir (CCl_4) 2900, 1770, 1670, 1620, and 1200 cm^{-1}; uv max (95% C_2H_5OH) 242 mμ (ε 19,000); nmr ($CDCl_3$) τ 8.28 (d, 3, J = 8.2 Hz, =CHCH_3), 7.94 (s, 3, $OCOCH_3$), and 4.21 (m, 4, olefinic protons).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.60; H, 7.98. Found: C, 66.20; H, 7.91.

1,5,8,8a-Tetrahydro-1β,7,8aβ-trimethyl-5,8-dioxonaphthalene (5) **and** ***cis*-1,4,4a,5,8,8a-Hexahydro-1α-acetoxy-4α,7,8,8aβ-trimethyl-5,8-dioxonaphthalene** (4).—A solution of 10 g of 2,6-dimethylbenzoquinone and 20 g of 1-acetoxy-1,3-pentadiene in 50 ml of benzene was heated for 18 hr at 150° in a sealed tube. The brown reaction mixture was distilled at 100 mm. After the removal of benzene, 12 g of unreacted diene was collected, distilling at 100–105° (100 mm). The residue was then distilled at 0.2 mm.

A 2-g sample of unreacted 2,6-dimethylbenzoquinone was recovered by sublimation. Using tlc it was established that the residue contained two products along with a small amount of quinone. A quantitative glpc determination revealed that the molar ratio of **4** to **5** was 4:1. The two compounds were separated by chromatographing on a 75-fold amount of neutral alumina, eluting with ether–benzene (1:5). The small amount of residual quinone was destroyed on the surface of alumina.

From the first fractions, 2.06 g of bright yellow **5** was isolated, corresponding to a 16% yield based on the amount of quinone reacted. It was recrystallized from pentane: mp 36°; mass spectrum (70 eV) *m/e* (rel intensity) 202 (100, parent peak), 187 (43), 159 (93), etc.; ir (CCl_4) 2900, 1690, 1665, 1620, 1450, and 1300 cm^{-1}; uv max (95% C_2H_5OH) 342 mμ (ε 7000), 248 (12,650), and 217 (8650); nmr (CCl_4) τ 9.11, (d, 3, J = 7.3 Hz, CH_3-1), 8.67 (s, 3, CH_3-8a), 7.96 (s, 3, CH_3-7), 7.16 (q, 1, proton on Cl), 3.93 (m, 2, olefinic protons), 3.33 (m, 1, olefinic proton), and 3.14 (m, 1, olefinic proton).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.30; H, 6.99. Found: C, 77.10; H, 6.91.

The more polar product **4** was isolated from the subsequent chromatographic fractions; 10.45 g of crystalline **4** was isolated, corresponding to a 69% yield based on the amount of converted quinone. It was recrystallized from methanol: mp 136°; ir (CCl_4) 2950, 1750, 1690, 1370, and 1240 cm^{-1}; uv max (95% C_2H_5OH) 242 mμ (ε 10,200); mass spectrum (70 eV) *m/e* (rel intensity) 262 (53, parent peak), 220 (48), 202 (100), etc.; nmr ($CDCl_3$) τ 8.93 (s, 3, CH_3-8a), 8.80 (d, 3, J = 3.1 Hz, CH_3-4), 7.30 (m, 1, proton at C-4), 6.90 (d, 1, J = 6.7 Hz, proton at C-4a), 4.65 (d, 1, J = 4.5 Hz, proton at C-1), 4.20 (m, 2, olefinic protons at C-2 and -3), and 3.36 (m, 1, proton at C-6).

The coupling pattern is consistent only with the orientation represented by **4**; the opposite assumption is irreconcilable with the present nmr data.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.92. Found: C, 68.81; H, 6.95.

The combined yield for **4** and **5** corresponds to 85% based on the amount of quinone consumed.

***cis*-1α-Acetoxy-4α,7,9β-trimethyl-2-octal-5,8-dione** (7).—A solution of 1.268 g of the crystalline adduct **4** in 30 ml of glacial acetic acid was stirred and heated at 60° for 1 hr in the presence of 3 g of zinc dust. After cooling, acetone was added to the reaction mixture. The excessive zinc and zinc acetate was filtered using a Büchner funnel and the precipitate was washed with acetone. The filtrate was evaporated to incipient dryness using a rotary evaporator. The residue was dissolved in 50 ml of chloroform. The residual acetic acid was removed by washing the chloroform solution in succession with 10% sodium bicarbonate solution and water; it was dried with magnesium sulfate; and the chloroform was evaporated, yielding 1.218 g (96.2%) of crystalline diketone **7**. An analytical sample was prepared by recrystallization from methyl alcohol: mp 147.5°; ir (CCl_4) 2950, 1750, 1718, and 1250 cm^{-1}; uv end absorption; nmr ($CDCl_3$) τ 9.06 (s, 3, CH_3-9β), 8.92 (two coinciding doublets, J = 6.2 Hz, CH_3-6,4 and -7), 6.71–7.63 (m, 5, protons at C-4, -4α, -6, -7), 4.80 (t, 1, proton at C-1), and 4.56 (m, 2, olefinic protons), mass spectrum (70 eV) *m/e* (rel intensity) 264 (15, parent peak), 221 (40), and 190 (100).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.60; H, 7.62. Found: C, 68.81; H, 7.68.

***trans*-1α-Hydroxy-4α,7α,9β-trimethyl-2-octal-5,8-decaldione** (8).—A 1.10-g sample of **7** was dissolved in 10 ml of methyl alcohol containing 0.32 g of sodium methylate. The solution was allowed to stand for 1 hr at room temperature, 15 ml of water was added, and the solution was extracted with four 35-ml portions of ether. The combined ether extracts were washed with saline solution and dried with magnesium sulfate and the ether was evaporated. A crystalline material, yield 0.9 g (97%), was isolated. Tlc analysis of the product revealed the presence of one compound. It was recrystallized from methyl alcohol: mp 129°; mass spectrum (70 eV) *m/e* (rel intensity) 222 (15), 207 (25), and 133 (100); ir ($CHCl_3$) 3500, 2950, 1710, 1460, and 1000 cm^{-1}; uv end absorption; nmr ($CDCl_3$–D_2O) τ 9.18 (s, 3, CH_3-9), 8.88 (d, 6 H, J = 6.3 cps, CH_3-4 and -7), 8.16–6.77 (m, 5, protons at C-4, -6, -7, and -10), 5.82 (d, 1, CHOH), and 4.33 (m, 2, olefinic protons at C-2 and -3).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.30; H, 8.17. Found: C, 70.34; H, 8.15.

***trans*-1α-Hydroxy-4α,7α,9β-trimethyl-5,8-decaldione** (9).—A solution of 0.90 g of **8** in 50 ml of methanol was hydrogenated overnight in the presence of 20 mg of Adams catalyst. After the catalyst had been filtered, the methanol was evaporated, yielding 0.85 g (95%) of a chromatographically homogeneous crystalline product. An analytical sample was obtained by recrystallization from benzene: mp 127°; mass spectrum (70 eV) *m/e* (rel intensity) 224 (80), 177 (50), and 167 (100); ir ($CHCl_3$) 3500, 2900, 1710, and 1470 cm^{-1}; uv end absorption; nmr ($CDCl_3$) τ 9.17 (s, 3, CH_3-9), 8.98 (d, 3, J = 6 cps, CH_3-4), 8.92 (d, 3, J = 6 cps, CH_3-7), and 8.67–6.73 (m, 10).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 8.98. Found: C, 69.52; H, 8.90.

A solution of 20 mg of 9 in 5 ml of methanol–water (2:1) was refluxed for 5 hr in the presence of 1 ml of 10% sulfuric acid. After cooling, the solution was extracted with four 10-ml portions of ether. The combined ether extracts were washed with saline solution and dried with magnesium sulfate. After the evaporation of ether, the tlc and ir of the product were found to be identical with those of **9**.

***trans*-4α,7α,9β-Trimethyl-1-octal-5,8-dione** (10).—A solution of 1.50 g of **9** in 30 ml of methylene chloride and 5 ml of dry pyridine was cooled with ice water, 1.5 ml of phosphorus oxychloride was added, and the mixture was allowed to stand overnight. Next morning the reaction mixture was poured on ice. The solution was extracted four times with 20 ml of chloroform. The com-

(18) All melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. The elemental analyses were carried out by Pascher Mikroanalytical Laboratorium, Bonn, West Germany, and Schwarzhopf Mikroanalytical Laboratory, Woodside, N. Y. The ir spectra were recorded on a Perkin–Elmer Model 137 B infracord spectrophotometer. The uv spectrograms were taken on a Coleman–Hitachi Model 124 double-beam grating spectrophotometer. The nmr spectra were recorded on a Varian Associates 56.4-MHz spectrophotometer. The mass spectra were obtained with a Hitachi Perkin–Elmer Model RMS-4 spectrometer.

(19) R. Grunanger and D. Greco, *Gazz. Chim. Ital.*, **88**, 296 (1958).

bined chloroform extracts were washed in succession with water, dilute sulfuric acid (in the presence of ice), water, 5% sodium bicarbonate, solution and water. The chloroform solution was then dried with magnesium sulfate and evaporated to dryness, yielding 1.150 (85%) of a crystalline, tlc-homogeneous product. An analytical sample was prepared by recrystallization from benzene: mp 98°; mass spectrum (70 ev) *m/e* (rel intensity) 206 (20, parent peak), 191 (15), and 107 (100); ir ($CHCl_3$) 2900, 1720, and 1460 cm^{-1}; uv end absorption; nmr ($CDCl_3$) τ 9.00 (s, 3, CH_3-9), 8.81 (d, 6, J = 7 Hz, CH_3-4 and -7), 8.38–6.89 (m, 7), 4.37 (m, 1, olefinic protons), and 4.06 (m, 1, olefinic protons).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.70; H, 8.78. Found: C, 75.63; H, 8.74.

cis-1,4,4a,5,8,8a-Hexahydro-1α-carbomethoxy-4α-7,8aβ-trimethyl-5,8-dioxonaphthalene (6).—The methyl sorbate was prepared according to Wheeler[20] by the esterification of sorbic acid with methyl alcohol.

A solution of 37.8 g of methyl sorbate and 13.6 g of 2,6-dimethylbenzoquinone in 30 ml of benzene was heated at 150° for 36 hr in a sealed tube. After the tube had been opened, the reaction mixture was distilled under vacuum. A 15-g sample of diene was recovered from the fraction distilling at 50–65° (20 mm). A 1.5-g sample of the unreacted quinone was collected by sublimation at 100° (0.2–0.6 mm), corresponding to an 89% conversion of quinone. The brown residue was then chromatographed on 600 g of neutral alumina, eluting with benzene. The first fraction contained some unreacted sorbate. From the subsequent fractions, 18.6 g of chromatographically homogeneous **6** was collected corresponding to an 80% yield based on the quinone consumed. An analytical sample was obtained by recrystallization from methyl alcohol: mp 109–110°; mass spectrum (70 eV) *m/e* (rel intensity) 262 (50, parent peak), 247 (40), 230 (45), and 188 (100); ir (CCl_4) 2900, 1745, 1690, and 1610 cm^{-1}; uv max (96% C_2H_5OH) 242 mμ (ε 10,500); nmr ($CDCl_3$) τ 8.98 (s, 3, CH_3-8a), 8.80 (d, 3, J = 7.2 Hz, CH_3-4), 8.02 (s, 3, CH_3-7), 7.43 (m, 1, proton at C-4), 6.69 (m, 2, protons at C-10 and -1), 6.34 (s, 3, carbomethoxy), 4.42 (m, 2, protons at C-2 and -3), and 3.49 (m, 1, proton at C-6).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.92. Found: C, 68.78; H, 6.93.

Conversion of 6 into 1-Carbomethoxy-4α,7α,9β-trimethyl-$\Delta^{5,10}$-octal-8-one (14) and 8α-Hydroxy-4α,7α,9β-trimethyl-$\Delta^{5,10}$-octalin-1α-carboxylic Acid α-Lactone (17). A. Reduction with Sodium Borohydride.—To a solution of 2.097 g of **6** in 20 ml of methanol, cooled by ice water, 0.896 of sodium borohydride was added in 1 hr. The reaction was allowed to proceed at room temperature for 18 hr. The mixture was then poured onto ice and dilute hydrochloric acid and extracted three times with 40 ml of ether. The combined extracts were washed with saline solution, dried with magnesium sulfate, and evaporated to dryness. An oily product (2.27 g, 91%) was obtained. The material appeared to be homogeneous according to tlc. However, the spectral properties and chemical behavior described below revealed the presence of **12** and **15** in the ratio of 2:1: ir (CCl_4) 3500, 2950, 1745, 1710, 1690, and 1473 cm^{-1}; uv max (EtOH) 238 mμ (ε 7000). The mass spectrum of the mixture showed a prominent molecular peak for **12** at *m/e* 264. The nmr spectrum of the mixture indicated olefinic protons and signals corresponding to structures **12** and **15**. The two components were used without separation.

B. Hydrogenation.—The mixture of **12** and **15** (2.27 g) was hydrogenated in the presence of 200 mg of 10% palladium on charcoal in 30 ml of methyl alcohol for 18 hr at room temperature, at 10 psi. After the catalyst had been filtered, the methyl alcohol was evaporated, giving 2.00 g (90%) of an oily material, nmr of which revealed the complete absence of olefinic protons; ir (CCl_4) 3500, 3300, 2950, 1740, 1710, and 1475 cm^{-1}; uv end absorption. The mixture of **13** and **16** was used without isolation.

(20) J. Wheeler, *J. Amer. Chem. Soc.*, **70**, 3468 (1948).

C. Elimination.—To a dry solution of 1.128 g of **13** and **16** in 20 ml of methylene chloride, 10 ml of dry pyridine was added. Then 2 ml of phosphorus oxychloride dissolved in 10 ml of methylene chloride was dripped in while the solution was stirred and cooled with ice–water during 15 min. The solution was then allowed to stand for 18 hr at room temperature. The reaction mixture was then poured on ice and extrasted with four 50-ml portions of ether. The combined ether extracts were washed in succession, in the presence of crushed ice, with saline solution, twice with diluted sulfuric acid, saline solution, 10% sodium bicarbonate, and saline solution. The ether solution was then dried with magnesium sulfate and evaporated to dryness. The residue weighed 1.01 g. The product consisted of two well-defined components, which were separated by thick layer chromatography on silica gel plates using chloroform for the development. The bands were detected with the iodine spraying method. The more polar oily product amounted to 0.60 g, corresponding to a 50% yield based on **6**. The unsaturated keto ester **14** had the appropriate spectroscopic properties: mass spectrum (70 eV) *m/e* (rel intensity) 250 (20, parent peak), 218 (40), and 135 (100); ir (CCl_4) 2950, 1745, and 1710 cm^{-1}; uv max (96% C_2H_5OH) end absorption; nmr ($CDCl_3$) τ 8.95 (d, 6, J = 6.4 Hz, CH_3-4 and -7), 8, 76 (s, 3, CH_3-9), 6.45 (s, 3, CH_3COO), and 4.50 (t, 1, proton on C-5). An analytical sample was obtained by distilling the sample at 100–105° (0.2 mm).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.90; H, 8.79. Found: C, 72.05; H, 8.72.

A 20-mg sample of **14** was refluxed in 10 ml of methanol–water (1:1) in the presence of 10% sulfuric acid for 6 hr. The sample was recovered unchanged according to ir and tlc. An attempt at isomerization in the presence of sodium methylate in methanol under nitrogen led to similar results.

The less polar compound **17** (330 mg) was isolated in crystalline form, corresponding to a 31.5% yield based on **6**. The chromatographically homogeneous lactone was recrystallized from benzene–pentane: mp 83–84°; mass spectrum (70 eV) *m/e* (rel intensity) 220 (60, parent peak), 205 (20), 175 (20), and 159 (100); ir ($CHCl_3$) 2950, 1790, 1470, and 1100 cm^{-1}; uv end absorption; nmr ($CDCl_3$) τ 9.04 (d, 3, J = 7.7 Hz, CH_3-4), 8.86 (d, 3, CH_3-7), 8.75 (s, 3, CH_3-9), 6.1 (d, 1, J = 2.0 Hz, proton on C-8), and 4.6 (m, 1, proton on C-5).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.30; H, 9.13. Found: C, 76.37; H, 9.08.

Registry No.—**1**, 17616-45-4; **4**, 23804-07-1; **5**, 23804-08-2; **6**, 23804-09-3; **7**, 23804-10-6; **8**, 23804-11-7; **9**, 23804-12-8; **10**, 23804-13-9; **14**, 23804-14-0; **17**, 23804-15-1.

Acknowledgments.—The financial assistance of the Canadian National Research Council is gratefully acknowledged. The technical assistance of Miss V. Robertson[21] of Dalhousie University and Mr. D. Taylor of St. Dunstan's University, in the summer of 1967–1968, is greatly appreciated. The author is indebted to Mrs. E. Schmidt for providing technical assistance throughout the year. Special thanks are due to Professor Z. Valenta of the University of New Brunswick for having the nmr and mass spectra taken. Dr. J. R. Duffy, Dean of Science, is thanked for encouraging this work. The author also wishes to thank Miss P. Whelan for secretarial work.

(21) Recipient of a summer scholarship from the Atlantic Provinces Inter-University Committee on Sciences.

Bromination of Dehydroacetic Acid[1a]

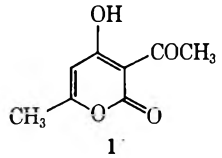
THOMAS M. HARRIS,[1b] CONSTANCE M. HARRIS, AND CHARLES K. BRUSH

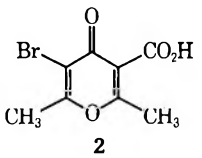
Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

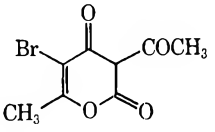
Received July 22, 1969

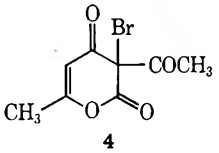
Selective bromination of dehydroacetic acid (1) afforded four different monobromination derivatives. Treatment of 1 with bromine yielded 5-bromodehydroacetic acid (5). A transient product, presumably 5,6-dibromo adduct 6, was detected by nmr. Hydrogen bromide catalyzed bromination of 1 yielded 3β-bromo derivative 9. The thermal (nonphotochemical) reaction of N-bromosuccinimide with 1 and the reaction of bromine with the anion of 1 both gave 3-bromo derivative 4. This compound was highly sensitive to hydrogen bromide, which reconverted it into 1. Photochemical bromination of 1 with N-bromosuccinimide in carbon tetrachloride gave 6α-bromo derivative 14. The 3β,3β-, the 3,5-, and the 3β,5-dibromo derivatives of 1 (10, 13, and 8, respectively) were also prepared. The related compounds, 4-hydroxy-6-methyl-2-pyrone (12) and its methyl ether, on treatment with N-bromosuccinimide, underwent monobromination at the 3 position to give 11 and 15, respectively. Further treatment of 11 with this reagent gave the 3,3-dibromo derivative 16.

Dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one) (1) was first prepared more than 100 years ago.[2] Subsequently the chemistry of this compound was investigated extensively. Controversy arose concerning its structure, which was not firmly established until 1924.[3] During the intervening years a bromination product was prepared by Oppenheim and Precht.[4] Although insufficient information was available to make a firm structural assignment for the derivative, structures 2, 3, and 4 were suggested by Perkin,[5] Feist,[6] and Staudinger and Becker,[7] respectively.


1


2


3


4

We have now reinvestigated the bromination of dehydroacetic acid, both by direct addition and by other methods, because of the possible utility of the bromo derivatives for the synthesis of complex pyrones. Recent interest in the chemistry of pyrones has stemmed from a possible relationship between their reactions with bases and the biosynthesis of phenolic compounds.[8]

(1) (a) Supported by Research Grant GM-12848 from the National Institutes of Health, U. S. Public Health Service. (b) Alfred P. Sloan Fellow and Research Career Development Awardee, K3-GM-27013, of the National Institutes of Health, U. S. Public Health Service.

(2) A. Geuther, *Z. Chem.* (Jena), **2**, 8 (1866); *Chem. Zentr.*, **11**, 801 (1866).

(3) C. F. Rassweiller and R. Adams, *J. Amer. Chem. Soc.*, **46**, 2758 (1924). See also J. A. Berson, *ibid.*, **74**, 5172 (1952); S. Forsen and M. Nilsson, *Arkiv Kemi*, **17**, 523 (1961); E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, **30**, 1255 (1965).

(4) A. Oppenheim and H. Precht, *Ber.*, **9**, 1099 (1876).

(5) W. H. Perkin, *J. Chem. Soc.*, **51**, 484 (1887).

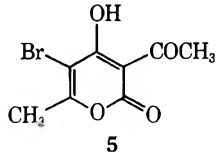
(6) F. Feist, *Ber.*, **25**, 315 (1892).

(7) H. Staudinger and H. Becker, *ibid.*, **50**, 1016 (1917).

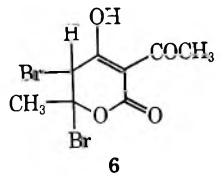
(8) For examples, see T. M. Harris, M. P. Wachter, and G. A. Wiseman, *Chem. Commun.*, 177 (1969); T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, **23**, 3435 (1967); J. L. Douglas and T. Money, *ibid.*, 3545 (1967); D. G. Pike, J. J. Ryan, and A. I. Scott, *Chem. Commun.*, 629 (1968); L. Crombie and A. W. G. James, *ibid.*, 357 (1966).

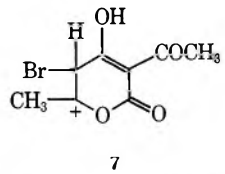
Results and Discussion

The initial studies with dehydroacetic acid involved bromination under the conditions described by the earlier workers,[4-7] because the structure of the resulting monobromination product had not been firmly established. Anhydrous dehydroacetic acid in chloroform was treated with 2.5 equiv of bromine containing 1 mol % iodine.[9,10] The mixture was allowed to stand for 72 hr at 5°. The product (48%) after recrystallization from methanol had the same melting point as had been reported previously. Elemental and mass spectral analysis showed that one hydrogen atom had been replaced by a bromine atom (see spectral section). The nmr spectrum indicated that the site of replacement was the 5 position giving derivative **5**, which is the enolized form of structure **3** proposed by Feist.[6]


5

To obtain additional information about the process by which **5** was formed, nmr spectra were recorded of reaction mixtures in deuteriochloroform while the reactions were taking place. Following the addition of bromine, immediate formation of a transient compound occurred. The compound was clearly distinguishable from other bromo derivatives on the basis of its nmr spectrum; in particular, the 5-proton signal was at much higher field than was observed with the other derivatives. Treatment of the solution with excess, aqueous sodium bisulfite caused a decrease in concentration of the compound, seemingly by return to **1**. However, the remaining material retained the characteristic spectrum. Adduct **6**, but not cation **7**, appeared to be compatible with this evidence.


6

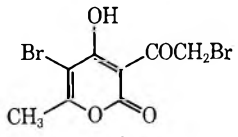

7

(9) Water appeared to lead to the formation of several unidentified by-products.

(10) The use of iodine had been suggested by Perkin.[5] However, Feist[6] considered it to be superfluous.

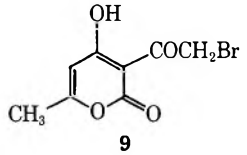
In the bromination reaction the concentration of **6** increased for several minutes. During this time the initial formation of **5** was observed, but it was not so fast as that of **6**. The subsequent course of reaction depended upon hydrogen bromide concentration. In tightly capped nmr tubes, where internally generated hydrogen bromide accumulated, acetyl bromination became a more important process than 5 bromination and the concentration of **6** decreased rapidly until it became undetectable. In uncapped tubes, much of the hydrogen bromide escaped and **6** was present for many hours, during which time gradual formation of **5** occurred. Attempts to isolate **6** were unsuccessful, in spite of the fact that under favorable conditions nearly 50% conversion into **6** could be obtained.

Dehydroacetic acid, when treated with 2 equiv of bromine at room temperature for 72 hr, afforded dibromination product **8** in 21% yield. Analysis of the nmr spectrum led to the conclusion that the second bromine atom had been introduced into the acetyl methyl group (see spectral section). Monobromo derivative **5** was treated with bromine in an attempt to synthesize **8** in a stepwise fashion. No reaction occurred until hydrogen bromide was added. Dibromo derivative **8** was isolated subsequently by chromatography. Addition of bromine across the 5,6 double bond of **5** was not observed.

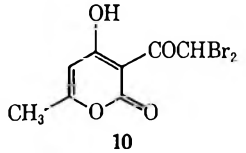


8

Various reaction conditions were investigated in a search for other bromination products. The observation that hydrogen bromide seemed to catalyze bromination at the acetyl position led to an experiment in which a solution of dehydroacetic acid in chloroform was saturated with hydrogen bromide prior to addition of bromine. The reaction afforded 50% bromoacetylpyrone **9**. Spectroscopic data confirmed the site of bromination. Surprisingly, further treatment of **9** with bromine gave only a trace of **8**; the major product (77%) was the geminal dibromo derivative **10**.



9

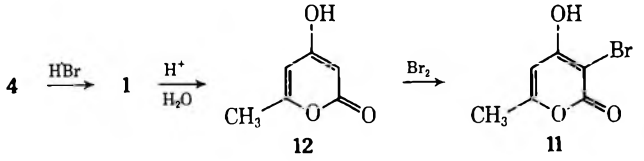


10

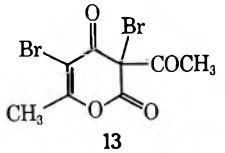
Bromination of dehydroacetic acid with N-bromosuccinimide was explored. 3-Bromodehydroacetic acid (**4**) was obtained as essentially the only product when the reaction was carried out in refluxing chloroform in darkness with a small amount of iodine as a catalyst. This bromo derivative was a liquid and decomposed on attempted distillation. The ir spectrum of **4** showed the presence of three distinguishable types of carbonyl groups.

The compound was also obtained by bromination of the anion of **1**. Treatment of the anhydrous sodium salt of **1** suspended in chloroform with 1 equiv of bromine caused immediate precipitation of sodium bromide and disappearance of the bromine color. Evaporation of the supernatant solution gave a 77% yield of **4**.

In contrast to the other bromopyrones which were relatively insensitive to anhydrous hydrogen bromide, compound **4** reacted instantaneously with it to give **1** and bromine. When this acidified mixture was allowed to stand for several hours, rebromination of **1** occurred forming **5** and **9**. A small amount of 3-bromo-4-hydroxy-6-methyl-2-pyrone (**11**) was isolated after **4** had been allowed to stand in contact with moist air for several days. This compound probably arose by conversion of **4** into dehydroacetic acid, deacetylation to form pyrone **12**, and rebromination (see below). However, direct deacetylation of **4** cannot be excluded rigorously.

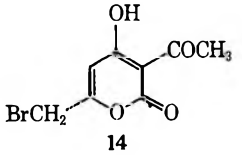


Interestingly, when the reaction of **1** with N-bromosuccinimide was carried out in the absence of iodine, a mixture of **4**, **5**, and a compound identified as dibromopyrone **13** was obtained. The source of the iodine effect is not understood. Dibromopyrone **13** was prepared directly and efficiently by treatment of **5** with N-bromosuccinimide and a catalytic amount of iodine in darkness. The compound was an unstable oil having an ir spectrum similar to that of **4**. Likewise, it reverted to **5** upon treatment with anhydrous hydrogen bromide.



13

Free-radical bromination of dehydroacetic acid afforded a fourth monobromination product. Dehydroacetic acid was treated with N-bromosuccinimide in carbon tetrachloride at ambient temperature in the presence of light from a sun lamp. The nmr spectrum of the product (**14**) indicated that bromine substitution had occurred at the 6-methyl position. None of the other monobromination products (**4**, **5**, and **9**) was detected. However, the nmr spectrum of the crude reaction mixture suggested that di- and possibly trisubstitution had occurred at the 6-methyl position. The photochemical reaction is undoubtedly a free-radical reaction involving abstraction of a hydrogen atom from the 6-methyl position. The high degree of selectivity toward the 6-methyl position may reflect the substantial resonance stabilization of the resulting radical.



14

The 3 position of dehydroacetic acid appears to be the most susceptible to electrophilic substitution, in

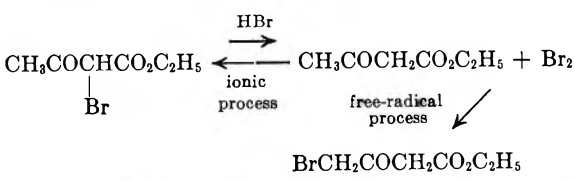
spite of the fact that reaction with molecular bromine was not observed at that position. The reaction of the anion of **1** with molecular bromine and the thermal reaction of **1** with N-bromosuccinimide both afford high yields of 3-bromo derivative **4**. However, **4** is extremely sensitive to hydrogen bromide and undergoes instantaneous and essentially quantitative debromination. We conclude that the reaction of **1** with molecular bromine to form **4** and hydrogen bromide is facile but lies far toward the side of starting materials.

$$1 + Br_2 \rightleftharpoons 4 + HBr$$

5-Bromo adduct **5** arises by a slower but less reversible reaction of **1** with molecular bromine; adduct **6** appears to be in a relatively slow equilibrium with **1** and bromine. The adduct may be an intermediate in the formation of **5**, but this point is difficult to prove. Alternatively, bromination may involve only the undetected cation **7**; interconversion of **1** (or of **7**) and **6** may play no essential part in the formation of **5**.

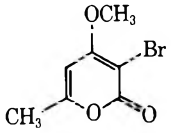
Hydrogen bromide inhibits the formation of **6** to a lesser extent than it inhibits the formation of **4**. Whereas in the latter reaction hydrogen bromide is a product and can participate directly in the reverse reaction, in the formation of **6** it merely serves to reduce the concentration of free dehydroacetic acid by conversion into the pyrylium ion.[11] Hydrogen bromide causes the site of bromination to shift to the acetyl position presumably as a result of acid-catalyzed enolization and simultaneous deactivation of the 5 position by pyrylium salt formation.

The influence of reaction conditions on the site of halogenation has been observed in other enolic systems.[12] The bromination of ethyl acetoacetate provides an interesting comparison with the present system. The initial site of substitution is the 2 position, but intermolecular rearrangement to the 4 position occurs in the presence of hydrogen bromide and free-radical initiators. The rearrangement reaction has been studied in detail.[13] Debromination of the 2-bromo ester is an acid-catalyzed, ionic process. Debromination, although facile, is reversible and the equilibrium lies almost entirely on the side of the 2-bromo ester. Rebromination at the 4 position is primarily a free-radical process; there is little tendency for acid-catalyzed enolization to occur at that position.

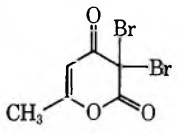


The bromination of dehydroacetic acid (**1**) differs from that of ethyl acetoacetate in two respects. First, removal of bromine from the 3 position of **1** by hydrogen bromide is essentially quantitative. Second, there are alternative ionic pathways by which **1** can undergo rebromination to give isomeric products, whereas with ethyl acetoacetate there is none. The two systems are similar to the extent that free-radical bromination is observed at sites not readily substituted by ionic means.

Two related pyrones, **12** and its 4-methyl ether, both underwent bromination exclusively at the 3 position to yield monobromo derivatives **11** and **15**, respectively.[14] Light had no effect on either reaction; both occurred rapidly at ambient temperature. Further treatment of **11** with N-bromosuccinimide gave geminally dibrominated pyrone **16**. Upon standing in air, **16** slowly reverted to pyrone **11**.



15



16

Spectral Assignments.—The structures of the bromopyrones were assigned on the basis of spectral characteristics. Nmr spectra were particularly helpful in this regard. The nmr spectra of dehydroacetic acid (**1**) and bromo derivatives **4–6, 8–10, 13,** and **14** are summarized in Table I.

TABLE I

NMR SPECTRA OF DEHYDROACETIC ACID AND ITS BROMINATION PRODUCTS

	Chemical shifts, δ[a] (relative areas)			
Compd	6-CH_3	3-$COCH_3$	5-H	OH
1	2.30 (3)	2.65 (3)	5.95 (1)	16.7 (1)
4	2.27 (3)	2.48 (3)	5.75 (1)	
5	2.48 (3)	2.70 (3)		18.0 (1)
6	2.34 (3)	2.70 (3)	4.87 (1)	16–18[b] (1)
8	2.52 (3)	4.67 (2)		16.7 (1)
9	2.33 (3)	4.70 (2)	6.06 (1)	15.5 (1)
10	2.35 (3)	7.48 (1)	6.09 (1)	15.0 (1)
13	2.46[c] (3)	2.50[c] (3)		
14	4.13 (2)	2.68 (3)	6.25 (1)	16.7 (1)

[a] Parts per million. [b] Probable location; see text. [c] The relative assignment of the two methyl groups is uncertain.

The 6-methyl group of **1** is shielded with respect to the acetyl methyl group by 0.4 ppm;[15] a similar relationship is observed with the bromo derivatives of **1**.

The acetyl hydrogens of 3-, 5-, and 6α-bromination derivatives of dehydroacetic acid give singlets within the range of δ 2.48–2.70 ppm, whereas the 6-methyl signals of 3-, 3β-, and 5-brominated derivatives appear between δ 2.28 and 2.53 ppm. In spite of the small overlap in these ranges, the structural assignments appear to be secure. Moreover these assignments are supported by mass spectral evidence cited below. The substitution of bromine at either methyl position deshields the resulting methylene group by *ca.* 2 ppm. The chemical shifts of the methylene groups of **9** and **14** retain the same relative relationship as the signals of the acetyl and 6-methyl protons of dehydroacetic acid.

(11) Nmr spectra revealed the formation of the pyrylium ion from **1** in the presence of hydrogen bromide. Gradual downfield shifts were observed when the anhydrous gas was added to chloroform solutions of **1**.

(12) For examples, see K. Arakawa and M. Irie, *Pharm. Bull.* (Tokyo), **5**, 528 (1957); N. Schamp and M. Versele, *Bull. Soc. Chim. Belg.*, **73**, 81 (1964).

(13) M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *J. Amer. Chem. Soc.*, **59**, 1655 (1937); R. Altschul and P. D. Bartlett, *J. Org. Chem.*, **5**, 623 (1940).

(14) Bromopyrone **11** has been prepared previously by treatment of **12** with bromine in glacial acetic acid: F. Arndt and S. Avan, *Chem. Ber.*, **84**, 343 (1951). Bromopyrone **15** has been obtained from **11** by methylation with diazomethane: K. Yamada, *Bull. Chem. Soc. Jap.*, **35**, 1323 (1962).

(15) The assignment is made on the basis of observable allylic coupling between the 6-methyl group and the 5 proton: N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, Varian NMR Spectra Catalog, Vol. 2, 1963, Spectrum No. 504.

The vinylic 5 proton of **1** and its derivatives occurred near δ 6 ppm. In contrast, 5,6-dibromo adduct **6** produced a singlet at δ 4.87 ppm, reflecting the change of hybridization at the 5 position. The enol signal of **6** could not be observed directly. However, integral traces indicated that the proton gave a peak near δ 17 ppm.

Mass spectra of the monobromo derivatives of dehydroacetic acid (**1**) provided confirmatory structural information (Table II). In **1** methyl loss (*m/e* 153) is a prominent fragmentation process. A comparison of the spectrum of **1** with that of acetyl-deuterated **1** indicated that the methyl group can be lost from either the acetyl group or the 6 position. The former process is the more important of the two. Among the monobromo derivatives of **1**, only the 3β- and 6α-bromo derivatives, **9** and **14**, undergo the corresponding loss of CH_2Br to give *m/e* 153. The fragment ion from **9** is more intense than that from **14**, reflecting the same cleavage preference observed with **1**.

TABLE II

MASS SPECTRA OF DEHYDROACETIC ACID AND ITS MONOBROMO DERIVATIVES[a]

	Compounds, % of base peak				
m/e	**1**	**4**	**5**	**9**	**14**
248		<1[b]	26[b]	10[b]	13[b]
246		<1[b]	26[b]	10[b]	13[b]
178		1	12		
176		1	12		
168	100[b,c]	1[d]		16[d]	11[d]
167			100[c]	100[c]	100[c]
166			8	14	
153	75			100[c]	20
151				18	
140	6				
139				10	20
127				16	
125	39	3	18	8	7
111	18			6	21
98	26				
97	4	3	5		20
93	4	2		17	
85	82	7		62	7
84	16		6		
69	72	26	14	29	25
67		2	11		
55	15	3	10	16	20
53	12	10	10	15	15
43	75	100[c]	68	100[c]	63
42	12			15	13

[a] Spectra were obtained with an LKB-9000 mass spectrometer operated at 70 eV. The samples were introduced by means of the direct insertion probe. Intensities of $\geq$1% are tabulated for all *m/e* values at which one or more of the compounds afforded ions of $\geq$10% intensity. [b] Parent ion. [c] Base peak. [d] Probable contamination by **1**.

The structure of 3,3-dibromopyrone **16** was supported by both nmr and mass spectral evidence. The nmr spectrum was very similar to that of 3-bromopyrone **4** and consisted of signals for the 5 proton and the 6-methyl group at δ 5.74 and 2.3 ppm, respectively. The mass spectrum confirmed the geminal relationship of the bromine atoms; significant ions were $Br_2C{=}C{=}O\cdot^+$ and $CBr_2\cdot^+$.

Experimental Section[16]

Dehydroacetic acid (**1**), obtained from Eastman Organic Chemicals, Inc., was dried *in vacuo* for 12 hr before use. Acetyl-deuterated dehydroacetic acid was prepared by equilibrating 0.40 g (2.3 mmol) of dehydroacetic acid with 5 ml of 2 *M* NaOD in D_2O for 2 hr at ambient temperature. The solution was poured onto a mixture of ice and 3 ml of 12 *M* HCl. Recovered dehydroacetic acid was filtered, dried, and sublimed, mp 109.5–110.5°. Nmr indicated that the relative protium content at the 5,6α,3β, and hydroxyl positions was 1.00, 2.84, 0.19, and 0.96 H, respectively. The mass spectrum indicated the following extent of deuteration: d_0, <0.3; d_1, <0.3; d_2, 5.7; d_3, 77.6; d_4, 12.8; d_5, 2.6; d_6, <0.3; d_7, <0.3; d_8, <0.3%.

5-Bromodehydroacetic Acid (3-Acetyl-5-bromo-4-hydroxy-6-methyl-2H-pyran-2-one, 5).—To a solution of 2.5 g (15 mmol) of **1** in chloroform (35 ml) was added a solution of 6 g (37.5 mmol) of Br_2 and 0.10 g of I_2 in chloroform (35 ml) at 0°. After 72 hr at 5°, the solution was washed with 5% sodium bisulfite solution and evaporated. An ethereal solution of the residue was dried ($MgSO_4$) and evaporated to leave 3.1 g (83%) of crude pyrone **5**, mp 125–135°. Two recrystallizations from methanol gave 1.8 g (48%) of pure **5**: mp 136–138° (lit.[5] mp 137°); ir (KBr) 3400 (OH), 1730 (s, C=O), 1598 (s), and 1540 cm^{-1} (s). Pyrone **5** was stable to hydrogen bromide at ambient temperature and gave no observable reaction with sodium iodide in acetone.

Anal. Calcd for $C_8H_7O_4Br$: C, 38.89; H, 2.86; Br, 32.34. Found: C, 39.08; H, 2.75; Br, 32.55.

Nmr Spectra of Reaction Mixtures.—Mixtures of **1** and Br_2 in $CDCl_3$ were allowed to stand at ambient temperature. Nmr spectra were recorded at frequent intervals. Aliquots were treated with 5% sodium bisulfite solution and spectra were recorded. The chemical shifts prior to bisulfite treatment were at slightly lower field and were dependent upon hydrogen bromide and/or bromine concentration. The chemical shifts (Table I) were highly reproducible after treatment. The procedure caused a decrease in the mole fraction of dibromo adduct **6**. This may result from differences in distribution coefficients of the various compounds between the two phases. However, the disappearance of **6** appeared to result from partial reversion to dehydroacetic acid.

3β,5-Dibromodehydroacetic Acid (5-Bromo-3-bromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one, 8).—A solution of 2.5 g (15 mmol) of **1** and 5 g (31 mmol) of Br_2 in chloroform (20 ml) was refluxed briefly and allowed to stand for 72 hr at ambient temperature. The solution was washed with 5% sodium bisulfite solution and evaporated. The residue was washed with a small volume of carbon tetrachloride to leave 1.04 g (21%) of dibromopyrone **8**: mp 122–129° and 130–131.5° after recrystallization from chloroform–hexane; ir (KBr) 3405 (s, OH), 1720 (s, C=O), 1610 (s), and 1580–1537 cm^{-1}. The compound gave a weak "positive halogen" test with sodium iodide in acetone.

Anal. Calcd for $C_8H_6O_4Br_2$: C, 29.48; H, 1.86; Br, 49.03. Found: C, 29.72; H, 1.89; Br, 49.08.

The nmr spectrum and tlc of the carbon tetrachloride washings from above indicated that the solution contained **1**, **5**, and several minor components. A singlet at δ 7.45 ppm indicated that one of the latter may have been the dibromoacetyl compound.

No reaction occurred when a solution of 0.5 g (2 mmol) of **5**, 0.5 g (3 mmol) of Br_2, and 0.01 g of I_2 in chloroform (10 ml) was allowed to stand at ambient temperature for 24 hr. Hydrogen bromide was bubbled through the solution briefly and, after an additional 6 hr, nmr indicated that *ca.* 50% conversion into pyrone **8** had occurred. Isolation was more difficult than in the previous preparation; however a small amount (7%) of **8**, mp 129–131°, was obtained by chromatography on silicic acid.

3β-Bromodehydroacetic Acid (3-Bromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one, 9).—To a HBr-saturated solution of 1.68 g (10 mmol) of **1** in chloroform (15 ml) was added 1.75 g (11 mmol) of Br_2 and 0.05 g of I_2 in chloroform (10 ml). After 24 hr, the solution was washed with 5% sodium bisulfite solution, dried ($MgSO_4$), and evaporated to leave a viscous oil.

(16) All melting points were taken in unsealed capillaries with a heated oil bath and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined with a Beckman IR-10 spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer using *ca.* 10% solutions in deuteriochloroform. Tetramethylsilane was employed as an internal standard. The ir, nmr, and mass spectrometers were purchased with funds provided by the National Science Foundation.

Trituration with carbon tetrachloride caused crystallization of 1.25 g (50%) of bromopyrone **9**: mp 111–114° and 118–119° after recrystallization from chloroform–hexane; ir (KBr) 3335 (s, OH), 1732 (s, C=O), 1717, and 1641 cm^{-1} (s). The compound gave a weak positive halogen test with sodium iodide in acetone.

Anal. Calcd for $C_8H_7O_4Br$: C, 38.89; H, 2.86; Br, 32.34. Found: C, 39.10; H, 2.80; Br, 32.51.

3β,3β-Dibromodehydroacetic Acid (3-Dibromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one, 10).—A solution of 1.25 g (51 mmol) of bromopyrone **9** and 0.86 g (54 mmol) of Br_2 in ethanol-free chloroform (15 ml) was stoppered and allowed to stand for 48 hr at ambient temperature, during which time the bromine color disappeared. The solvent was evaporated *in vacuo*. The residue was washed with carbon tetrachloride to afford 1.28 g (77%) of dibromopyrone **10**: mp 81–82.5° and 85–86° after recrystallization from carbon tetrachloride–hexane; ir (KBr) 3400, 1730, 1630, and 1570 cm^{-1}. The compound gave a positive halogen test with sodium iodide in acetone and an intense red color with base.

Anal. Calcd for $C_8H_6O_4Br_2$: C, 29.48; H, 1.86; Br, 49.03. Found: C, 29.52; H, 1.91; Br, 48.92.

3-Bromodehydroacetic Acid (3-Acetyl-3-bromo-3,4-dihydro-6-methyl-2H-pyran-2,4-dione, 4).—Bromine (0.50 g, 3.1 mmol) was added to a suspension of 0.657 g (3.5 mmol) of the anhydrous salt of **1**[17] in ethanol-free chloroform (10 ml). The bromine color was discharged rapidly and after 5 min only a faint yellow color remained. The mixture was filtered and the residue was washed with chloroform. The filtrate and washings were combined and the solvent was removed *in vacuo* to leave 0.592 g (77%) of **4** as a yellow oil: ir (CCl_4) 1801 (s, ester C=O), 1755 (s, $COCH_3$), 1714 (s, 4-C=O), 1654, and 1623 cm^{-1}. Extensive decomposition occurred when distillation was attempted at 0.1 mm. The compound gave an intense positive halogen test with sodium iodide in acetone. Treatment of **4** with hydrogen bromide in chloroform at 0° gave instantaneous formation of bromine and dehydroacetic acid. Bromo derivatives **5** and **9** formed gradually when this mixture was allowed to stand. Bromopyrone **4** underwent a slow reaction with moist air to form a low yield (5%) of 3-bromo-4-hydroxy-6-methyl-2H-pyran-2-one (**11**), mp 203–204° dec (lit.[14] mp 210° dec).

A mixture of 1.5 g (9 mmol) of **1**, 2.0 g (11 mmol) of N-bromosuccinimide, and 0.05 g of I_2 in carbon tetrachloride (20 ml) was refluxed for 2 hr in darkness. The solution was filtered to remove succinimide and evaporated to leave 2.23 g of bromopyrone **4** as a straw-colored oil. The spectral properties of this material were identical with those of **4** prepared with the sodium salt.

3,5-Dibromodehydroacetic Acid (3-Acetyl-3,5-dibromo-3,4-dihydro-6-methyl-2H-pyran-2,4-dione, 13).—A mixture of 0.758 g (3.1 mmol) of **5**, 0.630 g (3.5 mmol) of N-bromosuccinimide, and 0.024 g of I_2 in carbon tetrachloride was refluxed for 1.5 hr in darkness. An nmr spectrum of the supernatant showed singlets of equal area at δ 2.46 and 2.50 ppm. No vinyl or enol proton signals could be detected. The nmr spectrum was unaltered by an additional 4.5 hr of reflux. Succinimide was removed by filtration and the solvent was evaporated to leave dibromopyrone **13** as a yellow oil: ir (neat) 1795 (s), 1760 (w), 1725 (s), 1710 (sh), and 1615 cm^{-1}.

Treatment of 0.367 g (1.1 mmol) of **13** in chloroform with anhydrous hydrogen bromide gave rapid debromination. Evaporation of the solvent left 0.232 g of solid material, the nmr spectrum of which showed the presence of **5** plus a trace of **8**. Recrystallization from methanol gave **5**, mp 132–136°.

6α-Bromodehydroacetic Acid (3-Acetyl-6-bromomethyl-4-hydroxy-2H-pyran-2-one, 14).—A mixture of 1.68 g (10 mmol) of **1** and 2.0 g (11 mmol) of N-bromosuccinimide in carbon tetrachloride contained in a Pyrex flask was irradiated with a 275-W sun lamp for 7 hr at 23°. The mixture was filtered and the filtrate was evaporated. Nmr indicated the residue to be mainly a mixture of **1** and bromo derivative **14**. A small peak at δ 6.95 ppm was tentatively assigned as the 6α proton of 6α,6α-dibromodehydroacetic acid. The crude product was washed with a small volume of ether. Dehydroacetic acid was removed from the residue by sublimation at 40° (0.025 mm). Recrystallization of the remainder from methanol gave 0.58 g (23%) of **14**: mp 113–116° and 117–119° after further recrystallization from methanol: ir (KBr) 3400, 1720, 1640, and 1615 cm^{-1}.

Anal. Calcd for $C_8H_7O_4Br$: C, 38.89; H, 2.86; Br, 32.34. Found: C, 38.95; H, 2.74; Br, 32.25.

3-Bromo-4-hydroxy-6-methyl-2H-pyran-2-one (11).—A mixture of 1.29 g (10 mmol) of 4-hydroxy-6-methyl-2H-pyran-2-one (**12**) and 2.0 g (11 mmol) of N-bromosuccinimide in *t*-butyl alcohol was stirred in darkness for 2 hr at 30°. The usual isolation afforded 1.62 g (77%) of **11**, mp 198–201°. Recrystallization from glacial acetic acid raised the melting point to 203–204° (lit.[14] mp 210° dec). The nmr spectrum of **11** confirmed the location of the bromine atom. Allylic coupling (J = 0.9 Hz) between the methyl group (δ 2.22 ppm) and the 5 proton (6.12) was readily observed. The compound gave an immediate positive halogen test with sodium iodide in acetone.

3-Bromo-4-methoxy-6-methyl-2H-pyran-2-one (15).—A mixture of 0.70 g (5 mmol) of 4-methoxy-6-methyl-2H-pyran-2-one[18] and 1.0 g (5.6 mmol) of N-bromosuccinimide in carbon tetrachloride (25 ml) was stirred for 5 hr in darkness at 50°. Work-up afforded 0.530 g (49%) of bromopyrone **15**: mp 155–156° (lit.[14] mp 151–152°); ir (KBr) 3415, 1740, 1710, and 1640 cm^{-1}; nmr ($CDCl_3$) δ 2.3 (d, 3, J = 0.7 Hz, 6-CH_3), 3.98 (s, 3, OCH_3), and 6.27 ppm (q, 1, J = 0.7 Hz, 5-H). The compound gave a weak positive halogen test with sodium iodide in acetone.

3,3-Dibromo-2,3-dihydro-6-methyl-4H-pyran-2,4-dione (16).—A mixture of 1.02 g (5 mmol) of **11**, 1.11 g (6.2 mmol) of N-bromosuccinimide, and 0.05 g of I_2 in carbon tetrachloride (20 ml) was refluxed for 3 hr in darkness. The mixture was cooled, filtered, and evaporated to leave 1.42 g (100%) of dibromopyrone **16** as a yellow oil. The oil crystallized on standing: mp 53–60°; ir (Nujol) 1790, 1690, and 1660 cm^{-1}; nmr ($CDCl_3$) δ 2.3 (d, 3, J = 0.9 Hz, 6-CH_3) and 5.7 ppm (q, 1, J = 0.9 Hz, 5-H); mass spectrum (direct inlet, 70 eV) m/e 286, 284, and 282. Attempted recrystallization caused extensive decomposition. Slow reversion to **11** occurred upon standing.

Registry No.—**1**, 771-03-9; **4**, 23668-02-2; **5**, 23668-03-3; **6**, 23668-04-4; **8**, 23668-05-5; **9**, 23754-53-2; **10**, 23668-06-6; **11**, 23668-07-7; **13**, 23668-08-8; **14**, 23754-54-3; **15**, 670-35-9; **16**, 23668-10-2.

Acknowledgment.—We are indebted to Professor D. E. Pearson for helpful discussions during the course of this investigation and to Mr. C. T. Wetter for mass spectral determinations.

(17) J. N. Collie and H. R. LeSueur, *J. Chem. Soc.*, **65**, 254 (1894).

(18) J. D. Bu'Lock, *ibid.*, 502 (1960).

Positional and Geometrical Orientation in Eliminations from 2-Bromoalkanes Induced by Sodium Methoxide–Methanol, Potassium *t*-Butoxide–*t*-Butyl Alcohol, and Potassium *t*-Butoxide–Dimethyl Sulfoxide[1,2]

RICHARD A. BARTSCH[3]

University of California at Santa Cruz, Santa Cruz, California 95060

Received June 30, 1969

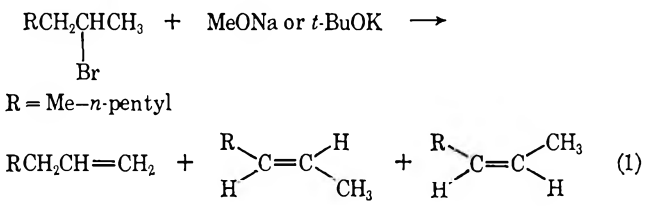
Olefinic products from reactions of a series of 2-bromoalkanes (C_4–C_8) with MeONa–MeOH, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO are reported. Compositions of the olefin mixtures are determined over ranges of temperatures under conditions of negligible product isomerization. In all three base–solvent systems, the percentage of 1-alkene increases in an attenuated fashion as the alkyl group of the substrate is varied from 2-butyl through 2-octyl. With MeONa–MeOH and *t*-BuOK–DMSO, the *trans*-/*cis*-2-alkene ratio is dependent upon the alkyl group of the 2-bromoalkane, increasing in the order 2-butyl < 2-octyl < 2-heptyl < 2-hexyl < 2-pentyl, whereas with *t*-BuOK–*t*-BuOH the order is 2-octyl < 2-heptyl < 2-hexyl < 2-butyl < 2-pentyl. The effects of the nature of the alkyl group upon positional and geometrical orientation are discussed.

Recent investigations of base-catalyzed eliminations of 2-substituted alkanes[4] have demonstrated that positional and geometrical orientation[5] may vary widely with changes in the leaving group, the base, and the solvent. The influence of the nature of the alkyl group of the 2-substituted alkane upon orientation has remained relatively unexplored.

Orientation in eliminations from 2-alkyl bromides (C_4–C_6) and 2-alkyl arenesulfonate esters (C_4–C_6, C_8) has been reported.[4] However, results determined under a variety of conditions in several laboratories must be compared.

Results

Using gas–liquid partition chromatography (glpc), the relative proportions of the three isomeric olefins formed in dehydrohalogenations from a series of 2-bromoalkanes (C_4–C_8) induced by MeONa–MeOH, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO (eq 1) have been measured.



Reactions with Sodium Methoxide–Methanol.—The relative amounts of the isomeric olefins formed in reactions of the 2-bromoalkanes with MeONa–MeOH were determined at four temperatures from 30–90°. The results are listed in Table I. Previous investigations have demonstrated kinetically controlled formation of products under the reaction conditions.[4a]

At a given temperature, the percentage of terminal olefin shows an attenuated increase as the series is traversed from 2-bromobutane to 2-bromoheptane. The relative olefinic proportions are the same for 2-bromoheptane and 2-bromooctane. The *trans*-/*cis*-2-alkene ratio is lowest for 2-bromobutane, maximal for 2-bromopentane, and intermediate for the other series members.

Reactions with Potassium *t*-Butoxide–*t*-Butyl Alcohol.—The olefins resulting from reactions of the 2-bromoalkanes with *t*-BuOK–*t*-BuOH at four temperatures in the range 30–90° are reported in Table II. Under the employed reaction conditions, isomerization of the product olefins is negligible.[4b]

Hofmann orientation predominates and an attenuated increase is again noted in passing from 2-bromobutane to the higher homologs. The *trans*-/*cis*-2-alkene ratio increases as the 2-alkyl group is varied: 2-octyl < 2-heptyl < 2-hexyl < 2-butyl < 2-pentyl.

Reactions with Potassium *t*-Butoxide–Dimethyl Sulfoxide.—Although special experimental techniques were utilized, the propensity of *t*-BuOK–DMSO for isomerization of olefins[6] limited observation of reactions of 2-bromoalkanes with this base–solvent system to 30 and 50°. Higher temperatures resulted in isomerized olefinic products. Results are given in Table III.

Differences between the present results and reported values[4c] for 2-bromohexane are due to improvements in experimental procedure. Reaction with *t*-BuOK–DMSO is so rapid that essentially complete reaction occurs upon mixing. In the earlier study, mixing (and reaction) took place at room temperature. In agreement, the present results at 30° are the same as those reported at 50°.

The reaction of 2-bromohexane with *t*-BuOK–DMSO at 50° yields 90 ± 2% hexenes.

Again the percentage of terminal olefin increases markedly between 2-bromobutane and 2-bromopentane

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Portions of this work were described at the 24th Northwest Regional Meeting of the American Chemical Society, Salt Lake City, Utah, June 1969.

(3) Department of Chemistry, Washington State University, Pullman, Washington 99163.

(4) (a) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **90**, 408 (1968); (b) **91**, 1376 (1969); (c) **91**, 1382 (1969); (d) H. C. Brown and R. L. Klimisch, *ibid.*, **87**, 5517 (1965); (e) **88**, 1425 (1966); (f) A. K. Colter and R. D. Johnson, *ibid.*, **84**, 3289 (1962); (g) D. H. Froemsdorf and M. E. McCain, *ibid.*, **87**, 3983 (1965); (h) D. H. Froemsdorf, M. E. McCain, and W. W. Wilkison, *ibid.*, **87**, 3984 (1965); (i) D. H. Froemsdorf, W. Dowd, and K. E. Leimer, *ibid.*, **88**, 2345 (1966); (j) D. H. Froemsdorf and M. D. Robbins, *ibid.*, **89**, 1737 (1967); (k) D. L. Griffith, D. L. Meges, and H. C. Brown, *Chem. Commun.*, 90 (1968); (l) W. H. Saunders, Jr., S. R. Fahrenholtz, E. A. Caress, J. P. Lowe, and M. Schreiber, *J. Amer. Chem. Soc.*, **87**, 3401 (1965); (m) C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **30**, 673 (1965).

(5) Positional orientation refers to the relative proportions of 1- and 2-alkenes formed, whereas geometrical orientation compares the relative amounts of *trans*- and *cis*-2-alkene produced.

(6) A. Schriesheim, J. Hofmann, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **83**, 3731 (1961).

TABLE I

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BROMOALKANES WITH 0.55 *M* SODIUM METHOXIDE–METHANOL

R of RBr[a]	Temp, °C	Total alkenes, % 1-Alkene	*trans*-2-Alkene	*cis*-2-Alkene	2-Alkene/ 1-alkene	*trans*-2-Alkene/ *cis*-2-alkene
2-Butyl	30.0[b]	12.7 ± 0.4[c]	68.7 ± 0.5	18.6 ± 0.6	6.9	3.7
	49.8[d]	14.6 ± 0.3	65.8 ± 0.7	19.6 ± 0.7	5.8	3.4
	69.6	16.6 ± 0.3	62.7 ± 0.3	20.7 ± 0.1	5.0	3.0
	89.6	18.3 ± 0.4	60.6 ± 0.4	21.1 ± 0.4	4.5	2.9
2-Pentyl	30.0[b]	16.1 ± 0.3	69.1 ± 0.1	14.8 ± 0.4	5.2	4.7
	49.8[b]	18.4 ± 0.1	66.2 ± 0.2	15.4 ± 0.2	4.4	4.3
	69.6	21.0 ± 0.3	63.0 ± 0.2	16.0 ± 0.2	3.8	3.9
	89.6	23.0 ± 0.3	60.3 ± 0.3	16.7 ± 0.3	3.4	3.6
2-Hexyl[e]	30.0	18.3 ± 0.4	65.8 ± 0.7	15.9 ± 0.3	4.5	4.1
	49.8[f]	20.7 ± 0.5	62.5 ± 0.5	16.8 ± 0.3	3.8	3.7
	69.6	23.2 ± 0.2	59.8 ± 0.2	17.0 ± 0.1	3.3	3.5
	89.6	26.1 ± 0.3	57.0 ± 0.2	16.9 ± 0.1	2.8	3.4
2-Heptyl	30.0	19.7[g]	64.4	15.9	4.1	4.0
	49.8[f]	22.0 ± 0.1	61.2 ± 0.1	16.8 ± 0.1	3.6	3.6
	69.6	25.0[g]	57.8	17.2	3.0	3.4
	89.6	26.9[g]	55.8	17.3	2.7	3.2
2-Octyl	30.0	20.5 ± 0.2	62.5 ± 0.1	17.0 ± 0.1	3.9	3.7
	49.8	21.9 ± 0.3	61.3 ± 0.4	16.8 ± 0.2	3.6	3.6
	69.6	24.2 ± 0.2	58.3 ± 0.4	17.5 ± 0.1	3.1	3.3
	89.6	27.2 ± 0.4	55.6 ± 0.2	17.2 ± 0.5	2.7	3.2

[a] [RBr] = 0.14–0.66 *M*. [b] Two runs. [c] Deviations are standard deviations of the set. [d] Four runs. [e] These results are in accord with extensive studies of products from reactions of 2-bromohexane with MeONa–MeOH reported in ref 4a, except that *trans*-2-hexene and 1-hexene were consistently 1.0% higher and lower, respectively, in this work. [f] Three runs. [g] Single sample.

TABLE II

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BROMOALKANES WITH 1.0 *M* POTASSIUM *t*-BUTOXIDE–*t*-BUTYL ALCOHOL

R of RBr[a]	Temp, °C	Total alkenes, % 1-Alkene	*trans*-2-Alkene	*cis*-2-Alkene	2-Alkene/ 1-alkene	*trans*-2-Alkene/ *cis*-2-alkene
2-Butyl[b]	30.0	50.8 ± 0.5[c]	29.8 ± 0.2	19.4 ± 0.3	0.97	1.54
	49.8	50.0 ± 0.3	30.1 ± 0.1	19.9 ± 0.3	1.00	1.51
	69.6	48.8 ± 0.6	30.7 ± 0.2	20.5 ± 0.1	1.05	1.50
	89.6	49.0 ± 0.2	30.5 ± 0.4	20.5 ± 0.4	1.04	1.48
2-Pentyl	30.0	83.6 ± 0.4	10.4 ± 0.2	6.0 ± 0.2	0.20	1.73
	49.8	81.2 ± 0.3	12.0 ± 0.3	6.8 ± 0.2	0.23	1.76
	69.6	79.4 ± 0.1	12.8 ± 0.1	7.8 ± 0.1	0.26	1.64
	89.6	77.7 ± 0.1	13.9 ± 0.1	8.4 ± 0.2	0.29	1.65
2-Hexyl[d]	30.0	86.6 ± 0.1	7.7 ± 0.1	5.7 ± 0.1	0.15	1.35
	49.8	83.6 ± 0.3	9.7 ± 0.1	6.7 ± 0.2	0.20	1.45
	69.6	81.9 ± 0.4	10.5 ± 0.3	7.6 ± 0.2	0.22	1.38
	89.6	80.0 ± 0.4	11.7 ± 0.3	8.3 ± 0.1	0.25	1.41
2-Heptyl	30.0	87.5 ± 0.3	7.2 ± 0.2	5.3 ± 0.1	0.14	1.36
	49.8	84.6 ± 0.4	8.8 ± 0.2	6.6 ± 0.2	0.18	1.33
	69.6	82.9[e]	10.0	7.1	0.20	1.40
	89.6	81.4 ± 0.2	10.6 ± 0.1	8.0 ± 0.2	0.23	1.32
2-Octyl	30.0	86.2 ± 0.1	7.8 ± 0.1	6.0 ± 0.1	0.16	1.29
	49.8	85.5[e]	8.1	6.4	0.17	1.26
	69.6	82.8 ± 0.6	9.6 ± 0.3	7.6 ± 0.3	0.21	1.26
	89.6	81.7 ± 0.7	10.2 ± 0.3	8.1 ± 0.4	0.22	1.26

[a] [RBr] = 0.17–0.46 *M*. [b] Reference 4e reports 54% 1-butene and *trans*-/*cis*-2-butene = 1.47 under the same conditions, while ref 4h records 53% 1-butene and *trans*-/*cis*-2-buten = 1.64 at 55°. [c] Deviations are standard deviations of the set. [d] Reference 4b reports the following data (% 1-hexene, *trans*-/*cis*-2-hexene, temp, °C): 89.2, 1.34, 29.7; 86.6, 1.22, 50.8; 83.6, 1.30, 75.8; 80.2, 1.39, 99.0. [e] Single sample.

and exhibits progressively smaller increases for the higher series members. The very large *trans*-/*cis*-2-alkene ratios are noteworthy. The ratio is minimal for 2-bromobutane, maximal for 2-bromopentane, and intermediate for the others.

For comparison, the olefinic products from the reaction of 2-bromobutane with *t*-BuOK–DMF were measured. The results, which are included in Table III, show that changing the solvent from DMSO to DMF only slightly affects the relative olefinic proportions. This provides strong evidence that *t*-butoxide ion and not the anion of DMSO is the effective base in *t*-BuOK–DMSO.[4m]

Differences in Enthalpies and Entropies of Activation between Two Isomeric Olefins.—The relative proportions of the isomeric olefins from the series of 2-bromoalkanes were measured at several temperatures. Therefore, the differences in the enthalpies and entropies of activation, $\Delta\Delta H^{\ddagger}_{A-B}$ and $\Delta\Delta S^{\ddagger}_{A-B}$, respectively, between isomeric alkenes A and B could be calculated from the slopes and intercepts of linear plots of log (per cent olefin A/per cent olefin B) *vs.*

TABLE III

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BROMOALKANES WITH 0.8 *M* POTASSIUM *t*-BUTOXIDE–DIMETHYL SULFOXIDE

R of RBr[a]	Temp, °C	Total alkenes, % 1-Alkene	*trans*-2-Alkene	*cis*-2-Alkene	2-Alkene/1-alkene	*trans*-2-Alkene/*cis*-2-alkene
2-Butyl[b]	30.0[c]	29.5 ± 0.4[d]	55.0 ± 0.6	15.5 ± 0.3	2.39	3.6
	49.8[c]	30.4 ± 0.5	53.8 ± 0.5	15.8 ± 0.4	2.29	3.4
	49.8[e]	30.5 ± 0.2	55.1 ± 0.2	14.4 ± 0.2	2.28	3.8
2-Pentyl	30.0[c]	43.2 ± 0.2	48.4 ± 0.1	8.4 ± 0.2	1.31	5.8
	49.8	43.5 ± 0.1	46.8 ± 0.2	9.7 ± 0.2	1.30	4.8
2-Hexyl[f]	30.0	46.9 ± 0.1	44.3 ± 0.1	8.8 ± 0.2	1.13	5.0
	49.8[c]	46.8 ± 0.1	43.3 ± 0.2	9.9 ± 0.2	1.14	4.4
2-Heptyl	30.0	49.0 ± 0.1	42.3 ± 0.1	8.7 ± 0.1	1.04	4.9
	49.8	49.2 ± 0.1	41.1 ± 0.2	9.7 ± 0.1	1.03	4.2
2-Octyl	30.0[g]	50.4 ± 0.1	41.7 ± 0.1	7.9 ± 0.1	0.98	5.3

[a] [RBr] = 0.08–0.62 *M*. [b] Reference 4h reports 31% 1-butene and *trans*-/*cis*-2-butene = 3.65 at 55°, and ref 4k records 31.5% 1-butene and *trans*-/*cis*-2-butene = 3.76 at 25°. [c] Two runs. [d] Deviations are standard deviations of the set. [e] In dimethylformamide. [f] Reference 4c lists 47.0 ± 0.4% 1-hexene and *trans*-/*cis*-2-hexene = 4.86 ± 0.02 at 51°. [g] Olefinic products from reaction at 50° could not be determined without apparent isomerization.

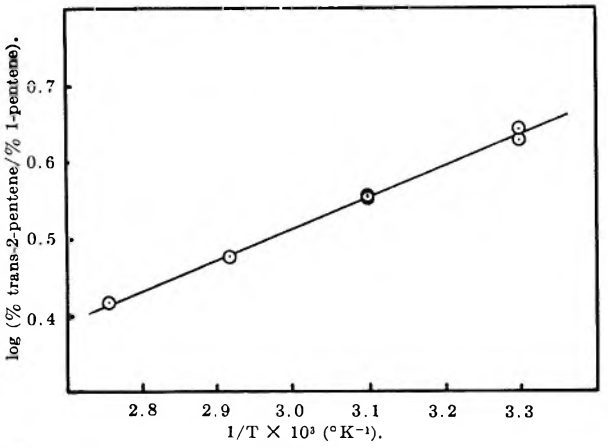


Figure 1.—Arrhenius plot of relative amounts of *trans*-2-pentene and 1-pentene from reaction of 2-bromopentane with MeONa–MeOH.

$1/T$. An Arrhenius plot from the reaction of 2-bromopentane with MeONa/MeOH is shown in Figure 1.

The computed values[7] are displayed in Tables IV–VI for reactions with MeONa–MeOH, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO, respectively. Uncertainties in differences in enthalpies of activation are estimated to be 0.3 kcal/mol, and those in entropies, 1 cal/deg mol. For the reaction of 2-bromohexane with MeONa–MeOH, the calculated differences in enthalpies and entropies of activation are within experimental error of those determined by kinetic studies.[4a]

Discussion

Effect of Base–Solvent System upon Orientation.—For a given 2-bromoalkane, the influence of the base–solvent systems upon positional and geometrical orientation observed in this investigation is in agreement with earlier studies of eliminations from 2-bromobutane and 2-bromohexane.[4b,c,h] In these previous investigations, the percentage of 1-alkene and the *trans*-/*cis*-2-alkene ratio were interpreted as indicating, respectively, the ratio of C–H to C–Br stretching in the elimination transition states and the degree of double-bond character in the internal olefin transition states. For eliminations from 2-bromoalkanes induced by MeONa–MeOH and *t*-BuOK–DMSO, the transition states were suggested to have similar amounts of heterolysis of the C–H and C–Br bonds and a high degree of double-bond character, whereas, for eliminations promoted by *t*-BuOK–*t*-BuOH, more advanced C–H bond rupture than C–Br bond cleavage and an only slightly developed carbon–carbon double bond were postulated. At present, the factors responsible for the changes in

TABLE IV

$\Delta\Delta H^{\ddagger}$ AND $\Delta\Delta S^{\ddagger}$ VALUES FOR FORMATION OF PAIRS OF OLEFINS IN REACTIONS OF 2-BROMOALKANES WITH SODIUM METHOXIDE–METHANOL

R of RBr	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$[a]	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$[b]	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta\Delta H^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta\Delta S^{\ddagger}$
2-Butyl	−1830	−0.4	−860	+0.1	−970	−0.5
2-Pentyl	−1850	−0.9	−940	−1.1	−910	+0.1
2-Hexyl	−1840	−1.3	−1110	−1.6	−730	+0.4
2-Heptyl	−1730	−1.1	−890	−1.1	−830	0
2-Octyl	−1510	−0.4	−960	−1.3	−550	+0.8

[a] In cal/mol. [b] In cal/deg mol.

TABLE V

$\Delta\Delta H^{\ddagger}$ AND $\Delta\Delta S^{\ddagger}$ VALUES FOR FORMATION OF PAIRS OF OLEFINS IN REACTIONS OF 2-BROMOALKANES WITH POTASSIUM *t*-BUTOXIDE–*t*-BUTYL ALCOHOL

R of RBr	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$[a]	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$[b]	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta\Delta H^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta\Delta S^{\ddagger}$
2-Butyl	250	+2.0	370	+1.5	−120	+0.5
2-Pentyl	1300	+2.4	1530	+2.0	−230	+0.4
2-Hexyl	1770	+3.3	1670	+2.3	100	+1.0
2-Heptyl	1700	+2.9	1710	+2.3	−20	+0.6
2-Octyl	1280	+1.6	1390	+1.4	−110	+0.1

[a] In calories/mole. [b] In calories/degree mole.

TABLE VI

$\Delta\Delta H^{\ddagger}$ AND $\Delta\Delta S^{\ddagger}$ VALUES FOR FORMATION OF PAIRS OF OLEFINS IN REACTIONS OF 2-BROMOALKANES WITH POTASSIUM *t*-BUTOXIDE–DIMETHYL SULFOXIDE

R of RBr	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$[a]	*trans*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$[b]	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta H^{\ddagger}$	*cis*-2-Alkene vs. 1-alkene $\Delta\Delta S^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta H\Delta^{\ddagger}$	*trans*-2-Alkene vs. *cis*-2-alkene $\Delta\Delta S^{\ddagger}$
2-Butyl	−510	+1.7	−140	+0.5	−370	+1.3
2-Pentyl	−370	+1.2	+1350	+3.4	−1740	−2.3
2-Hexyl	−210	+1.4	+1170	+2.7	−1380	−1.3
2-Heptyl	−280	+1.0	+1090	+2.2	−1320	−1.3

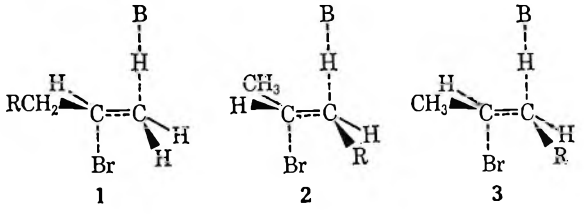
[a] In calories/mole. [b] In calories/deg mole.

(7) Grateful acknowledgment is made to the University of Würzburg, Würzburg, West Germany, for the use of computing facilities.

orientation produced by variation of the base–solvent system are not fully understood.[4b,c,8]

For transition states with a high degree of double-bond character (productlike), correlation between *trans*- and *cis*-2-alkene isomer composition and the relative stabilities of the *trans*- and *cis*-2-alkenes might be anticipated. The relative stabilities of the geometrical 2-butene, 2-pentene, and 2-heptene isomers in the gas phase have been determined by iodine-catalyzed equilibration.[9] Figure 2 is a comparison of *trans*- and *cis*-2-alkene composition from reactions of 2-bromoalkanes with MeONa–MeOH, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO and *trans*- and *cis*-2-alkene isomer stabilities expressed as free-energy differences. Although these plots are only qualitative owing to limited ranges of free energies and numbers of points, there appears to be a crude correlation with MeONa–MeOH and *t*-BuOK–DMSO, but a complete lack of correlation with *t*-BuOK–DMSO. These results are in accord with the transition-state characters given above.

Effect of 2-Alkyl Groups upon Positional Orientation.—Transition states for formation of 1-alkene, *trans*-2-alkene, and *cis*-2-alkene by base-catalyzed elimination from a 2-bromoalkane, $RCH_2CHBrCH_3$, are represented by structures **1**, **2**, and **3**, respectively. In all three



base–solvent systems, the relative proportion of 1-alkene increased in an attenuated fashion as R was varied from methyl through *n*-pentyl. Larger increases were noted when potassium *t*-butoxide was the base than with sodium methoxide.

An attractive explanation for both observations is destabilization of transition states **2** and **3** owing to steric interactions between the base and R. It would be anticipated that variation of R would have little effect upon transition state **1**. The data presented in Table VII indicate a relatively small effect upon the rate of formation of 1-alkene for replacement of a methyl R group with ethyl in two base–solvent systems. However, this change produces an overriding decrease in rate of formation of the internal olefins.

Two types of steric interactions between the base and R are possible.[10] Restrictions on the rotational freedom of R (for R > Me), producing a rate-retarding decrease in entropy, might arise if transition states **2** and **3** were obliged to assume certain strain-free conformations to avoid direct compressions of the base against R.[12] Alternatively, unavoidable crowding of the base against R with concomitant restricted rotation of R (for R > Me) would increase the enthalpy and decrease the entropy of transition states **2** and **3**. Both the restricted-rotation and direct-compression steric proposals predict decreases in the transition-state entropy of **2** and **3** as R is increased.

Since formation of 1-alkene from $RCH_2CHBrCH_3$ is relatively insensitive to the nature of R, differences in $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ for *trans*-2-alkene *vs.* 1-alkene and *cis*-2-alkene *vs.* 1-alkene for the series of 2-bromoalkanes (Tables IV–VI) represent primarily changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for formation of *trans*- and *cis*-2-alkene wrought by variation of R. If the destabilization of transition states **2** and **3** is indeed due to the proposed steric effects, decreases in $\Delta\Delta S^{\ddagger}$ for *trans*-2-alkene

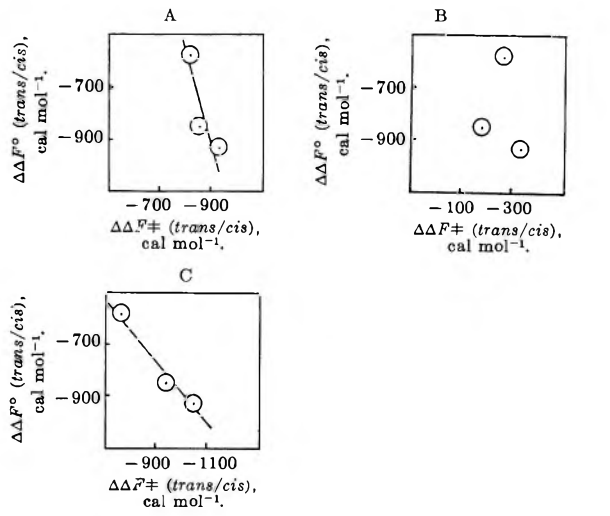


Figure 2.—Plots of $\Delta\Delta F°$, the free energy corresponding to the *trans*-2-alkene–*cis*-2-alkene equilibria (at 237°), *vs.* $\Delta\Delta F^{\ddagger}$ (*trans*–*cis*), the difference in the free energy of activation for *trans*- and *cis*-2-alkene formation from reactions of 2-bromoalkanes at 30° with (A) MeONa–MeOH, (B) *t*-BuOK–*t*-BuOH, and (C) *t*-BuOK–DMSO.

TABLE VII

RATE CONSTANTS[a] FOR FORMATION OF ISOMERIC OLEFINS IN REACTIONS OF 2-BUTYL AND 2-PENTYL BROMIDE WITH 1.0 *M* SODIUM ETHOXIDE–ETHANOL AND POTASSIUM *t*-BUTOXIDE–*t*-BUTYL ALCOHOL AT 25°

		$-k_2^b \times 10^6$ for formation of—		
R of RBr	Base–solvent	1-Alkene	*trans*-2-Alkene	*cis*-2-Alkene
2-Butyl	EtOK–EtOH	0.55	2.30	0.63
2-Pentyl	EtOK–EtOH	0.63	1.73	0.40
2-Butyl	*t*-BuOK–*t*-BuOH	0.71	0.42	0.27
2-Pentyl	*t*-BuOK–*t*-BuOH	0.66	0.080	0.045

[a] Rate constants for overall reaction and olefin yields from M. L. Dhar, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2058 (1948); H. C. Brown, I. Moritani, and Y. Okamoto, *J. Amer. Chem. Soc.*, **78**, 2193 (1956). Relative proportions of isomeric olefins determined as follows (base–solvent, alkyl bromide, % 1-alkene, % *trans*-2-alkene, % *cis*-2-alkene); KOEt–EtOH, 2-butyl bromide, 15.9, 66.5, 18.6; KOEt–EtOH, 2-pentyl bromide, 22.7, 62.7, 14.6; *t*-BuOK–*t*-BuOH, 2-butyl bromide, 50.9, 29.8, 19.3; *t*-BuOK–*t*-BuOH, 2-pentyl bromide, 84.0, 10.2, 5.8. [b] In l./sec mol.

(8) I. N. Feit and W. H. Saunders, Jr., *Chem. Commun.*, 610 (1967); W. H. Saunders, Jr., D. G. Bushman, and A. F. Cockerill, *J. Amer. Chem. Soc.*, **90**, 1775 (1968).

(9) D. M. Golden, K. W. Egger, and S. W. Benson, *ibid.*, **86**, 5416 (1964); K. W. Egger and S. W. Benson, *ibid.*, **88**, 236 (1966); K. W. Egger, *ibid.*, **89**, 504 (1967).

(10) The following discussion is a refinement of the steric theory of orientation presented previously by Brown, *et al.* (Table VII, footnote *a*) and in ref 11.

(11) H. C. Brown and I. Moritani, *J. Amer. Chem. Soc.*, **75**, 4112 (1953).

(12) A well-documented case of entropy decrease caused by restricted rotation in Finkelstein reactions of ethyl and *n*-propyl halides is discussed in ref 13.

(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 410.

vs. 1-alkene and *cis*-2-alkene *vs.* 1-alkene are expected as R is made larger.

Examination of $\Delta\Delta H^{\pm}$ and $\Delta\Delta S^{\pm}$ for eliminations from the series of 2-bromoalkanes induced by MeONa–MeOH (Table IV), *t*-BuOK–*t*-BuOH (Table V), and *t*-BuOK–DMSO (Table VI) reveals none of the anticipated decreases in $\Delta\Delta S^{\pm}$ as R is changed from methyl to higher homologs. Failure to observe detectable steric effects with MeONa–MeOH might be attributed to the limited steric requirements of the base. However, even with the bulky base potassium *t*-butoxide, steric interactions between the base and R are apparently unimportant.

Another conceivable explanation[14] of the destabilization of **2** and **3** as R is increased is an unfavorable electronic interaction of R. Transition states for elimination from 2-bromoalkanes promoted by *t*-BuOK–*t*-BuOH are proposed to have a high degree of C–H bond cleavage, but an only slightly ruptured C–Br bond.[4h] Such timing would result in partial negative charges on the β-carbon atoms and a high sensitivity to destabilizing, electron-donating properties[15] of R in the transition states leading to internal olefin. Both the magnitude and rapid attenuation of the increases in transition-state enthalpy for formation of *trans*- and *cis*-2-alkene relative to 1-alkene as R is increased in *t*-BuOK–*t*-BuOH (Table V) are consistent with this explanation. However, this proposal is seemingly inapplicable to eliminations induced by MeONa–MeOH and *t*-BuOK–DMSO, in which the transition states are postulated to have similar amounts of heterolysis of the C–H and C–Br bonds.

Experimental Section

2-Bromoalkanes.—2-Bromobutane (Eastman) was distilled, yielding only one fraction. Other 2-bromoalkanes were prepared by reaction of secondary alcohols[16] with triphenylphosphine and bromine in dimethylformamide.[4a,17] Homogeneity of the 2-bromoalkanes was demonstrated by glpc using a 20 ft × 0.25 in. column of 15% Carbowax 20M on Chromosorb P. Physical properties for the 2-bromoalkanes corresponded to literature values.

Base–solvent solutions were prepared as before.[4a-c]

Reactions of 2-bromoalkanes with sodium methoxide in methanol and potassium *t*-butoxide in *t*-butyl alcohol were conducted and elimination products were analyzed as before.[4b]

Reactions of 2-Bromoalkanes with Potassium *t*-Butoxide in Dimethyl Sulfoxide.—The base–solvent solution (5.0 ml) was pipeted into an apparatus designed to sweep olefinic products from the reaction solution with nitrogen and carry them to a receiving trap. A sweep of dry nitrogen was started (200–400 ml/min) and the reaction vessel and attached trap were lowered into a thermostat and a liquid nitrogen filled dewar flask, respectively. The neat 2-bromoalkane (0.4–2.3 mmol) was injected through a rubber septum into the base–solvent solution with a syringe. After 5–15 min, the nitrogen sweep was halted. The reaction vessel and trap were removed and the trap was separated. *n*-Hexane (2 ml) (for 2-heptyl and 2-octyl bromide reactions) or methanol (for reactions of other 2-bromoalkanes) was added to the trap. Resulting solutions were cooled with Dry Ice–isopropyl alcohol (solutions of heptenes and octenes were kept at room temperature) and were analyzed by direct injection of a 0.1–0.3-μl portion into the gas chromatograph.

In one run at 50°, a mixture of weighed amounts of 2-bromohexane and *n*-hexane (internal standard) was subjected to the reaction procedure. From comparison of hexene and hexane peak areas, an olefin yield of 90 ± 2% was calculated.

Glpc analysis of olefinic reaction products was accomplished with a Varian Aerograph Model 204 flame-ionization gas chromatograph. Separation of isomeric olefins from each other, solvent, and unreacted 2-bromoalkane was usually achieved with 30 ft × 0.125 in. columns of 20% UcON 50HB100 on Chromosorb P operated at ambient temperatures (for butenes, pentenes, and hexenes), at 70° (for heptenes), or at 90° (for octenes). Owing to similar retention times for heptenes and methanol on these columns, 20 ft × 0.125 in. columns of 20% XF-1150 on Chromosorb P operated at 0° were used to analyze elimination products from reactions of 2-bromoheptane with MeONa–MeOH. Relative areas of the cleanly separated peaks for the isomeric olefins were determined with a disk integrator.

Stability of Olefinic Products to Reaction Conditions.—To test for isomerization of olefinic products in eliminations induced by *t*-BuOK–DMSO, a synthetic mixture of 55.6 ± 0.5% 1-hexene, 3.4 ± 0.2% *trans*-2-hexene, and 41.0 ± 0.5% *cis*-2-hexene was subjected to the reaction procedure. The trapped hexene mixture analyzed as follows: (A) from reaction at 50°, 54.6 ± 0.5% 1-hexene, 3.6 ± 0.2% *trans*-2-hexene, and 41.8 ± 0.5% *cis*-2-hexene; and (B) from reaction at 70°, 47.3 ± 0.5% 1-hexene, 4.2 ± 0.3% *trans*-2-hexene, and 48.5 ± 0.5% *cis*-2-hexene.

Calculations.—For eliminations of each 2-bromoalkane in the three base–solvent systems, plots of log (per cent *trans*-2-alkene/per cent 1-alkene), log (per cent *cis*-2-alkene/per cent 1-alkene), and log (per cent *trans*-2-alkene/per cent *cis*-2-alkene) *vs.* $1/T$ were prepared and the data were analyzed by a computer programmed for linear regression least squares analysis. The intercepts were equal to $\Delta\Delta S^{\pm}/2.303R$, while the slopes were equal to $-\Delta\Delta H^{\pm}/2.303R$. A statistical factor correcting for the number of β hydrogens available was applied to entropy of activation calculations involving formation of 1-alkenes.[4b] Uncertainties in $\Delta\Delta H^{\pm}$ and $\Delta\Delta S^{\pm}$ were estimated from the standard deviations of the slopes and intercepts, respectively.

Registry No.—Sodium methoxide, 124-41-4; potassium *t*-butoxide, 3999-70-0; methanol, 67-56-1; *t*-butyl alcohol, 75-65-0; dimethyl sulfoxide, 67-68-5; 2-bromobutane, 78-76-2; 2-bromopentane, 107-81-3; 2-bromohexane, 3377-86-4; 2-bromoheptane, 1974-04-5; 2-bromooctane, 557-35-7.

Acknowledgment.—We wish to thank Professor J. F. Bunnett for helpful discussions.

(14) We thank a referee for pointing out that external effects, such as steric hindrance of R to solvation or to ionic aggregation, could play an important role.

(15) As judged from Taft σ^* values: R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 591.

(16) Commercially available alcohols were distilled and shown to be homogeneous by glpc.

(17) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

Copper Chloride–Ethanolamine Catalyzed Addition of Polyhaloalkanes to 1-Octene[1]

DONALD J. BURTON AND LAWRENCE J. KEHOE

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52240

Received August 6, 1969

The copper chloride–ethanolamine redox system initiates the addition of a variety of polyhaloalkanes to 1-octene, giving good yields of the 1:1 addition products. This redox system of radical initiation offers several advantages when compared with ordinary initiation techniques. The preparation and characterization of several new addition adducts are reported.

The extensive number of reports concerned with the free-radical addition of polyhaloalkanes to olefins have given close scrutiny to the scope and effectiveness of a variety of systems for the initiation of these reactions.[2] However, the redox system of radical initiation has received limited study. This redox system, as described by Asscher and Vofsi,[3,4] utilizes iron or copper salts to catalyze the addition of carbon tetrachloride and chloroform to olefins.

$$CCl_4 + PhCH{=}CH_2 \xrightarrow[\text{solvent, } 120^\circ]{CuCl_2} PhCHClCH_2CCl_3 \quad 78\%$$

The redox system has several advantages when compared to ordinary initiation techniques: (a) telomerization reactions are minimized, with a corresponding increase in the yield of the 1:1 addition adduct; (b) the use of a large excess of alkyl polyhalide is no longer necessary to ensure a respectable yield of the 1:1 adduct, a distinct advantage as the haloalkane is generally the more expensive and more difficult reactant to obtain; (c) vigorous reaction conditions and the need for special apparatus can be avoided. Because of these advantages, the redox technique holds much promise for the preparation of many polyhalogenated compounds, and a study of the scope and utility of this system was of interest.

Results and Discussion

Many alkyl halide–olefin additions (utilizing conventional methods of radical initiation) have been described in the literature, and thus are provided convenient models for investigation of the applicability of the redox system.

In this study, 1-octene was used as a model olefin for the initial survey of the scope of the reaction. The additions were carried out by refluxing the olefin, alkyl polyhalide, copper chloride, ethanolamine, and *t*-butyl alcohol, with stirring, for 24–48 hr. The results of these addition reactions are summarized in Table I.

An examination of the data in Table I reveals that this redox method successfully initiates the addition of polyhaloalkanes containing a reactive chlorine, bromine, or iodine atom to a number of olefins to give good yields of the 1:1 addition products. Gas chromatography showed that in almost every reaction, in addition to the major product, small amounts (generally less than 5% of the total product) of isomeric compounds were formed. These by-products were not identified.

In order to determine the structure of the major products (and thereby obtain proof of the course of the addition reactions), it was necessary to establish two points: (a) which halogen atom was abstracted from the polyhaloalkane; (b) which carbon atom of the double bond underwent attack by the polyhaloalkane radical.

An example of a structure proof *via* chemical means has been reported by Tarrant and Gilman[5] for the $CF_2BrCFClBr$ + 1-octene adduct. The structure was shown to be I by the following reactions.

$$\underset{\text{I}}{CF_2BrCFClCH_2CHBr(CH_2)_5CH_3} \xrightarrow{\text{base}} CF_2BrCFClCH{=}CH(CH_2)_5CH_3$$

$$CF_2BrCFClCH{=}CH(CH_2)_5CH_3 \xrightarrow{Zn} CF_2{=}CFCH{=}CH(CH_2)_5CH_3$$

This same series of dehydrohalogenation and dehalogenation reactions was employed in this study for structure elucidation. Additionally, the adducts synthesized in this study gave a pmr signal in the vicinity of δ 4.0 for the protons geminal to a single halogen atom. Thus, it was possible to determine if the halogen atom had become attached to the terminal or to the internal carbon of the double bond. For example, the methine proton in $CF_2BrCFClCH_2CHBr(CH_2)_5CH_3$ appeared as a multiplet centered at δ 4.4 and integrated for one proton. With the alternative structure, $CH_2BrCH(CFClCF_2Br)(CH_2)_5CH_3$, a signal with an intensity corresponding to two protons would be anticipated in the δ 4.0 region.

It was found that redox-initiated additions proceeded in the same manner as that described for additions initiated by ordinary techniques. Therefore it was valid to make direct comparisons of reaction yields and products to previously reported information.

The series of reactions utilizing 1-octene as a model olefin provides some straightforward data on the relative reactivity of several polyhalides. The data in Table I indicate that increasing reactivity of the halogenated alkane directly parallels the ease with which a halogen atom is abstracted from the molecule. An examination of the experimental results does indeed show increased reactivity of bromo compounds over

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966; (b) abstracted from the Ph.D. thesis of L. J. Kehoe, University of Iowa, Feb 1967; (c) preliminary report in *Tetrahedron Lett.*, 5163 (1966). (d) This investigation was supported in part by the U. S. Public Health Service, Grant GM 11809.

(2) For an extensive review of this work, *cf.* (a) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 6; (b) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Co., New York, N. Y., 1964, Chapter 2.

(3) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963).

(4) M. Asscher and D. Vofsi, *ibid.*, 3921 (1963).

(5) P. Tarrant and E. Gilman, *J. Amer. Chem. Soc.*, **76**, 5423 (1954).

TABLE I
DATA ON ADDITION ADDUCTS

Reaction	Halide	Adduct	% yield[a]	% conversion[b]	Ratio of halide: olefin	Reaction time, hr	Bp, °C (mm)	$n^{20}D$	Calcd % C	Calcd % H	Found % C	Found % H
I	CH_2Br_2		0	0	1:1	48						
II	CF_2Br_2	$CF_2BrCH_2CHBr(CH_2)_5CH_3$	68	47	2:1	53	42 (0.1)	1.4583	33.6	4.97	33.7	5.26
III	$CHClBr_2$	$CHClBrCH_2CHBr(CH_2)_5CH_3$	99	57	2:1	79	100 (0.55)	1.5021	33.8	5.32	33.6	5.01
IV	$CHBr_3$	$CHBr_2CH_2CHBr(CH_2)_5CH_3$	95	41	2:1	48	98 (0.2)	1.5192	29.6	4.67	29.9	4.73
V	$CHCl_3$	$CHCl_2CH_2CHCl(CH_2)_5CH_3$	37	25	2:1	53	63 (0.15)	1.4654	46.8	7.36	46.9	7.53
VI	CCl_4	$CCl_3CH_2CHCl(CH_2)_5CH_3$	77	52	2:1	24	107 (2)	1.4763	40.6	6.02	40.6	5.97
VII	CCl_3Br	$CCl_3CH_2CHBr(CH_2)_5CH_3$	96	100	2:1	24	70 (0.05)	1.4942	34.9	5.17	34.6	4.90
VIII	CF_2BrCF_2Br	$CF_2BrCF_2CH_2CHBr(CH_2)_5CH_3$	77	57	2:1	48	84 (1)	1.4380	32.3	4.31	32.6	4.60
IX	$CF_2BrCFClBr$	$CF_2BrCFClCH_2CHBr(CH_2)_5CH_3$	95	96	2:1	24	88 (0.4)	1.4612	30.9	4.13	30.7	4.19
X	$CF_2ClCFCl_2$	$CF_2ClCClCH_2CHCl(CH_2)_5CH_3$	62	45	2:1	48	79 (0.95)	1.4305	40.2	5.35	40.4	5.59
XI	CF_3CHBr_2	$CF_3CHBrCH_2CHBr(CH_2)_6CH_3$	97	80	2:1	48	54 (0.05)	1.4475	33.9	4.80	34.2	5.03
XII	CF_3CClBr_2	$CF_3CClBrCH_2CHBr_2(CH_2)_5CH_3$	98	97	2:1	48	68 (0.1)	1.4619	30.9	4.13	30.7	4.00
XIII	CF_3CBr_3	$CF_3CBr_2CH_2CHBr(CH_2)_5CH_3$[c]	74	100	2:1	43	80 (0.15)	1.4776	27.7	3.69	27.5	3.68
XIV	CF_3CCl_3	$CF_3CCl_2CH_2CHCl(CH_2)_5CH_3$	83	100	2:1	48	54 (0.15)	1.4304	40.2	5.35	40.0	5.07
XV	CCl_2BrCCl_2Br		0	0	1:1	30						
XVI	CCl_3CCl_3		Trace	8	1:1	45						
XVII	$CF_2ClCFClI$	$CF_2ClCFClCH_2CHI(CH_2)_5CH_3$	73	51	1:1	43	82 (0.25)	1.4722	30.7	4.19	30.6	4.03
XVIII	$CF_3CF_2CF_2I$	$CF_3CF_2CF_2CH_2CHI(CH_2)_5CH_3$	57	36	1:1	24	54–55 (0.4)	1.4116	32.4	3.92	32.6	3.77
XIX	CF_3CFICF_3	$(CF_3)_2CFCH_2CHI(CH_2)_5CH_3$	66	54	1:1	24	43 (0.2)	1.4132	32.4	3.92	32.2	4.07
XX	$CF_3CFBrCFBrCF_3$		0	0	1:1	48						

[a] Yield (*via* glpc) = moles of adduct formed/moles of olefin consumed. [b] Conversion (*via* glpc) = moles of olefin consumed/moles of olefin charged. [c] The structure of this adduct was not unequivocally determined.

chloro compounds. For example, the dibromoalkane CF_2BrCF_2Br gave a 77% yield (57% conversion) of the addition adduct, while the closely related chloro compound $CF_2ClCFCl_2$ gave only a 62% yield (45% conversion). Compare also reactions VI and VII.

With the iodo compounds, however, seemingly anomalous results are observed. In these instances, the relatively low yields of addition adducts were traceable directly to the formation of large amounts of olefins, the product formed by the loss of HI from the adduct. The reaction of $CF_3CF_2CF_2I$, for example, gave a product mixture composed of 57% $CF_3CF_2CF_2CH_2CHI(CH_2)_5CH_3$ and 42% $CF_3CF_2CF_2CH{=}CH(CH_2)_5CH_3$.

The susceptibility of these iodo compounds to loss of HI under the redox reaction conditions points out one other aspect of this catalysis system. The adduct, as well as the reactants, must be stable in the presence of the copper salt and the ethanolamine for addition to be successful. In the case of the iodo compounds, the ethanolamine is probably a strong enough base to remove HI from the product. Approximately 0.05 mol of olefin was formed, and 0.05 mol of ethanolamine was used to initiate the addition.

If a bulkier atom is added to each of a series of alkyl polyhalides, each successive compound would be expected to be more reactive (owing to both steric considerations and to the activating influence of each added halogen atom) than the one preceeding it in the series. The series CF_3CHBr_2 (80% conversion), CF_3CClBr_2 (97% conversion), CF_3CBr_3 (100% conversion) is a case in point.

While most of the polyhalo compounds examined did undergo successful addition, several others are worthy of note. For example, the tetrachloro compound CCl_2BrCCl_2Br gave only tetrachloroethylene under these conditions, and no addition adduct. The closely related tetrafluoroethane CF_2BrCF_2Br however, added readily to 1-octene. The failure of $CF_3CFBrCFBrCF_3$ to react was somewhat unexpected, since debromination of this halide was not observed.

One final comparison of halide reactivities is between CH_2Br_2 and CF_2Br_2. While CH_2Br_2 gave no addition, CF_2Br_2 formed the desired adduct in a 68% yield, an indication of the ability of the fluorine atoms to activate the bromine atom toward radical attack.

Several reaction parameters were examined. One interesting reaction series revealed that the addition of very reactive polyhalides, such as $CF_2BrCFClBr$, can be catalyzed by ethanolamine alone, while the less reactive halides, such as CF_2BrCF_2Br and $CF_2ClCFCl_2$, undergo successful addition *only* in the presence of both copper salt and amine. These results are summarized in Table II.

TABLE II
EFFECT OF COPPER ON REACTION

Olefin	Halide	% conversion	% yield
A. 1 mmol of CuCl + 50 mmol of Ethanolamine			
1-Octene	$CF_2BrCFClBr$	96	95
	CF_2BrCF_2Br	57	77
	$CF_2ClCFCl_2$	45	62
B. No Added CuCl–50 mmol of Ethanolamine			
1-Octene	$CF_2BrCFClBr$	88	73
	CF_2BrCF_2Br	4	100
	$CF_2ClCFCl_2$	0	0

When CuCl was utilized in the absence of ethanolamine, $CF_2BrCFClBr$ gave no addition. It was also found that the initial oxidation state of the copper salt did not affect the yield of adduct. Both CuCl and $CuCl_2 \cdot 2H_2O$ gave a 62% yield of adduct (45% conversion) with $CF_2ClCFCl_2$.

Butylamine was substituted for the ethanolamine with no loss in reactivity. However, both aniline and triethylamine were considerably less effective.

One final parameter was considered, this being the effect of solvent on the yield of adduct. The results are summarized in Table III and are indicative of some type of solvent effect since all three solvents have approximately the same boiling point and the reaction temperature was therefore the same in each case.

While the immediate goal of this study was an evaluation of the scope of this redox system of radical

TABLE III
EFFECT OF SOLVENT ON $CF_2BrCFClBr$ + 1-OCTENE REACTION

Solvent	% yield	% conversion
t-Butyl alcohol	95	96
Isopropyl alcohol	98	79
Acetonitrile	85	77

initiation, one observation is discussed here in an attempt to clarify previous mechanistic hypotheses.

Asscher and Vofsi have postulated the following mechanism for their oxidation–reduction-type additions[3,4]

$$M^+ + CHCl_3 \longrightarrow M^+(\dot{C}l) + CHCl_2\cdot \quad (a)$$

$$CHCl_2\cdot + CH_2{=}CHR \longrightarrow CHCl_2CH_2\dot{C}HR \quad (b)$$

$$CHCl_2CH_2\dot{C}HR + M^+(\dot{C}l) \longrightarrow CHCl_2CH_2CHClR + M^+ \quad (c)$$

where M^+ represented copper(I) or iron(II) ion and M^+ ($\dot{C}l$) represented copper(II) or iron(III) ion with at least one chlorine ligand in the coordination shell. Asscher thus called the oxidation–reduction steps a and c "redox-transfer."[6] The authors comment that in the presence of an amine much less vigorous conditions are necessary to bring about this reaction. The data in Table II lend support to this observation as, with less reactive alkyl polyhalides, no reaction occurred under mild conditions without the presence of added ethanolamine. Thus, as both the amine and the copper salt are indispensable for addition of the less reactive halides, a complex of the amine with copper ion is strongly suggested as the reactive species.

$$Cu^+(\text{ammine}) + CCl_4 \longrightarrow Cu^+(\text{ammine})(\dot{C}l) + CCl_3\cdot$$

Experimental Section

Boiling points are uncorrected. Elemental analyses were performed by personnel in this laboratory. Infrared spectra were obtained on a Perkin–Elmer Model 21 double-beam recording spectrophotometer. The pmr spectra were recorded on a Varian A-60 instrument with tetramethylsilane as an internal standard. Glpc analyses were obtained with a F & M Model 720 gas chromatograph, and peak areas were used to calculate the yield of addition adducts.

Copper chloride was purified *via* the method of Keller and Wycoff.[7] Bromoform and bromotrichloromethane were distilled before use. $CF_3CFBrCFBrCF_3$,[8] CCl_2BrCCl_2Br,[9] $CF_2ClCFClI$,[10] $CF_2BrCFClBr$,[5] and CF_3CCl_3,[11] were prepared by reported methods.

1,1-Dibromo-1-chloro-2,2,2-trifluoroethane.—$CF_2BrCFClBr$ (176 g) and anhydrous aluminum chloride (13 g) were allowed to react at room temperature for 2 hr. The organic product was extracted with ether and distilled to give 146 g of CF_3CClBr_2, bp 91–92°.

1,1,2-Tribromo-2,2,2-trifluoroethane.—CF_2BrCF_2Br (400 g) and anhydrous aluminum chloride (10 g) were refluxed for 22 hr. The organic product was extracted with ether and distilled to give 148 g of CF_3CBr_3, bp 114–115°.

All other materials were best commercial grade used without further purification.

Addition of Perhaloalkanes to Olefins.—The experimental data for these addition reactions are compiled in Table I. A typical reaction procedure is described in detail. The additions were carried out in a 500-ml flask containing a Teflon-covered stirring bar and fitted with a cold-water condenser, topped by a tube leading to a Dry Ice cooled trap.

Initial reactions were catalyzed by freshly prepared copper(I) chloride. The copper(I) chloride is slowly oxidized by moist air to yield a green compound, $CuCl_2\cdot 3Cu(OH)_2$. However, it was found that this partially oxidized mixture of Cu(I) and Cu(II) was an effective catalyst for these additions, and the mixture was therefore used to initiate subsequent addition reactions.

Typical Reaction Procedure. Reaction of $CF_2BrCFClBr$ with 1-Octene.—Utilizing the reaction apparatus described above, 55.3 g (0.2 mol) of $CF_2BrCFClBr$, 11.2 g (0.1 mol) of 1-octene, 0.1 g (~0.001 mol) of copper chloride [Cu(I)–Cu(II) mixture], 3 g (0.05 mol) of ethanolamine, and 100 ml of *t*-butyl alcohol were refluxed, with stirring, for 24 hr. After cooling to room temperature, the reaction mixture was diluted with ether and the organic layer was separated. Glpc analysis on a silicone rubber column indicated a 95% yield of the 1:1 adduct, based on 1-octene. Subsequent fractionation yielded 27.0 g (70%) of pure addition adduct, bp 88° (0.4 mm), $n^{20}D$ 1.4612.

Dehydrohalogenation of $CF_2BrCF_2CH_2CHBr(CH_2)_5CH_3$ (VIII).—A mixture of KOH (3.6 g) in ethanol (150 ml) was dripped slowly into 18.2 g of VIII at 100°. After refluxing for 3 hr the reaction mixture was poured into water and the organic layer separated, washed, and dried. Distillation gave 9.25 g of product, bp 54° (0.9 mm), identified as $CF_2BrCF_2CH{=}CH(CH_2)_5CH_3$. *Anal.* Calcd for $C_{10}H_{15}BrF_4$: C, 41.4; H, 5.16. Found: C, 41.6; H, 5.45. The pmr and ir spectra were consistent with the above structure (*cf.* Table IV).

Dehydrohalogenation of $CF_2BrCFClCH_2CHBr(CH_2)_5CH_3$ (IX).—A mixture of KOH (9.9 g) in ethanol (150 ml) was dripped slowly into 45.9 g of IX at 100°. The reaction mixture was then poured into water and the organic layer separated, washed, and dried. Distillation gave 12.7 g of product, bp 69–70° (1 mm), identified as $CF_2BrCFClCH{=}CH(CH_2)_5CH_3$ (XXI). *Anal.* Calcd for $C_{10}H_{15}BrClF_3$: C, 39.1; H, 4.88. Found: C, 39.0; H, 5.12. The reported[5] boiling point for XXI was 62° (0.5 mm). The pmr and ir spectra were consistent with the above structure.

Dehydrohalogenation of CF_3CBr_3 + 1-Octene Adduct (XIII).—A mixture of KOH (29 g) in ethanol (200 ml) was dripped slowly into 163.2 g of XIII at 100°. After refluxing for 3 hr the reaction mixture was worked up in the usual manner. Distillation gave two compounds: (a) 17.1 g, bp 79–80° (2 mm); (b) 14.0 g, bp 102–105° (1 mm).

Compound a gave the following analysis. Calcd for $C_{10}F_3BrH_{14}$: C, 44.3; H, 5.20. Found: C, 44.2; H, 5.21. The ir spectrum of this fraction showed no double-bond absorption; pmr δ 5.4 (m, 1, methine), 2.5 (m, 2, methylene), 0.7–1.9 (m, 11, remaining protons). The pmr spectra, the lack of double-bond absorption in the infrared and the elemental analysis, suggest that this compound is $CF_3CHBrC{\equiv}CCH_2(CH_2)_4CH_3$, formed by the loss of two molecules of HBr from the 1:1 adduct and rearrangement (in the basic reaction media) of the intermediate allene.

Compound b gave the following analysis. Calcd for $C_{10}F_3Br_2H_{15}$: C, 34.1; H, 4.29. Found: C, 34.0; H, 4.28. The ir spectrum showed double-bond absorption at 6.0 μ; pmr δ 4.5–7.0 (m, 2, methine + vinyl), 0.7–2.4 (m, 13, remaining protons). The structure of this fraction could not be unequivocally determined, but the pmr spectrum suggests that it is a mixture of both possible compounds: $CF_3CBr{=}CHCHBr(CH_2)_5CH_3$ and $CF_3CBr_2CH{=}CH(CH_2)_5CH_3$.

Dehydrohalogenation of $CHClBrCH_2CHBr(CH_2)_5CH_3$ (III).—The attempted dehydrohalogenation of III gave a mixture of products, none of which were identified.

Dehalogenation of $CF_2BrCFClCH_2CHBr(CH_2)_5CH_3$ (IX).—IX (38.8 g) in isopropyl alcohol (50 ml) was added slowly to a slurry of granulated zinc (6.5 g) in isopropyl alcohol (100 ml) at 100°. After refluxing for 3 hr the reaction mixture was poured into water and the organic layer separated, washed, and dried. Distillation gave 12.3 g of product, bp 57–58° (0.4 mm), identified at $CF_2{=}CFCH_2CHBr(CH_2)_5CH_3$. *Anal.* Calcd for $C_{10}H_{16}BrF_3$: C, 44.0; H, 5.87. Found: C, 44.4; H, 5.91. The pmr and ir spectra were consistent with the above structure.

Dehalogenation of $CF_2ClCFClCH_2CHCl(CH_2)_5CH_3$ (X).—X (11.0 g) in isopropyl alcohol (50 ml) was added slowly to a slurry of granulated zinc (2.6 g) in isopropyl alcohol (100 ml) at 100°. After refluxing for 24 hr the reaction mixture was worked up in

(6) This same redox reaction has been called "ligand-transfer" by Kochi and coworkers: J. K. Kochi, *Tetrahedron*, **18**, 483 (1962).
(7) R. N. Keller and H. D. Wycoff, *Inorg. Syn.*, **2**, 1 (1946).
(8) T. J. Brice, J. D. Lazerte, and W. H. Pearlson, *J. Amer. Chem. Soc.*, **75**, 2698 (1953).
(9) E. Malaguti, *Ann.*, **56**, 276 (1845).
(10) M. Hauptschein, M. Braid, and A. Fainberg, *J. Amer. Chem. Soc.*, **83**, 2495 (1961).
(11) W. T. Miller, E. Fager, and P. Griswald, *ibid.*, **72**, 705 (1950).

TABLE IV
PROTON MAGNETIC RESONANCE DATA[a]

Adduct	Chemical shifts, δ (ppm) $CH_3(CH_2)_5$	Isolated $-CH_2-$	$-CHX$	Rel intensities
II	0.8–2.0 (m)	3.0 (m)	4.2 (5), J_{HH} = 6	13:2:1
III	0.8–2.0 (m)	2.7 (m)	4.1 (5), J_{HH} = 6.5 6.0 (3), J_{HH} = 6.5	13:2:1:1
IV	0.8–2.0 (m)	2.8 (4), J_{HH} = 6.0, $J_{HH'}$ = 8.0	4.2 (m) 6.0 (m)	13:2:1:1
V	0.8–2.0 (m)	4.0 (m)	5.9 (3), J_{HH} = 6.5	13:2:1
VI	0.7–2.1 (m)	3.2 (4), J_{HH} = 5.5, $J_{HH'}$ = 5.0	4.2 (m)	13:2:1
VII	0.8–2.2 (m)	3.3 (3), J_{HH} = 5.5	4.4 (m)	13:2:1
VIII	0.8–2.2 (m)	2.7 (6), J_{HH} = 6.5, J_{HF} = 18	4.2 (5), J_{HH} = 6.0	13:2:1
IX	0.7–2.2 (m)	2.2–3.2 (m)	4.4 (m)	13:2:1
X	0.7–2.2 (m)	2.2–3.0 (m)	4.3 (m)	13:2:1
XI	0.7–2.7 (m)		4.0–4.8 (m)	15:1
XII	0.8–2.2 (m)	2.9 (m)	4.4 (m)	13:2:1
XIII	0.7–3.1 (m)		4.3 (m)	15:1
XIV	0.8–2.1 (m)	2.8 (4), J_{HH} = 5.5, $J_{HH'}$ = 5.0	4.2 (5), J_{HH} = 5.5	13:2:1
XVII	0.7–2.1 (m)	2.5–3.3 (m)	4.4 (m)	13:2:1
XVIII	0.7–2.1 (m)	2.4–3.3 (m)	4.4 (5), J_{HH} = 6.5	13:2:1
XIX	0.7–2.1 (m)	2.6–3.2 (m)	4.4 (m)	13:2:1

[a] In parentheses is given the multiplicity of the peak; the coupling constants are in cycles per second.

the usual manner and the organic layer distilled to give 2.4 g of product, bp 54–55° (0.8 mm), identified as $CF_2{=}CFCH_2CHCl(CH_2)_5CH_3$. The pmr and ir spectra were consistent with the above structure.

Registry No.—II, 459-78-9; III, 23885-03-2; IV, 1071-51-8; V, 10575-86-7; VI, 1070-27-5; VII, 1070-26-4; VIII, 23885-08-7; IX, 461-01-8; X, 23885-10-1; XI, 23885-11-2; XII, 23885-12-3; XIII, 23885-13-4; XIV, 23885-14-5; XVII, 23885-15-6; XVIII, 23885-16-7; XIX, 23885-17-8; $CF_2BrCF_2CH{=}CH(CH_2)_5CH_3$, 23885-18-9; $CF_2BrCFClCH{=}CH(CH_2)_5CH_3$, 310-63-4; $CF_3CHBrC{\equiv}CCH_2(CH_2)_4CH_3$, 23885-20-3; $CF_3CBr{=}CHCHBr(CH_2)_5CH_3$, 23885-21-4; $CF_3CBr_2CH{=}CH(CH_2)_5CH_3$, 23885-22-5; $CF_2{=}CFCH_2CHBr(CH_2)_5CH_3$, 23942-63-4; $CF_2{=}CFCH_2CHCl(CH_2)_5CH_3$, 23885-23-6; copper chloride, 7447-39-4; ethanolamine, 141-43-5.

Aluminum Chloride Catalyzed Diene Condensation. V.[1,2] Selectivity–Reactivity Relationship of Dienophiles toward Butadiene, Isoprene, and 2-Trifluoromethylbutadiene

TAKESHI KOJIMA AND TAKASHI INUKAI

The Central Research Laboratories, Chisso Corporation, Kamariya, Kanazawa-ku, Yokohama, Japan

Received September 15, 1969

The relative rates of reactions of isoprene and butadiene, k^i/k^b, with tetracyanoethylene, methyl acrylate–aluminum chloride complex, fumaryl chloride, vinylidene cyanide, maleic anhydride, dimethyl fumarate, dimethyl acetylenedicarboxylate, methyl acrylate, acrylonitrile, and dimethyl maleate were determined and plotted against the *reactivities* (the second-order rate constants with cyclopentadiene in dioxane at 20°) of the dienophiles. The k^i/k^b value increases with the increasing reactivity of the dienophile, in contrast to the accepted selectivity–reactivity relationship. Corresponding data for the 2-trifluoromethylbutadiene–butadiene pair of substrates are reported. The selectivity, based on the relative rate of the *s-cis* species, increases with the increasing reactivity of the dienophiles, here the selectivity being in favor of butadiene. The mechanistic implications of these results are discussed in connection with the selectivity–reactivity relationship and varying electrophilic character of the dienophiles. From the normal position taken by the methyl acrylate–aluminum chloride complex in the correlation line, the mechanism of the aluminum chloride catalyzed diene condensation is assumed to be one of the variety of the Diels–Alder reactions.

It was shown in previous papers that the methyl acrylate–aluminum chloride complex (MA–$AlCl_3$)[1] is a more discriminating dienophile than uncomplexed methyl acrylate in reactions with isoprene–butadiene[3] or *trans*-piperylene–butadiene[4] pairs of diene substrates, whereas the former dienophile is more reactive than the latter.[1] The higher selectivity was also found in stereochemical (*endo–exo*)[4–6] and orientational (*meta–para* or *ortho–meta*)[3,4] phenomena. These ob-

(1) Part IV: T. Inukai and T. Kojima, *J. Org. Chem.*, **32**, 872 (1967).

(2) Presented in part: Abstracts, 18th Symposium on Organic Reaction Meehanism of the Chemical Society of Japan, Kyoto, Japan, Oct 1967, p 122; Abstracts, 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, Japan, April 1969, p 1658.

(3) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

(4) T. Inukai and T. Kojima, *ibid.*, **32**, 869 (1967).

(5) T. Inukai and T. Kojima, *ibid.*, **31**, 2032 (1966).

(6) J. Sauer and J. Kredel, *Tetrahedron Lett.*, 731 (1966).

servations apparently contradict the accepted selectivity–reactivity relationship, according to which the more reactive reagents should be the less selective species and *vice versa*.[7]

This anomaly may be supposed to occur because the reaction of MA–$AlCl_3$ as a dienophile (the aluminum chloride catalyzed Diels–Alder reaction) proceeds by a mechanism different from that of methyl acrylate (uncatalyzed) reaction. If this is shown to be true we could draw a better inference on the mechanism of the Diels–Alder reactions by contrasting their characteristics to those of the catalyzed modification that is presumably more polar in nature. The anomalous selectivity–reactivity relationship may, however, be a characteristic feature of the Diels–Alder reactions in general.

We therefore undertook to examine fully this relationship by using a series of common dienophiles covering a wide range of dienophilic reactivity and to investigate whether the MA–$AlCl_3$ complex is singular or not with respect to the selectivity–reactivity relationship.

Results

The relative rates of isoprene *vs.* butadiene, k^i/k^b, and of 2-trifluoromethylbutadiene *vs.* butadiene, k^t/k^b, toward several dienophiles were determined mostly by the competitive reaction technique similar to that reported earlier.[3,4] The reaction conditions and results for the isoprene–butadiene pair of dienes are summarized in Table I. The corresponding data for the 2-trifluoromethylbutadiene–butadiene pair are shown in Table II. The relative rates, k^t/k^b, for dimethyl maleate and maleic anhydride are those calculated from the second-order rate constants of respective reactions, which are presented in Table III. There is no reason for this inhomogeneity of the method adopted except that we could not afford to use 2-trifluoromethylbutadiene sufficiently to carry out the competitive experiments.

Since the adducts are thermally stable at the reaction temperature of 20°, it is unlikely that the observed relative rates are thermodynamically influenced. Indeed it was ascertained experimentally in some cases that the observed ratio is kinetically determined.

The *meta* to *para* ratios of the products from isoprene and unsymmetrical dienophiles are listed in Table IV.

Discussion

We wish to have an appropriate measure of reactivities of the dienophiles in order to test the selectivity–reactivity relationship. Although obviously the reactivity of a reagent is an entity not expressible by a single number in a quantitative manner, it is useful to define a convenient scale, applicable to a particular type of reaction, on which various reagents will lie in an order almost invariable when the substrate varies. As the measure of the reactivities of the dienophiles, the second-order rate constants of the reactions with cyclopentadiene in dioxane at 20° [8] will be employed, although it would be preferable to use the rate constants of the reactions of the dienophiles with butadiene,

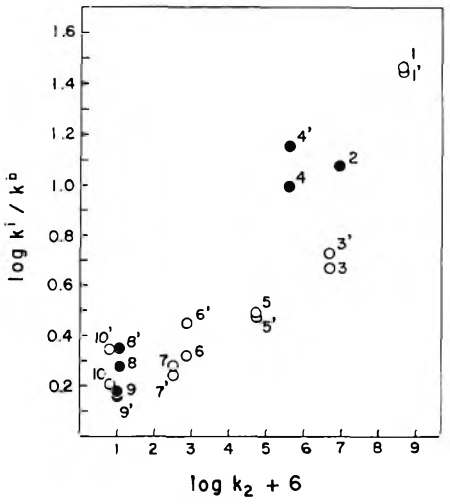


Figure 1.—The relation between relative rates of isoprene *vs.* butadiene, k^i/k^b, at 20° and *reactivities* of dienophiles: k_2 (ref 8) in unit of l./mol sec. The numerals attached to the points correspond to the set numbers of Table I: ○, symmetrical dienophile; ●, unsymmetrical dienophile.

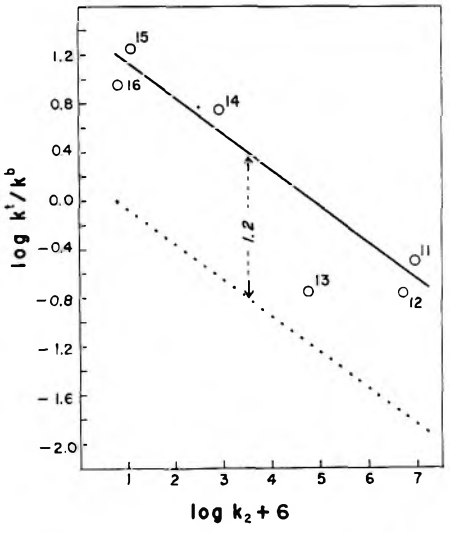


Figure 2.—The relative rates of 2-trifluoromethylbutadiene *vs.* butadiene, k^t/k^b, at 20° and *reactivities* of dienophiles: k_2 (ref 8) in unit of l./mol sec. Maleic anhydride, 13; dimethyl maleate, 16; others correspond to the set numbers of Table II.

the standard substrate, if they were available. Since the reactivity of MA–$AlCl_3$ cannot be obtained in this standard system, the rate constant in benzene solution at 20° determined in a somewhat indirect way (see Experimental Section) was used as a substitute.[9]

The correlation between the observed relative rate and reactivity is plotted in log–log scale in Figures 1 and 2. It appears from Figure 1 that the dienophiles of symmetrically substituted ethylene structure define a rising curve, although the scatter is considerable. The upward deviation of the unsymmetrical dienophiles is reasonable because their transition complexes would be more polarized than those from the symmetrical dienophiles, so as to receive more the stabilizing effect of the methyl substituent. It should be noted that, although

(7) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, p 162.

(8) J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).

(9) (a) This can be justified because the rate of Diels–Alder reactions is comparatively solvent (and even phase) insensitive.[9a,10] (b) A. Wassermann, "Diels–Alder Reactions," Elsevier Publishing Co., Amsterdam, 1965, pp 50–52.

(10) See, *e.g.*, J. Sauer, *Angew. Chem.*, **79**, 76 (1967).

TABLE I

RELATIVE RATES, ISOPRENE *vs.* BUTADIENE, k^i/k^b, AT *ca.* 20°[a]

Dienophile, mmol	Isoprene, mmol	Butadiene, mmol	Solvent, g	Reaction period, days	Product ratio[b]	k^i/k^b Obsd	k^i/k^b Avg
			Set 1. TCNE, Benzene				
0.78	15.87	730.8	443	19	0.614	28.8	
0.78	21.30	859.4	464	7	0.747	30.4	29.7
0.78	27.33	1244.	428	9	1.581	29.8	
			Set 1′. TCNE, Acetonitrile				
0.94	22.04	790.2	426	4	0.784	27.9	
							27.5
0.94	19.10	773.9	439	5	0.653	27.0	
			Set 2. MA–$AlCl_3$, Benzene[c]				
							12.1
			Set 3. Fumaryl Chloride, Benzene				
4.05	369.8	475.7	300	25	3.58	4.62	
							4.67
4.05	314.6	408.7	311	26	3.60	4.71	
			Set 3′. Fumaryl Chloride, Acetonitrile				
3.92	370.1	523.2	356	40	3.79	5.37	
							5.34
3.92	433.0	620.8	354	41	3.69	5.30	
			Set 4. Vinylidene Cyanide, Benzene				
2.10	553.5	856.3	435	9	6.41	9.92	
							9.94
1.73	481.6	689.8	461	10	6.87	9.95	
			Set 4′. Vinylidene Cyanide, Nitromethane				
5.51	406.7	615.9	366	3	9.93	15.1	
							14.5
5.00	353.8	521.6	356	3	9.73	13.8	
			Set 5. Maleic Anhydride, Benzene				
6.33	592.1	611.5	334	24	3.00	3.09	
							3.11
7.35	357.9	596.0	324	24	1.86	3.12	
			Set 5′. Maleic Anhydride, Acetonitrile				
3.06	456.2	649.1	417	30	2.12	3.02	
							3.01
3.06	460.9	563.9	437	31	2.45	3.00	
			Set 6. Dimethyl Fumarate, Benzene				
3.47	333.0	532.5	289	36	1.27	2.09	
							2.08
2.08	87.8	198.4	295	37	0.907	2.06	
			Set 6′. Dimethyl Fumarate, Benzene				
5.55	317.6	501.0	None	24	1.72	2.72	
							2.82
5.55	377.0	570.0	None	6	1.91	2.92	
			Set 7. Dimethyl Acetylenedicarboxylate, Benzene				
4.22	425.8	711.8	336	240	1.08	1.81	
							1.76
4.22	395.5	707.7	365	240	0.954	1.71	
			Set 7′. Dimethyl Acetylenedicarboxylate, Benzene				
3.73	311.2	513.2	None	60	0.871	1.91	
							1.91
3.52	312.2	413.5	None	60	1.438	1.91	
			Set 8. Methyl Acrylate, Benzene				
17.4	473.3	862.9	346	240	1.06	1.92	
							1.89
11.9	500.9	677.8	393	240	1.36	1.85	
			Set 8′. Methyl Acrylate, None[b]				
							2.16

TABLE I
(*Continued*)

Dienophile, mmol	Isoprene mmol	Butadiene, mmol	Solvent, g	Reaction period, days	Product ratio[b]	k^i/k^b Obsd	k^i/k^b Avg
			Set 9. Acrylonitrile, Benzene				
19.6	437.5	722.0	397	240	1.02	1.68	1.52
20.6	510.6	770.4	339	240	0.903	1.36	
			Set 9′. Acrylonitrile, None				
18.9	290.1	521.2	None	62	0.845	1.51	1.51
9.43	318.1	625.0	None	62	0.769	1.51	
			Set 10. Dimethyl Maleate, Benzene				
7.35	297.7	545.4	413	240	0.854	1.57	1.61
7.70	301.3	998.6	352	240	0.496	1.64	
			Set 10′. Dimethyl Maleate, None				
7.29	295.8	448.1	None	144	1.185	2.26	2.22
3.47	280.9	484.4	None	142	1.23	2.18	

[a] Dienophile and solvent are given for each set. [b] Mole ratio of isoprene adduct to butadiene adduct. [c] Previous work; see ref 3.

TABLE II
RELATIVE RATES, 2-TRIFLUOROMETHYLBUTADIENE *vs.* BUTADIENE, k^t/k^b, AT *ca.* 20°[a]

Dienophile, mmol	2-CF_3–butadiene, mmol	Butadiene, mmol	Solvent, g[b]	Reaction period, days	Product ratio[c]	k^t/k^b Obsd	k^t/k^b Avg
			Set 11. Ma–$AlCl_3$				
10.0[d]	99.97	85.12	23.1	1/6	0.381	0.315	0.320
10.0[d]	99.97	125.1	20.5	1/6	0.271	0.330	
			Set 12. Fumaryl Chloride				
1.96	102.6	167.9	117.0	2	0.106	0.175	0.173
1.96	102.2	44.37	122.0	14	0.398	0.171	
			Set 14. Dimethyl Fumarate				
19.1	28.67	582.7	315.0	39	0.269	5.80	5.65
4.72	26.21	697.3	322.0	38	0.206	5.51	
			Set 15. Dimethyl Fumarate				
5.00	49.16	50.88	None	69	15.37	17.0	17.7
5.23	49.14	66.56	None	69	12.96	18.4	

[a] Dienophile is given for each set. [b] Benzene solvent. [c] Mole ratio of the 2-CF_3–butadiene adduct to butadiene adduct. [d] Methyl acrylate (10.0 mmol) and aluminum chloride (4.0 mmol); see ref 1 for the basis of this expression.

TABLE III
RELATIVE RATE, k^t/k^b, FROM KINETIC MEASUREMENTS AT 20°

Dienophile, mmol/l.[a]	R	2 R-butadiene, mmol/l.[a]	Solvent	k_2, l./mol sec	k^t/k^b
			A. Dimethyl Maleate		
6894	CF_3	1079	None[b]	2.27×10^{-8}	9.00
7717	H	324.7	None[b]	2.52×10^{-9}	
			B. Maleic Anhydride		
493.6	CF_3	150.4	Benzene	5.08×10^{-6}	0.19
157.1	H	244.7	Benzene	2.71×10^{-5}	

[a] Initial concentration [b] In excess of dimethyl maleate.

TABLE IV
ISOMER DISTRIBUTION OF ISOPRENE ADDUCTS[a]

Dienophile	*meta*, %	*para*, %
MA–$AlCl_3$[b]	5.0	95.0
Vinylidene cyanide[c]	8.7	91.3
Methyl acrylate[b]	30.5	69.5
Acrylonitrile[c,d]	25.5	74.5

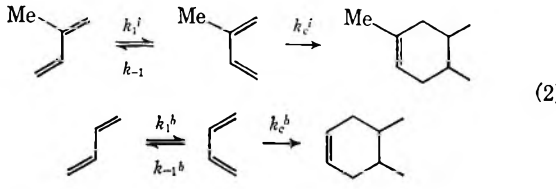
[a] From reaction at *ca.* 20°. [b] Previous work; see ref 3. [c] A Hitachi K53 gas chromatograph with a Golay column HB 2000–90 (polypropylene glycol, 90 m) was used; peak area ratio was assumed to be equal to the isomer ratio. [d] The literature reports *meta* 21.8%, *para* 78.2%: J.-C. Soula, D. Lumbroso, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 2059 (1966).

the reactivity scale is numerically presented, it is not more than semiquantitative in principle;[11] hence a quantitative significance cannot be attached to the shape (*i.e.*, straight, concave, or convex) of the correlation line. The trend is, however, definitely that the more reactive dienophiles are generally more selective, which is opposite to the normal selectivity–reactivity relationship. To the level of accuracy of this correlation and argument the MA–$AlCl_3$ should not be regarded as a singular dienophile.

The selectivity to be compared with the reactivity, in theoretical considerations, must properly be in terms of the ratio of rates of reactions of *s-cis* subspecies of isoprene and butadiene, k_c^i/k_c^b, rather than the observed relative rate, k^i/k^b. The relation between these two ratios is expressed by eq 1, where k values are

$$k^i/k^b = [k_c^i/k_c^b][k_1^i/(k_{-1} + k_1^i)][(k_{-1}^b + k_1^b)/k_1^b]$$
$$= [k_c^i/k_c^b][K^i/(1 + K^i)][(1 + K^b)/K^b] \quad (1)$$
$$\cong [k_c^i/k_c^b][K^i/K^b] \quad (1')$$

related to eq 2 on the assumption that the cisoid–transoid interconversion is much faster than the diene



(2)

condensation. Since K^i/K^b is a constant under the uniform experimental conditions, the relationship between selectivity and reactivity holds irrespective of the true value of K^i/K^b.[12]

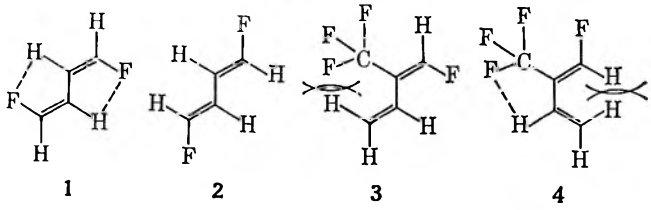
The reaction series of 2-trifluoromethylbutadiene *vs.* butadiene (Figure 2) includes both cases, $k^t > k^b$ and $k^t < k^b$, making the selectivity–reactivity correlation appear complicated at first sight. In the similar way as above the observed ratio, k^t/k^b, is expressed by eq 3,

$$k^t/k^b = [k_c^t/k_c^b][K^t/(1 + K^t)][(1 + K^b)/K^b]$$
$$\cong [k_c^t/k_c^b][K^t/(1 + K^t)/K^b] \quad (3)$$

where the meaning of the symbols is self-evident. The dienophiles may be expected to react with the *s-cis* subspecies of 2-trifluoromethylbutadiene slower than with that of butadiene because the trifluoromethyl group is electron withdrawing.[13] It then should be the term $K^t/(1 + K^t)/K^b$ that makes k^t larger than k^b in reactions with less selective dienophiles; to paraphrase, 2-trifluoromethylbutadiene has a higher population of *s-cis* conformer than butadiene such that the observed rate, k^t, may happen to be larger than k^b when k_c^b is not sufficiently greater than k_c^t.[14] This view sets the lower limit of log $K^t/[(1 + K^t)/K^b]$ at *ca.* 1.2 from the correlation of Figure 2.

Although direct physical studies on the conformation of 2-trifluoromethylbutadiene have not been reported, the notion of larger K^t than K^b values can be supported on the following bases. (A) The stabilizing interaction between hydrogen and halogen atoms at the 1,3-position is well known.[16] In particular the higher thermodynamic stability of *cis,cis*-1,4-difluorobutadiene (**1**) over *trans,trans*-1,4-difluorobutadiene (**2**), which is otherwise supposed to be more stable, was ascribed to this sort of interaction (Chart I).[17] Irrespective of

CHART I



the true reason why this stability order prevails in these cases, we may infer that 2-trifluoromethylbutadiene would have similar stabilization by taking an *s-cis* form (**3**), whereas the *s-trans* form (**4**) is sterically strained (Chart I). (B) Uv absorption of 2-trifluoromethylbutadiene in hexane was found at λ_{max} 215 mμ (ϵ_{max} 11,000 ± 1000). This extinction coefficient falls in the general range of ϵ_{max} values for the *cis* 1,3-dienes and seems to be too small for the *trans* dienes.

These reasons are not enough alone to conclude that the compound predominantly takes the *s-cis* form, but support the conclusion that K^t is larger than K^b. Incidentally, K^b is generally believed to be *ca.* 0.03 at room temperature,[18] and may be even smaller according to more precise, microwave studies which failed to detect the *cis* form.[19]

The selectivity–reactivity correlation line in terms of the relative rates of *s-cis* subspecies, k_c^t/k_c^b, will be located somewhere below, and shifted parallel to, the dotted line drawn in Figure 2. The more reactive dienophiles are more selective, the selectivity here being in favor of unsubstituted butadiene over 2-tri-

(11) The order of reactivity of dienophiles will be inverted only in exceptional cases of reactions with very electrophilic dienes like hexachlorocyclopentadiene (Diels–Alder reactions with inverse electron demand[10]).

(12) Approximate eq 1′ holds in this case, since K^i and K^b are much smaller than 1 (see later discussions).

(13) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem.*, **74**, 352 (1962).

(14) The increasing order of the reaction rate, 2-methyl- < 2-ethyl- < 2-isopropyl- < 2-*t*-butylbutadiene, for the Diels–Alder reactions with maleic anhydride, was explained with the increasing steric hindrance in the transoid conformation.[15]

(15) D. Craig, J. J. Shipman, and R. B. Fowler, *J. Amer. Chem. Soc.*, **83**, 2885 (1961).

(16) See ref 17 and the literature cited therein.

(17) H.-G. Viehe, *Angew. Chem.*, **75**, 783 (1963); H.-G. Viehe and E. Franchimont, *Chem. Ber.*, **97**, 602 (1964).

(18) (a) J. G. Aston, G. Szasz, H. W. Woolley, and F. G. Brickedde, *J. Chem. Phys.*, **14**, 67 (1946); (b) W. B. Smith and J. L. Massingill, *J. Amer. Chem. Soc.*, **83**, 4301 (1961).

(19) D. R. Lide, Jr., *J. Chem. Phys.*, **37**, 2074 (1962). For isoprene see D. R. Lide, Jr., and M. Jen, *ibid.*, **40**, 252 (1964).

fluoromethylbutadiene, and again the MA–$AlCl_3$ is not singular.

Consequently, the relation between selectivity and reactivity in the Diels–Alder reactions is opposite to the selectivity rule, which is expressed in an explicit form by eq 4.[6,20] The prerequisite for this equation is

$$\frac{\text{selectivity of hot reagent}}{\text{selectivity of cold reagent}} = \frac{\delta_R \Delta F^{\ddagger}_H}{\delta_R \Delta F^{\ddagger}_C} = \frac{\alpha_H \delta_R \Delta \bar{F}^{\circ}_H}{\alpha_C \delta_R \Delta \bar{F}^{\circ}_C} \quad (4)$$

$$(\alpha_H < \alpha_C)$$

that the reactions to be compared are *similar* in nature or belong to the same series. The limiting cases of application of eq 4, *i.e.*, very high and very low reactivity, quite appeal to the intuition, but in the moderate range of reactivity no convincing justification has been demonstrated.[21] Although the electrophilic aromatic substitutions, for example, are thought of as similar in some respect, there is no experimental evidence for this selectivity rule as far as the authors are aware. It is indeed difficult to examine the relationship in such cases, because those complications such as the prior equilibrium generating the true reagent (*e.g.*, nitronium ion) or the solvation of the species involved make the concentration of the true reagent, hence the rate constant of the elementary step, unknown.[22] The Diels–Alder reactions are comparatively free from these complications[23] and there was expected a fair opportunity of examining the relationship.

However, the results of the present study indicate that the electrophilicity of the dienophiles is the determining factor. The influence of the diene substituents on rate of reaction may be greater the more electrophilic the dienophile is;[24] since there is a general parallelism between the reactivity of the dienophiles and their presumable electrophilicity, k_c^i/k_c^b and k_c^b/k_c^t will increase with the increasing reactivity. The intramolecular selectivity (Table IV) can be similarly explained. This explanation may not be unconditionally accepted, however, because the actual weight of this factor cannot be estimated. The reason for emphasizing this reservation in this particular case is that the present knowledge of principal factors determining the substituent effect in the Diels–Alder reactions is only rudimentary and the conventional argument based on the electrophilicity of the reagents is not well grounded.[25] The electrophilicity factor, in cooperation with the high polarizability of the 1,3-diene electron system, will make the precise topography of the energy surface of the transition state sensitive to the variation of the reagents. In such a case the α value (eq 4) might increase as the electron affinity of the dienophile substituent increases, because it must lose the conjugative share of the α,β double bond electrons as the reorganization of electrons proceeds to complete the two new σ bonds.[26]

In conclusion, the aluminum chloride catalyzed diene condensation is thought to be one of the variety of normal Diels–Alder reactions because its position in the reactivity–selectivity correlation is not singular.[27]

Experimental Section

All melting points are uncorrected. Nmr spectra were taken using a Varian A-60A spectrometer on 10 wt % carbon tetrachloride solutions containing tetramethylsilane as internal standard. The glpc analyses were carried out with an Ohkura Model 1200 and a Hitachi K23 instrument using appropriate calibration curves for peak area ratio *vs.* molar ratio, unless otherwise indicated.

Reagents.—Butadiene used is as described in the previous paper.[28] Commercial isoprene was distilled and was gas chromatographically homogeneous. 2-Trifluoromethylbutadiene was prepared from 1,1,1-trifluoroacetone (Aldrich) by the known method,[29] bp 35–36° (lit. bp 41–42°,[29] 35.0–35.5°[30]). Dimethyl maleate, acrylonitrile, methyl acrylate, and MA–$AlCl_3$ complex are the same as described previously.[5,28] Vinylidene cyanide, bp 52.5–53° (12 mm) [lit.[31] bp 50.5° (10 mm)], was prepared by the method of Adris, *et al.*[31] Tetracyanoethylene (Aldrich) was used directly as obtained. Other dienophiles were prepared by the known methods and had correct boiling or melting points: dimethyl acetylenedicarboxylate, bp 74.5–76.5° (7 mm); dimethyl fumarate, mp 101°; fumaryl chloride, bp 52–52.5° (12 mm); maleic anhydride, mp 53°. Solvents were purified in the usual way and were anhydrous.

Authentic samples of Diels–Alder adducts required for the quantitative glpc analyses of the products were prepared by reactions at *ca.* 20° for varying periods according to the rate of the reaction of each pair of the diene and dienophile. Their physical constants are listed in Table V. Proofs of structures of the four new compounds are as follows.

The isoprene–vinylidene cyanide adduct gave the following nmr data: τ 4.61 (m, 1 H), 7.30 (m, 2 H), 7.72 (br s, 4 H), and 8.21 (d, J = 2 cps, 3 H).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.1. Found: C, 73.7; H, 7.1; N, 18.8.

The 2-trifluoromethylbutadiene–dimethyl fumarate adduct gave the following nmr data: τ 3.66 (m, 1 H), 6.31 (s, 6 H), 6.94–7.33 (m, 2 H), and 7.33–7.83 (m, 4 H).

Anal. Calcd for $C_{11}H_{13}F_3O_4$: C, 49.6; H, 4.9. Found: C, 49.5; H, 5.1.

The 2-trifluoromethylbutadiene–methyl acrylate adduct gave the following nmr data: τ 3.65 (m, 1 H), 6.30 (s, 3 H), and 7.1–8.5 (m, 7 H).

Anal. Calcd for $C_9H_{11}F_3O_2$: C, 51.9; H, 5.3. Found: C, 52.0; H, 5.2.

(20) Here δ_R is an operator that gives the substituent (R) effect on the operand and α is a parameter measuring *the approximate fractional displacement of the transition state along the reaction coordinate from reagents to products.*[6]

(21) In hydrogen abstraction by free radicals the selectivity rule seems to apply, but the electronegativity of radicals must also be taken into account: W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 154, 170.

(22) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(23) That the diene and dienophile themselves are the *true* reagents is vindicated by the practical absence of effects of medium and additives on rates and the generally clean second-order rate law of the reactions.

(24) (a) This idea will require a theoretical proof. Empirical support may be rendered by the following data concerning hydrogen abstractions from nuclear-substituted toluenes by the free radicals (R·) of similar R–H dissociation energy (103–104 kcal/mol) (Hammett ρ *vs.* σ^+): 0 (ref 24b), −0.3 (ref 24c), −0.35 (ref 24d), and −0.66 (ref 24e) for Me·, Ph·, *t*-BuO·, and Cl·, respectively, in the order of increasing electron affinity of the radicals. (b) R. E. Pearson and J. C. Martin, *J. Amer. Chem. Soc.*, **85**, 354 (1963). (c) W. A. Pryor, J. T. Echolo, Jr., and K. Smith, *ibid.*, **88**, 1189 (1966). (d) H. Sakurai and A. Hosomi, *ibid.*, **89**, 458 (1967). (e) G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964).

(25) The fact that *ortho* (>*meta*) or *para* (>*meta*) orientation of Diels–Alder reactions is observed irrespective of the electronic characteristics of the substituent R in 1-R- or 2-R-butadienes cannot be explained on the basis of the electronic theory.

(26) (a) It can be misleading in general to assume a higher reactivity to a reagent simply because of its lower selectivity, as has been sometimes done, even in comparison of a series of reactions of presumed similarity. (b) It was recently reported that the Hammett ρ value for E2 reaction of *para*-substituted phenyl β-chloroethyl sulfones is larger with a stronger amine (faster reaction) under uniform reaction conditions: Y. Yano and S. Oae, Abstract, 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April 1969, p 1648.

(27) In paper I of this series was proposed a different view which is not retainable now.

(28) T. Inukai and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965).

(29) R. D. Richardson and P. Tarrant, *ibid.*, **25**, 2254 (1960).

(30) P. Tarrant and R. E. Taylor, *ibid.*, **24**, 1888 (1959).

(31) A. E. Adris, S. J. Averill, H. Gilbert, F. F. Miller, R. F. Schmidt, F. D. Stewart, and H. L. Trumbull, *J. Amer. Chem. Soc.*, **72**, 1305 (1950).

TABLE V
PHYSICAL CONSTANTS OF DIELS–ALDER ADDUCTS

Dienophile[a]	Mp or bp of butadiene adduct, °C (mm)	Mp or bp of isoprene adduct, °C (mm)	Mp or bp of 2-CF_3–butadiene adduct, °C (mm)
1	201.5–202[b]	115–116[c]	
4	100–105 (9)[d]	114 (10)[e]	
5	99[f]	63.5–64[g]	106[h]
	116.5–118 (5)	125–127.5 (5)	
6	94.5 (3)[i]	127–129.5 (6)[j]	114.5 (5)[e]
7	100.5–102 (2.5)[k]	132–134 (5)[l]	
8	73–73.5 (20)[m]	90–93 (20)[n]	112 (30)[e]
9	76 (19)[o]	93 (20)[p]	
10	110.5 (5)[q]	121.5–121.7 (6)[r]	119–120 (5)[e]

[a] Dienophile number corresponds to the set number of Table I. [b] Literature mp 201–202°: W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Amer. Chem. Soc.*, **80**, 2783 (1958). [c] Literature mp 114–116°: C. A. Stewert, Jr., *J. Org. Chem.*, **28**, 3320 (1963). [d] Literature bp 114° (10 mm): ref 31. [e] New compound; see text for identification. [f] Literature mp 101–102°: L. F. Fieser and R. C. Novello, *J. Amer. Chem. Soc.*, **64**, 802 (1942); [g] Literature mp 63–64°: O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **470**, 101 (1929). [h] Literature mp 107–107.5°: A. L. Henne and P. E. Hinkamp, *J. Amer. Chem. Soc.*, **76**, 5147 (1954). [i] Literature bp 137° (20 mm): I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 329 (1954); *Chem. Abstr.*, **49**, 5329 (1955). [j] Literature bp 149–149.5° (20 mm): A. A. Petrov and N. P. Sopov, *Sb. Statei Obshch. Khim.*, **2**, 853 (1953); *Chem. Abstr.*, **49**, 5329 (1955). [k] Literature bp 138.5–139.5° (10 mm): N. P. Sopov and V. S. Milkashevskaya, *Zh. Obshch. Khim.*, **26**, 1914 (1956); *Chem. Abstr.*, **51**, 4968 (1957); [l] Literature bp 151.5–152.5° (10 mm): footnote *k*. [m] Literature bp 80–82° (23 mm): E. D. Bergmann and D. F. Hermann, *J. Appl. Chem.* (London), **3**, 42 (1953). [n] Literature bp 85–86° (15 mm): H. E. Hennis, *J. Org. Chem.*, **28**, 2570 (1963). [o] Literature bp 83° (20 mm): A. A. Petrov and N. P. Sopov, *J. Gen. Chem. USSR*, **17**, 2228 (1947); *Chem. Abstr.*, **42**, 4957 (1948). [p] Literature bp 102–104° (25 mm): I. N. Nazarov, Yu. A. Titov, and A. I. Kuznetsova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1412 (1959); *Chem. Abstr.*, **54**, 1409 (1960). [q] Literature bp 114–115° (5 mm): footnote *i*. [r] Literature bp 149.5–150° (20 mm): footnote *j*.

The 2-trifluoromethylbutadiene–dimethyl maleate adduct gave the following nmr data: τ 3.62 (m, 1 H), 6.27 (s, 6 H), 6.72–7.18 (m, 2 H), and 7.18–7.61 (m, 4 H).

Anal. Calcd for $C_{11}H_{13}F_3O_4$: C, 49.6; H, 4.9. Found: C, 49.5; H, 5.0.

Competitive Experiments.—The reaction conditions are shown in Tables I and II. With no solvent runs the reactions were carried out in thick-wall, sealed tubes. The method of analysis of the relative rate is similar to that reported previously,[3] except that in runs with fumaryl chloride the product was converted into the dimethyl ester by treatment with absolute methanol before glpc analysis. Carbowax 6000 (10 wt %) on Diasolid M (Nihon Chromato Industries Co., Ltd.) was used for analyses in sets 1, 1′, 3, 3′, and 6–15 (Tables I and II). For sets 4, 4′, 5, and 5′, Silicon DC 550 on Diasolid M (the same supplier) was employed.

Kinetic experiments were carried out in a conventional way in a thermostat, with a known amount of dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate added as the internal standard for glpc analysis (silicon DC 550 column) of the product formed by appropriate intervals of reaction period.

Rate Constant of MA–$AlCl_3$–Cyclopentadiene Reaction in Benzene.—This reaction is too fast to measure directly in the usual way. The relative rate, cyclopentadiene *vs.* isoprene, in benzene at 20° toward MA–$AlCl_3$ was determined to be 646:1 by the competitive experiments similar to those described above (silicon DC 550 column). Since k^i/k^h is 12.1 (Table I) and k^h = 1.15×10^{-3} l/mol sec,[1] the desired rate constant is calculated to be 8.99 l/mol sec.

Proof of Kinetic Control of the Product Ratio.—The Diels–Alder adduct from butadiene (or isoprene) was treated with a large excess of isoprene (or butadiene) at room temperature for a period longer than that of the corresponding competitive experiment. It was ascertained by glpc that no cross-adduct was formed under the experimental conditions.

Registry No.—Butadiene, 106-99-0; isoprene, 78-79-5; 2-(trifluoromethyl)butadiene, 381-81-7; isoprene–vinylidene cyanide adduct, 23884-89-1; 2-(trifluoromethyl)-butadiene–dimethyl fumarate adduct, 23884-90-4; 2-(trifluoromethyl)butadiene–methyl acrylate adduct, 23884-91-5; 2-(trifluoromethyl)butadiene–dimethyl maleate adduct, 23884-92-6.

Preparation of Di- and Triaroylamides by Means of *n*-Butyllithium and Aroyl Halides. Influence of Lewis Bases[1]

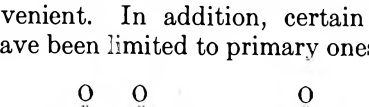
EDWIN M. KAISER AND HYUCK H. YUN

Department of Chemistry, University of Missouri, Columbia, Missouri 65201

Received July 23, 1969

Aroylations of the N-lithio salts of various amides, amines, and phthalimide have been accomplished by aroyl halides in the presence of Lewis bases such as 1,4-diazabicyclo[2.2.2]octane (dabco) to afford conveniently di- and triaroylamides in good to excellent yield. Presumably, the Lewis bases coordinate with the lithium cations and perhaps with the acid halides, resulting in enhanced reactivities of the nitrogen anions toward electrophiles, and of the carbonyl group of the acid chlorides toward nucleophiles.

Aroylation of amides and related organic nitrogen compounds to afford di- and triaroylamides such as **1** and **2**, respectively, has been accomplished under a variety of conditions, but there does not appear to be a general method for synthesizing such compounds. For example, benzamide has been benzoylated by benzoyl chloride to afford dibenzamide (**1**) in some cases,[2] and tribenzamide (**2**) in others.[3] An especially interesting method of preparing amide **2** involves tribenzoylation of lithium nitride.[4] Although good yields of di- and triaroylamides have often been reported,[2-4] reaction times and conditions have usually been inconvenient. In addition, certain aroylations of amides have been limited to primary ones.[3]



1 **2**

(1) Supported by the Petroleum Research Fund, administered by the American Chemical Society, on Grant PRF 959-G.

(2) A. W. Titherly, *J. Chem. Soc.*, **85**, 1673 (1904).

(3) Q. E. Thompson, *J. Amer. Chem. Soc.*, **73**, 5841 (1951).

(4) F. P. Baldwin, E. J. Blanchard, and P. E. Koenig, *J. Org. Chem.*, **30**, 671 (1965).

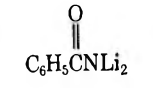
TABLE I
DIAROYLATION OF AMIDES BY MEANS OF *n*-BUTYLLITHIUM AND LEWIS BASES[a]

Amide	Lewis base	Acid chloride	Aroylation time, hr	Product	Yield, %
Benzamide	...	Benzoyl chloride	5	2	33
Benzamide	Dabco	Benzoyl chloride	5	2	67
Benzamide	Dabco	Benzoyl chloride	1	2	72
Benzamide	Dabco	Benzoyl chloride	0.5	2	64
Benzamide[b]	Dabco	Benzoyl chloride	1	2	30
Benzamide	Diglyme	Benzoyl chloride	5	2	65
Benzamide[c]	...	Benzoyl chloride	5	2	71
Benzamide[c]	...	Benzoyl chloride	1	2	36
Benzamide	TMEDA	Benzoyl chloride	1	2	64
Benzamide	Dabco	*p*-Toluoyl chloride	5	4	62
Benzamide	Dabco	*p*-Toluoyl chloride	1	4	14
Benzamide	Dabco	Anisoyl chloride	5	5	59
Benzamide	Dabco	Cinnamoyl chloride	5	6	67
p-Toluamide	Dabco	*p*-Toluoyl chloride	5	7	71
p-Toluamide	Dabco	*p*-Toluoyl chloride	1	7	45
Anisamide	Dabco	Anisoyl chloride	5	8	58
Benzanilide[d]	...	Benzoyl chloride	1	11	68
Benzanilide[d]	Dabco	Benzoyl chloride	1	11	75
N-Methylbenzamide[d]	Dabco	Benzoyl chloride	1	12	66
Diphenylthiourea	Dabco	Benzoyl chloride	1	14	51

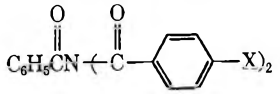
[a] Unless indicated, all reactions were run in THF employing 1 equiv of the amide, 2.2 equiv of 1.6 *M* *n*-butyllithium in hexane, 2 equiv of the Lewis base, and 2.2 equiv of the acid chloride. [b] The solvent was ethyl ether. [c] The solvent was diglyme. [d] One equivalent each of the amide, *n*-butyllithium, and dabco and 1.1 equiv of benzoyl chloride were employed.

The present study was prompted by the fact that the reactivity of various carbanions[5] and of aroyl halides[6] is enhanced by appropriate Lewis bases. It was thus of interest to determine if more facile aroylations of nitrogen anionic compounds might be realized in the presence of Lewis bases like 1,4-diazabicyclo[2.2.2]-octane (dabco).

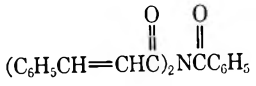
First, aroylations of amides, as listed in Table I, will be considered. This table shows that N,N-dilithiobenzamide (**3**), prepared from benzamide and 2 equiv of *n*-butyllithium in various ethereal solvents, underwent dibenzoylation with 2 equiv of benzoyl chloride to afford tribenzamide (**2**) in 33[7]–72% yields. The higher yields of **2** were realized in the presence of added Lewis bases or in diglyme solvent. Similar treatment of **3** with *p*-toluoyl, anisoyl, and cinnamoyl chlorides afforded triaroylamides **4**, **5**, and **6**, respectively, in good yields. Also, *p*-toluamide and anisamide were diaroylated with their corresponding aroyl halides to give adducts **7** and **8**, respectively.



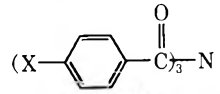
3



4, X = CH_3
5, X = OCH_3

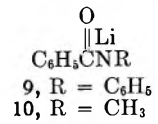


6

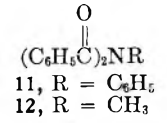


7, X = CH_3
8, X = OCH_3

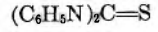
In contrast to earlier reports,[3] mono-N-substituted amides such as benzanilide and N-methylbenzamide likewise underwent benzoylation *via* their lithio salts **9** and **10** to afford adducts **11** and **12**, respectively. Similarly, benzoylation of 1,3-dilithiophenylthiourea (**13**) gave diaroyldiamide **14** in good yield.



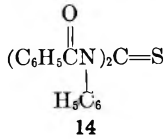
9, R = C_6H_5
10, R = CH_3



11, R = C_6H_5
12, R = CH_3



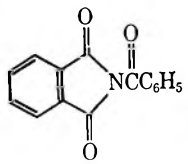
13



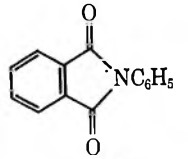
14

Certain other organic nitrogen compounds were also converted into their corresponding N-lithio derivatives, which were then aroylated. Thus N-lithiophthalimide in THF–hexane underwent benzoylation to give derivative **15** in 52% yield in the absence of dabco; the yield of **15** was increased to 80% in the presence of this base. Likewise, N,N-dilithioaniline was dibenzoylated to afford amide **11** in 40 and 81% yields in the absence and presence of dabco, respectively.

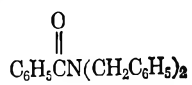
That cyclizations could be realized in such systems was shown by the condensation of N,N-dilithioaniline with phthaloyl chloride to give phthalanil (**16**) in 57% yield. Also, dibenzylamine, an aliphatic amine, was benzoylated *via* its lithio salt in the presence of dabco to give amide **17** in 83% yield.



15



16



17

(5) For example, see (a) T. L. Brown, D. W. Dickerhoof, and D. A. Bafus, *J. Amer. Chem. Soc.*, **84**, 1371 (1962); (b) C. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (c) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).

(6) P. Leduc and P. Chabrier, *Bull. Soc. Chim. Fr.*, 2271 (1963), and references cited therein.

(7) E. M. Kaiser, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **32**, 3640 (1967).

Finally, lithium nitride was tribenzoylated in THF in the presence of dabco to afford tribenzamide (2) in 44% yield after only a 5-hr reflux period; in the absence of dabco, 2 was obtained in only 18% yield under similar conditions. Lithium nitride has previously been benzoylated in diglyme for 48 hr to give 2 in 61% yield.[4]

Discussion

The aroylations of certain organic nitrogen anions described above represent a convenient and useful method for the preparation of various amides in which all of the ionizable hydrogen atoms on the nitrogen atom have been replaced by aroyl groups. In most cases, the yields of the desired products are at least doubled by the presence of dabco or other Lewis bases. The presumably quite general reactions are clean and the products are purified without difficulty.

The structures of the products which appear to be new, **4**–**6**, were supported by elemental analyses and by infrared and nmr spectroscopy (see Experimental Section).

Certain entries in Table I deserve special comment. In the benzoylations of N,N-dilithiobenzamide (**3**) the yields of tribenzamide (**2**) were highly dependent on the choice of solvent, but not on the choice of added Lewis base. Thus, in the absence of added Lewis base, **2** was obtained in 71% yield in diglyme–hexane, but only in 33% yield in THF–hexane. In the presence of added Lewis base in THF–hexane, comparable yields of **2** were obtained regardless of whether dabco, diglyme, or TMEDA were employed. Ethyl ether–hexane, though, proved to be a less satisfactory solvent for the preparation of **2**, even in the presence of dabco. With the exception of the benzoylation of **3** in THF–hexane, all diaroylations of N,N-dilithioamides were accomplished in higher yields after 5-hr rather than 1-hr reflux periods.

There appear to be at least three explanations for the positive effect of Lewis bases on these aroylations: (A) the reactivity of the *n*-butyllithium is enhanced[5] so that more extensive reaction with the original nitrogen compounds is realized; (B) the reactivity of the respective nitrogen anions is enhanced;[5] (C) the reactivity of the aroyl halides is enhanced.[6]

The first possibility was eliminated by gas-measurement experiments. For example, treatment of a refluxing mixture of phthalimide and dabco in THF with 1 equiv of *n*-butyllithium in hexane caused the same amount of gas to be evolved as in the absence of dabco.

Regarding the other two possibilities, it is generally recognized that Lewis bases like dabco coordinate with cations[5] even at relatively high temperatures[5c] to increase the reactivity of the counteranion toward electrophiles. However, similar molecular complexes of tertiary amines with acid chlorides appear to be stable only at relatively low temperatures.[3,6,8] Diglyme and other polyethers are also known to coordinate effectively with cations,[9] but similar coordination of these ethers with aroyl halides should be minimal. Thus, we favor explanation B, although C cannot be unequivocally eliminated.

Finally, it is interesting that such high yields of N-aroyl derivatives of the amides and phthalimide are obtained, since the corresponding O-aroyl derivatives were also possible. Incidentally, the 1,3-dibenzoylation of dilithiothiourea (**13**) is also interesting, since such 1,3 dianions usually undergo only a single condensation with electrophiles.[10]

Experimental Section[11]

Aroylation of Amides.—In Table I are summarized the results obtained by adding certain acid chlorides to N-lithioamides under various conditions; particulars are listed below.

A. General Method Illustrated by Benzamide and Benzoyl Chloride.—To a solution of 6.05 g (0.05 mol) of benzamide and 0.1 mol of the appropriate Lewis base (Table I) in 75 ml of anhydrous THF under nitrogen was added, during 3 min 70.3 ml (0.1125 mol) of 1.6 *M* *n*-butyllithium in hexane.[12] The mixture was brought to reflux for 20 min and then treated (without the heating mantle) with a solution of 16.1 g (0.1125 mol) of benzoyl chloride in 50 ml of THF added at such a rate (60 min) that the mixture continued to reflux gently. When the addition was completed, the reaction mixture was heated and maintained at reflux for 0.5–5 hr (Table I) and then it was cooled to 0° by an ice bath. After 100 ml of water had been added the resulting precipitate was collected, washed with water and ether, and air dried to afford tribenzamide (**2**), mp 206–208°; recrystallization of the product gave the pure product, mp 211–212° (lit.[13] mp 207–208°). Concentration of the original organic phase and that obtained from three extractions by ether of the aqueous phase gave small additional amounts of product **2**.

B. Benzamide and *p*-Toluoyl Chloride.—Addition of 17.5 g (0.1125 mol) of *p*-toluoyl chloride in 50 ml of THF to 0.05 mol of N,N-dilithiobenzamide (**3**) and 11.2 g (0.1 mol) of dabco in 75 ml of THF as above afforded, after recrystallization from benzene, 11.0 g (62%) of benzdi-*p*-toluamide (**4**): mp 215–216°; ir (Nujol) 1670 (C=O), 825, 747, and 680 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.47 (m, 13, ArH) and 2.15 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 77.31; H, 5.32; N, 3.92. Found: C, 77.59; H, 5.49; N, 3.90.

C. Benzamide and Anisoyl Chloride.—This reaction was accomplished essentially as above employing 19.3 g (0.1125 mol) of anisoyl chloride in THF for 5 hr to give 11.4 g (59%) of benzdianisamide (**5**): mp 166–168°; ir (Nujol) 1668 (C=O), 838, 742, and 685 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.68 (m, 13, ArH) and 4.6 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{19}NO_5$: N, 3.56. Found: N, 3.34.

D. Benzamide and Cinnamoyl Chloride.—This reaction was effected as above using 18.33 g (0.11 mol) of cinnamoyl chloride in THF for 1 hr to afford 12.8 g (67%) of benzdicinnamamide (**6**): mp 176–179°; ir (Nujol) 1650 (C=O), 1300, 962 (C=C), 730, and 690 cm^{-1} (ArH); nmr (CF_3CO_2H) δ 7.42 (m, 15, ArH) and 6.1 (m, 4, CH).

Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found: C, 78.65; H, 5.00; N, 3.48.

E. *p*-Toluamide and *p*-Toluoyl Chloride.—As above, 6.8 g (0.05 mol) of *p*-toluamide and 11.2 g (0.1 mol) of dabco in 75 ml of THF, 70.3 ml (0.1125 mol) of 1.6 *M* *n*-butyllithium in hexane,[12] and 17.5 g (0.1125 mol) of *p*-toluoyl chloride in THF, refluxed for 5 hr and recrystallized from 95% ethanol, gave 13.3 g (71%) of tri-*p*-toluamide (**7**), mp 250.5–251° (lit.[3] mp 246 ± 2°). Compound **7** was also obtained in 45% yield when the reflux period was diminished from 5 to 1 hr.

(8) For example, see H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).

(9) See H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968), and references cited therein.

(10) E. M. Kaiser and C. R. Hauser, *Tetrahedron Lett.*, 3341 (1967); E. M. Kaiser and R. D. Beard, *ibid.*, 2583 (1968).

(11) Melting points were taken on a Thomas–Hoover capillary melting point apparatus in open capillary tubes and are uncorrected. Infrared spectra were determined on a Perkin–Elmer Infracord Model 137 as Nujol mulls. Nmr spectra were obtained with a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(12) Supplied by the Foote Mineral Co., Exton, Pa.

(13) C. Blacher, *Chem. Ber.*, **28**, 435 (1895).

F. Anisamide and Anisoyl Chloride.—Anisamide (7.6 g, 0.05 mol) and 11.2 g (0.1 mol) of dabco in 75 ml of THF, 70.3 ml (0.1125 mol) of 1.6 *M* *n*-butyllithium in hexane,[12] and 19.3 g (0.1125 mol) of anisoyl chloride in THF gave, after recrystallization from 95% ethanol, 11.35 g (54%) of trianisamide (**8**), mp 195–196° (lit.[3] mp 197.5–198°). When the reaction was repeated for 1 hr instead of 5 hr, compound **8** was obtained in 58% yield.

Benzoylation of Lithiobenzanilide.—Lithiobenzanilide (0.05 mol), prepared in 75 ml of THF from 9.85 g (0.05 mol) of benzanilide, 11.2 g (0.1 mol) of dabco, and 40 ml (0.064 mol) of 1.6 *M* *n*-butyllithium in hexane[12] by heating for 1 hr, was treated in the usual fashion during 15 min with a solution of 8.05 g (0.056 mol) of benzoyl chloride in 50 ml of THF. After refluxing for 1 hr, the resulting solution was worked up to give, after recrystallization from 95% ethanol, 11.35 g (75%) of N,N-dibenzoylaniline (**11**), mp 161–162.5° (lit.[14] mp 160–162°). When the reaction was repeated in the absence of dabco, **11** was obtained in 68% yield.

Benzoylation of Lithio-N-methylbenzamide.—N-Methylbenzamide (6.75 g, 0.05 mol) was lithiated during 20 min in 75 ml of THF by 35 ml (0.056 mol) of 1.6 *M* *n*-butyllithium in hexane[12] in the presence of 5.6 g (0.05 mol) of dabco. The resulting suspension was treated during 30 min with a solution of 8.05 g (0.056 mol) of benzoyl chloride in 50 ml of THF, refluxed for 1 hr, and then worked up as usual. Recrystallization of the crude product from methanol afforded 7.85 g (66%) of N,N-dibenzoylmethylamine (**12**), mp 97–99° (lit.[15] mp 94–95°).

Dibenzoylation of Diphenylthiourea.—N,N′-Dilithiodiphenylthiourea (**13**, 0.025 mol) was prepared in 75 ml of THF from 5.7 g (0.025 mol) of diphenylthiourea, 5.6 g (0.05 mol) of dabco, and 39 ml (0.06 mol) of 1.6 *M* *n*-butyllithium in hexane[12] as above. The resulting yellow solution was treated during 15 min with a solution of 8.05 g (0.056 mol) of benzoyl chloride in 50 ml of THF and the mixture was refluxed for 1 hr. After the usual work-up, the crude product was recrystallized from 95% ethanol to give 5.3 g (51%) of N,N′-dibenzoyl-N,N′-diphenylthiourea (**14**), mp 159–162° (lit.[16] mp 160.5°).

Benzoylation of Phthalimide.—As above, 7.35 g (0.05 mol) of phthalimide and 5.6 g (0.05 mol) of dabco in 75 ml of THF was treated with 35 ml (0.055 mol) of 1.6 *M* *n*-butyllithium in hexane.[12] After 30 min, the resulting white suspension was treated during 10 min with a solution of 8.05 g (0.056 mol) of benzoyl chloride in 50 ml of THF; heat was applied for 5 hr. Work-up followed by recrystallization of the crude product from 95% ethanol gave 9.94 g (80%) of N-benzoylphthalimide (**15**), mp 167–168° (lit.[17] mp 168°). When the reaction was repeated without dabco, 6.56 g (52%) of compound **15** was obtained, mp 167–168°.

Aroylations of N,N-Dilithioaniline. A. With Benzoyl Chloride.—A solution of 4.65 g (0.05 mol) of aniline and 11.2 g (0.1 mol) of dabco in 75 ml of THF was treated with 70.3 ml (0.1125 mol) of 1.6 *M* *n*-butyllithium in hexane[12] and the mixture was refluxed for 10 min. Subsequent addition to the mixture of a solution of 16.1 g (0.1125 mol) of benzoyl chloride in 50 ml of THF followed by a 1-hr reflux period afforded, after recrystallization from ethanol, 12.21 g (81%) of **11**, mp and mmp 161–162.5°; the yield of **11** was only 40% in the absence of dabco.

B. With *o*-Phthaloyl Chloride.—Dilithioaniline (0.05 mol), prepared as in part A above, was treated during 1 hr with a solution of 10.1 g (0.05 mol) of *o*-phthaloyl chloride in 100 ml of THF. After the resulting mixture had been heated for 5 hr, it was worked up in the usual fashion. The crude product was recrystallized from ethanol to give 8.08 g (73%) of phthalanil (**16**), mp 209–210° (lit.[18] mp 203°).

Benzoylation of Dibenzylamine.—N-Lithiodibenzylamine was prepared in 75 ml of THF from 9.85 g (0.05 mol) of dibenzylamine, 5.6 g (0.05 mol) of dabco, and 35 ml (0.055 mol) of 1.6 *M* *n*-butyllithium in hexane.[12] After stirring for 1 hr at 25°, the bright red mixture was treated during 5 min with a solution of 8.05 g (0.056 mol) of benzoyl chloride in 50 ml of THF. The resulting mixture was stirred for 3 hr at 25°, and then it was worked up in the usual fashion to afford, after recrystallization from ethanol, 12.4 g (83%) of N-benzoyldibenzylamine (**17**), mp 112–113° (lit.[19] mp 112–113°). When the reaction was repeated without dabco, 9.22 g (61%) of product **17** was obtained, mp and mmp 112–113°.

Benzoylation of Lithium Nitride.—To a red suspension of 1.75 g (0.05 mol) of lithium nitride and 16.8 g (0.15 mol) of dabco in 75 ml of THF was added during 30 min a solution of 24.6 g (0.175 mol) of benzoyl chloride. Heat was evolved and the suspension turned purple, gray, and then yellow. The mixture was heated and maintained at reflux for 5 hr, and then it was worked up in the usual fashion to give 7.2 g (44%) of tribenzamide **2**, mp and mmp 211–212°. When the reaction was repeated in the absence of dabco, compound **2** was obtained in only 18% yield.

Registry No.—*n*-Butyllithium, 109-72-8; **2**, 602-88-0; **4**, 23825-26-5; **5**, 23825-27-6; **6**, 23825-28-7; **7**, 23825-29-8; **8**, 1107-48-8; **11**, 3027-01-8; **12**, 23825-32-3; **14**, 23796-78-3; **15**, 4583-50-0; **16**, 520-03-6; **17**, 23825-35-6.

(14) P. Kay, *Chem. Ber.*, **26**, 2855 (1893).
(15) O. Mumm, H. Hesse, and H. Volquartz, *ibid.*, **48**, 388 (1915).
(16) A. Deninger, *ibid.*, **28**, 1322 (1895).
(17) A. W. Titherly and W. L. Hicks, *J. Chem. Soc.*, **89**, 709 (1906).
(18) A. Laurent and C. Gerhardt, *Justus Liebigs Ann. Chem.*, **68**, 33 (1848).
(19) H. Franzen, *Chem. Ber.*, **42**, 2466 (1909).

Neighboring-Group Participation in Pyrolytic *trans* Eliminations

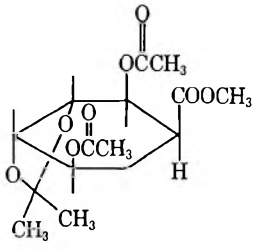
EDWARD E. SMISSMAN, J. PENGMAN LI, AND MARY WEIR CREESE

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

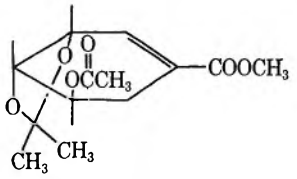
Received July 11, 1969

Pyrolytic elimination of acetic acid from a series of methyl 2-acetoxy-*trans*-decalin-3-carboxylates (**3**–**6**) demonstrated that *trans* elimination occurs to give α,β-unsaturated esters when the acetoxy and carbomethoxy groups are *cis*. The facility with which methyl 1*e*-methyl-2*a*-acetoxy-*trans*-decalin-3*e*-carboxylate (**6**) produced methyl 1-methyl-*trans*-Δ^2-octalin-3-carboxylate (**10**) in quantitative yield leads to the postulation of neighboring-group participation in this elimination. A plausible mechanism for this assist is given.

In a previously reported stereospecific synthesis of D-(−)-shikimic acid[1,2] we based the stereochemistry



1



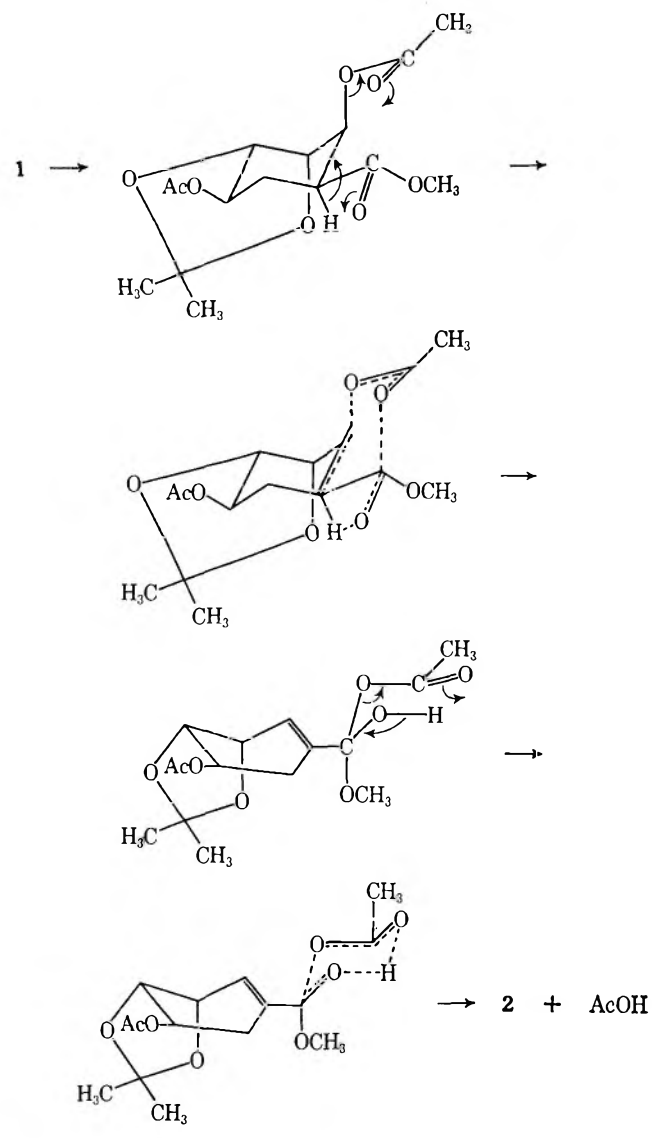
2

of the C-1 hydrogen atom (C-1 carboxy group) in the intermediate **1** on the fact that the latter, when heated to 285° in a sealed Pyrex tube, underwent pyrolytic elimination of acetic acid to give DL-methyl-3-O-acetylshikimate acetonide (**2**) in 95% yield. In an essentially identical synthetic sequence reported by Raphael and coworkers,[3] this acetonide was depicted as **1** with the C-1 carboxy group *cis* to the adjacent C-2 acetyl group. These authors also reported that although acetic acid elimination could be effected partially by conventional base catalysis, it occurred in 80% yield when the acetate **1** was pyrolyzed in the presence of magnesium oxide at 290°.

Subsequent nmr investigations[4−6] indicated that structure **1** is correct; in benzene solution the 100-MHz spectrum gives an eight-lined pattern at δ 2.83–3.20 with coupling constants of 11.5, 4.0, and 3.0 cps for the C-1 proton.

It thus appeared that the reported pyrolytic elimination of acetic acid[2,3] was a *trans* diaxial elimination in contrast to the more usual *cis* ester pyrolyses.[7,8] A possible mechanism is the concerted cyclic rearrangement depicted in col 2.

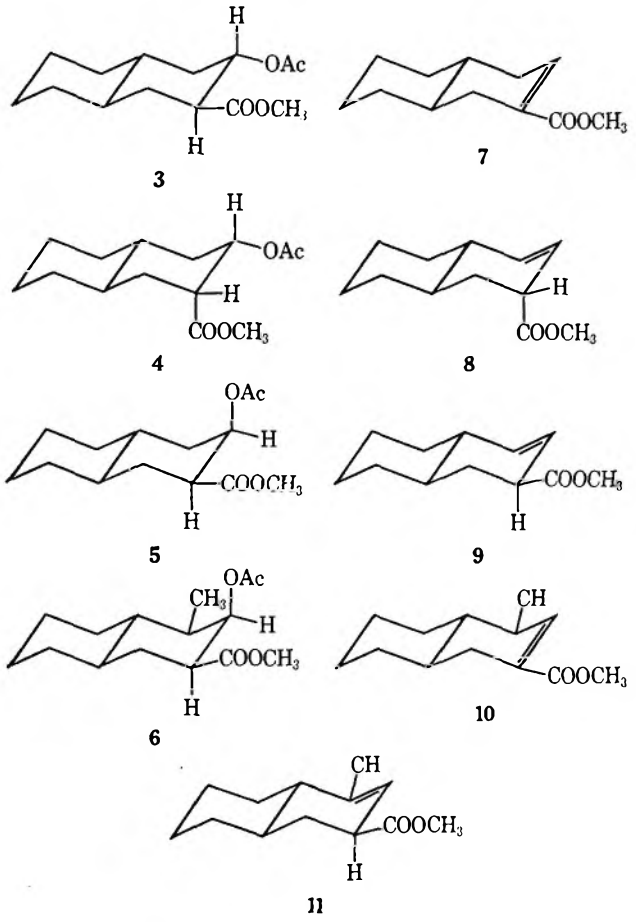
Although *trans* pyrolytic eliminations have been reported,[9−12] this unique neighboring-group participation required further investigation using model compounds.



The *trans*-decalin system, considered to be rigid, was selected and the four acetoxy decalincarboxylates **3**–**6** were prepared and pyrolyzed under conditions similar to those used with the shikimate acetonide precursor, **1**. The stereochemistry of the decalins was established by nmr analysis.

Compounds **3**–**5** were prepared from the common precursor, *trans*-2-decalone-3-carboxylic acid (**12**), which was obtained by carboxylation of *trans*-2-decalone *via* the potassium triphenylmethide reagent, followed by condensation with carbon dioxide.[13]

(1) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *J. Amer. Chem. Soc.*, **81**, 2909 (1959).
(2) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *ibid.*, **84**, 1040 (1962).
(3) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).
(4) R. McCrindle, K. H. Overton, and R. A. Raphael, *Tetrahedron Lett.*, 1847 (1968).
(5) R. K. Hill and G. R. Newkome, *ibid.*, 1851 (1968).
(6) E. E. Smissman and J. P. Li, *ibid.*, 4601 (1968).
(7) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(8) D. V. Banthorpe, "Elimination Reactions," Elsevier Publishing Co., New York, N. Y., 1963.
(9) E. R. Alexander and A. Mudrak, *J. Amer. Chem. Soc.*, **72**, 1810 (1950); **73**, 59 (1951).
(10) R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950).
(11) W. J. Bailey and L. Nicholas, *ibid.*, **21**, 854 (1956).
(12) D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Amer. Chem. Soc.*, **81**, 643 (1959).
(13) R. Levine, E. Baumgarten, and C. R. Hauser, *ibid.*, **66**, 1230 (1944).



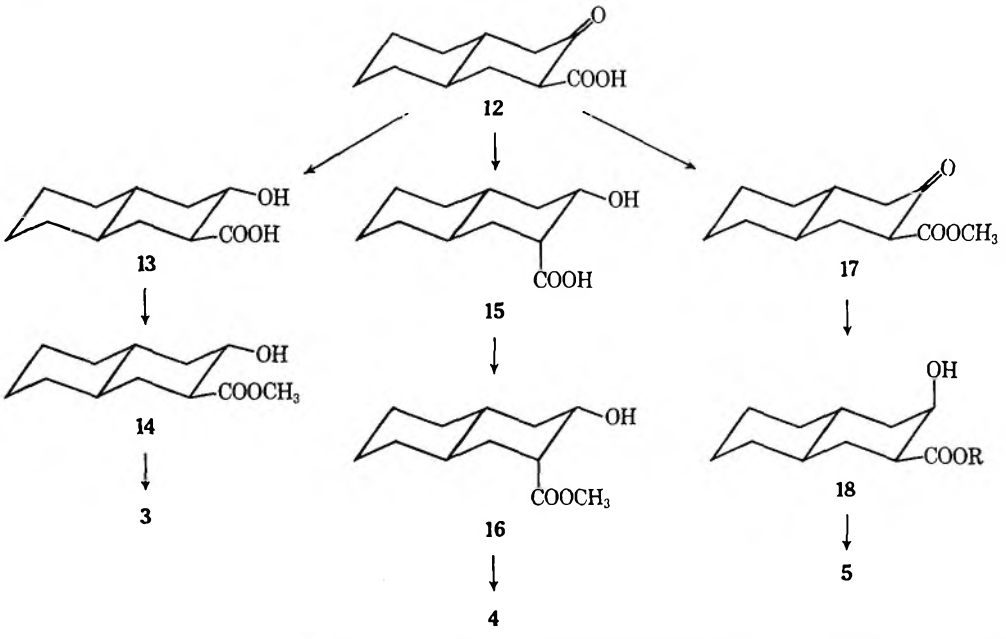
Reduction of **12** with sodium amalgam[14,15] gave the *trans*-hydroxy acid **13** in 25% yield, along with a small amount of the *cis* acid **18** (R = H). Esterification of **13** with diazomethane, followed by acetylation with acetic anhydride and pyridine, gave **3** in good yield. The nmr spectrum of **3** exhibited two broad bands centered at δ 4.92 and 2.40 corresponding to H-2 and H-3, respectively. In the free hydroxy acid **13**, these signals appear at δ 4.30 and 2.70.[15,16] Earlier reports of the course of the sodium amalgam reduction of **12** are somewhat conflicting: Sicher and coworkers[14] suggested that the *cis*-β-hydroxy acid **18** (R = H) was the product obtained, while Pavia and coworkers[15] reported a mixture of hydroxy acids, **13** and **15**, from the same reaction. The mixture was converted into **13** by epimerization of the methyl esters with sodium methoxide followed by saponification.

Hydrogenation of **12** under basic conditions, using a ruthenium catalyst, gave the hydroxy acid **15**. This was then methylated and acetylated to give **4**. In the nmr spectrum of **4** there appeared a pair of overlapping triplets at δ 4.87 and 4.69 (J = 10.5 and 6.0 cps, respectively) and a broad symmetrical signal at δ 3.05 ($W_{1/2}$ = 11 cps). Such a pattern would be expected from an axial H-2 and an equatorial H-3.[17]

It is noteworthy that while the nmr spectra of **3** and **4** are very similar in the H-2 region (δ 4.80–4.90), each exhibiting a broad signal of base of *ca.* 25 cps for this region, they differ markedly in the H-3 region. The observed chemical-shift difference of 0.65 ppm corresponds to the expected chemical-shift difference between an axial and an equatorial proton, the equatorial proton absorbing at the lower δ value.[17]

Conversion of **12** into the methyl ester **17**, followed by hydrogenation under neutral conditions, gave the *cis*-hydroxy ester **18** (R = CH_3), which was acetylated to yield **5**. The nmr spectrum of **5** exhibited an absorption at δ 5.35 ($W_{1/2}$ = 7 cps) and another broad multiplet at δ 2.45, both being in agreement with the structure indicated.

The preparative route to the acetoxy ester **6** involved the intermediate *anti-trans*-1-methyl-2-decalone obtained by the stereospecific synthesis recently described by Turner and coworkers.[18] They established that the equatorial position is the thermodynamically preferred



(14) J. Sicher, M. Tichy, F. Sipos, M. Svoboda, and J. Jonas, *Collect. Czech. Chem. Commun.*, **29**, 1561 (1964).

(15) A. Pavia, F. Winternitz, and R. Wylde, *Compt. Rend.*, **261**, 1026 (1965).

(16) W. L. Nelson, Ph.D. Dissertation, University of Kansas, 1965.

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 116.

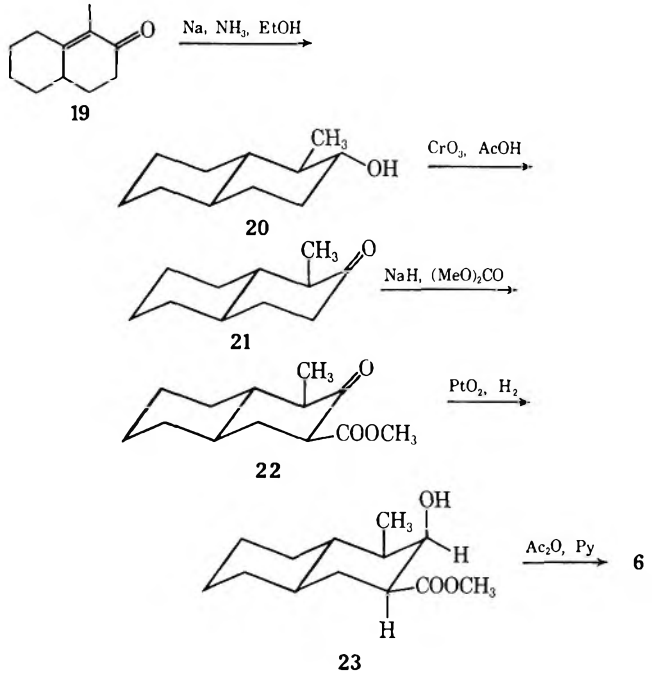
(18) R. B. Turner, R. B. Miller, and J. L. Lin, *J. Amer. Chem. Soc.*, **90**, 6124 (1968).

TABLE I

	Acetate				
	1[a]	3	4	5	6
Tube length, cm	...	35	35	34	27
Pressure, mm	...	2×10^{-4}	3×10^{-4}	2.5×10^{-4}	5×10^{-4}
Pyrolysis temp, °C	290	310–315	310–315	340–345	350–355
Pyrolysis period, min	...	200	300	240	240
Sample size, mg	...	380	263	106	192
Materials obtained from pyrolysate, mg	...	212	230	98	175
Yield of olefin, %	80	25	25	20	90

[a] The data for 1 are repeated[2] here for the purpose of comparison.

orientation for the methyl group. This observation holds for the corresponding alcohol as well as for the ketone. The reaction of *anti-trans*-1-methyl-2-decalone with sodium hydride and dimethyl carbonate[19] gave



the keto ester **22**, which underwent hydrogenation in the presence of platinum dioxide followed by acetylation to give the acetoxy ester **6**. The nmr spectrum of **6** showed an absorption at δ 5.45 ($W_{1/2}$ = 7 cps) and a broad multiplet centered at δ 2.75 (assigned to H-2 and H-3, respectively), which were similar to those exhibited by **5** and consistent with the proposed structure.

Of the possible olefinic pyrolysis products **7**–**11**, only the α,β-unsaturated ester **7** is reported in the literature.[20] It was prepared from the corresponding acid and used as a reference in the vapor phase chromatographic analysis of the pyrolysis products.

Results and Discussion

The pyrolyses were run in Pyrex tubes (0.8 × 35.0 cm) evacuated to *ca.* 10^{-4} mm before sealing; temperatures were 310–350°; reaction times varied from 1 to 5 hr (see Table I). The pyrolysis product mixtures were analyzed by gas–liquid partition chromatography (glpc) and by infrared, nmr, and mass spectral determinations.

When pyrolyzed for 1 hr, the *cis* acetate **3** gave small amounts of the α,β-unsaturated olefin **7**, as indicated by glpc, but the bulk of the starting material was recovered unchanged. A 3-hr pyrolysis period at 310–315° produced *ca.* 25% elimination to give again mainly **7**, but significant charring also occurred. Prolonged pyrolysis did not push the elimination to completion. Glpc analysis of the product mixture indicated the presence of two other products in minor amounts. A sharp 6.05-μ C=C absorption was present in the infrared spectrum of the pyrolysate.

A 1-hr pyrolysis period left **4** essentially unaffected, though trace amounts of **7** and one other product was detectable by glpc. Pyrolysis for 4 hr at 310–315° caused *ca.* 25% elimination without appreciable charring. The major product was again **7**, though three other minor constituents were present in the product mixture.

When pyrolyzed for 1 hr at 310°, **5** gave three products in small yield. Of these, one was **7** and another had a retention time equal to that of one of the minor products in the pyrolysis of **3**. The relative abundance of the latter to **7** was 1.4:1.0. A 4-hr pyrolysis period at 340–345° changed this ratio to 0.8:1.0 (*i.e.*, the relative proportion of the more thermodynamically stable **7** increased at higher temperatures and longer reaction time). Charring was slight. The overall yield of olefinic materials from the 4-hr pyrolysis was *ca.* 20%.

When subjected to a 4-hr pyrolysis at 350°, **6** underwent almost complete elimination to the α,β-unsaturated ester **10**, with negligible charring. One other minor product was present in the pyrolysate. The structure of the major product **10** was proven by infrared and nmr spectral analysis and by the mass spectrum of the product mixture. The infrared spectrum exhibited absorptions at 5.82 and 6.06 μ; the relative area of the olefinic hydrogen peak at δ 6.80 in the nmr spectrum was 0.9; the mass spectrum of the product mixture showed a parent peak at *m/e* 208. Glpc analysis, on both LAC 446 and DEGS columns, indicated a minimum purity of 95%.

The starting acetate was either recovered or its presence was established by glpc in all runs. No evidence (glpc or spectral) for epimeric forms could be obtained.

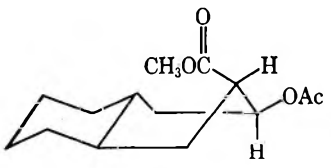
Of the possible olefinic products **7**–**11**, **7** and **10** are the most thermodynamically stable. In addition, assuming the possibility of *trans* elimination, the acidity of H-3 suggests that **7** is the major product from **3**–**5**. With **6**, where the only elimination pathways available are *trans*, the predominant product would be expected to be **10**. The results indeed suggest that the overriding factors governing the direction of elimination in these systems are the thermodynamic stability of the

(19) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, **86**, 485 (1964).

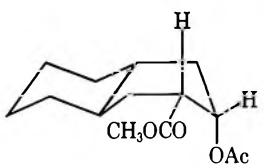
(20) W. R. Vaughan and R. Caple, *ibid.*, **86**, 4928 (1964).

olefinic product and the acidity of the leaving proton.[7,21] Here the two factors reinforce each other. However, the striking features in this series of reactions are (A) the similarity of the products (*ca.* 25% yield of mixtures of olefins from the pyrolysis of **3**–**5**); (B) the contrast between the latter and the near quantitative yields of pure products from the pyrolysis of **1** and **6**.

The above observations suggest that, while the conformations of **1** and **6** are fixed, by the five-membered ring and the methyl group, respectively, **3**–**5** may be present as a mixture of boat–chair conformers at the elevated temperatures utilized for pyrolysis. Under the conditions of the reaction, competing elimination mechanisms may be operative. Thus **5**, in which the carboxy-assisted *trans*-β elimination can occur, could be in equilibrium with the conformer **24** in which the *trans*-*e*,*e* elimination mechanism can operate. Similarly, **4**, in which *trans*-*e*,*e* elimination occurs, would be in equilibrium with the conformer **25**. The latter can now undergo carboxy assisted *trans*-β elimination. In **3**, where the acidic β proton is *cis* to the leaving group, other conformers are less likely to be important in the elimination reaction.



24



25

As noted above, one of the minor products from the pyrolysis of **3** also appeared in the pyrolysate of **5**, and in relatively higher proportion. Furthermore, in the latter pyrolysis, higher temperature and longer reaction time increased the proportion of **7** at the expense of this material. We surmise that this product is the β,γ-unsaturated ester **9**. Thus there would appear to be two types of elimination occurring in **5**. At 310° normal *cis* elimination toward C-1 predominates, producing 60% **9** in the olefinic product mixture. At 340° *trans* elimination accounts for 55% of the olefinic product mixture.

Initial formation of **9** by normal *cis* elimination followed by rearrangement to the more stable **7** seems unlikely; it has been demonstrated that such isomerization does not occur in the cyclohexane system;[11,22] and presumably this observation holds true for the decalin system. In **6**, where the conformation is fixed and in which *cis* elimination is blocked, the almost exclusive formation of **10** offers a further example of the assisted *trans*-β-elimination mechanism.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. Refractive indexes were measured on a Carl Zeiss refractometer. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Nmr spectra were measured on a Varian A-60 spectrometer, using tetramethylsilane (TMS) as internal standard. Chemical shifts were expressed in terms of δ in parts per million. Gas–liquid partition chromatography (glpc) was conducted on an F & M Model 810-19 analytical gas chromatograph, using a flame detector and 0.125 in. × 4 ft columns, packed with 5% w/w diethylene glycol adipate (LAC-446, F & M) on Gas-Chrom P (70–80 mesh, Applied Science Laboratories, Inc.) normally at 170°. Helium carrier gas flow was *ca.* 75 ml/min at 40 psi. Microanalyses were performed on an F & M Carbon Hydrogen Nitrogen Analyzer Model 185 in this department and by the Huffman Laboratories, Inc., Wheatridge, Colo. Mass spectral determinations were done on an Finnegan 1050 spectrometer.

trans-**2-Decalone-3-carboxylic Acid** (**12**).—A suspension of potassium triphenylmethide reagent in ether was prepared by the method of Hauser and coworkers.[13] To this reagent, cooled in an ice bath, was rapidly added a solution of *trans*-2-decalone, bp 75–77° (0.03–0.04 mm), n^{20}D 1.4829, yield 16.9 g (0.11 mol), in 35 ml of diethyl ether. The mixture was stirred for 15 min and the resulting white suspension was poured onto crushed Dry Ice (300 g). The mixture was stirred occasionally until the Dry Ice had completely evaporated. More diethyl ether was added to make a thin paste. It was extracted with cold 10% aqueous sodium hydroxide (three 100-ml portions). The alkaline aqueous extracts were washed with diethyl ether, cooled in an ice bath, acidified with concentrated hydrochloric acid, and extracted with diethyl ether (three 100-ml portions). The ethereal extracts were washed with water, filtered through anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. The product was obtained, mp 100–106° (lit. mp 108–111°, 100–105°,[16] 90° dec[15]), yield 24 g. The infrared spectrum was similar to those previously reported.[15] The crude material was used in subsequent reactions without further purification.

trans-**2***e*-**Decalol-3***e*-**carboxylic Acid** (**13**).[14,15]—The keto acid **12** (8.7 g, 44.33 mmol) was dissolved in aqueous sodium carbonate (20 g in 150 ml of water) and the resulting solution was diluted to a volume of 700 ml. Sodium amalgam (3.5%, 600 g) was added and the mixture was allowed to stand at 25° with occasional shaking for 4.5 days. The aqueous phase was decanted and filtered. The mercury and excess amalgam were washed with water. The filtrate and washings were combined, washed with dichloromethane (two 100-ml portions), cooled in ice, acidified with concentrated hydrochloric acid at 5–6°, saturated with sodium chloride, and extracted with diethyl ether (four 100-ml portions). The ethereal solution was filtered through anhydrous magnesium sulfate and evaporated to dryness *in vacuo;* 8.2 g of crystalline material was obtained. Recrystallization from acetone gave the *trans*-hydroxy acid, mp 173–174.5° (lit. mp 175–176°,[15] 177.5–179°[14]), yield 1.9 g. Concentration of the mother liquid gave a second crop of 0.2 g; the total yield was 2.1 g (23.8%).

Methyl *trans*-2*e*-**Decalol-3***e*-**carboxylate** (**14**).—A solution of diazomethane in diethyl ether (25 ml) generated from N-methyl-N′-nitro-N-nitrosoguanidine (Aldrich, 1.5 g, 10.2 mmol) and 2 *N* potassium hydroxide solution (25 ml) was mixed with absolute ethanol (15 ml) and added to a solution of the hydroxy acid **13** (0.878 g, 4.43 mmol) in diethyl ether and absolute ethanol (15 ml each). The mixture was stirred at room temperature for 2 hr. A few drops of concentrated hydrochloric acid were added to destroy the excess diazomethane. The reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in diethyl ether (30 ml), washed with 10% aqueous sodium carbonate solution (10 ml) and water (two 10-ml portions), filtered through anhydrous magnesium sulfate, and evaporated to dryness. Upon drying over phosphorus pentoxide *in vacuo*, the oily residue solidified in featherlike needles, yield 0.9 g (4.24 mmol, 95.7%).

Methyl 2*e*-**Acetoxy-***trans*-**decalin-3***e*-**carboxylate** (**3**).—The hydroxy ester **14** (1.4 g, 6.59 mmol) was dissolved in dry pyridine (8 ml). The solution was mixed with acetic anhydride (7.0 g, 68.56 mmol) and refluxed under anhydrous conditions for 1 hr. The reaction mixture was evaporated *in vacuo* at 60°. The oily residue thus obtained was stirred with water (10 ml) at room temperature for 1.5 hr and extracted with ethyl acetate (four 10-ml portions). The extracts were washed with water (two 5-ml portions) and filtered through anhydrous magnesium sulfate, and the solvent was removed. The oily residue was dried over phosphorus pentoxide *in vacuo*, yield 1.65 g (6.49 mmol, 98%). Vacuum distillation afforded the pure acetate: bp 82–84° (0.04–0.05 mm); n^{20}D 1.4742; nmr δ 4.92 ($W_{1/2}$ = 23 cps) and 2.40.

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.20; H, 8.93.

trans-2*e*-**Decalol-3***a*-**carboxylic Acid** (**15**).[16]—The keto acid **12** (2.8 g) was dissolved in 5% sodium carbonate solution (120

(21) R. Taylor, G. G. Smith, and W. H. Wetzel, *J. Amer. Chem. Soc.*, **84**, 4817 (1962).

(22) W. J. Bailey and R. A. Baylouny, *ibid.*, **81**, 2126 (1959).

ml) and ruthenium dioxide (500 mg, 54%) was added. This was hydrogenated in a Parr shaker for 3 days. The catalyst was then removed and the solution was washed with ethyl acetate. The aqueous solution was neutralized with hydrochloric acid and extracted with ethyl acetate. The solution was dried over magnesium sulfate and the solvent was removed, leaving a yellow oil. Crystals, mp 128–131°, were obtained from benzene.

Methyl 2*e*-Acetoxy-*trans*-decalin-3*a*-carboxylate (4).—The acetate 4 was prepared from the corresponding hydroxy acid **15** (0.68 g, 3.46 mmol) by esterification with diazomethane followed by refluxing the ester with acetic anhydride and pyridine, as described above. The product was a light yellow, oily liquid, (0.63 g after drying over phosphorus pentoxide and sodium hydroxide pellets at 0.15 mm, 2.46 mmol, 71% overall yield): $n^{20}D$ 1.4751; nmr δ 4.78 (a pair of overlapping triplets in a five-lined pattern, J = 10.5 and 6 cps) and 3.05 (symmetrical and broad, $W_{1/2}$ = 11 cps). Thin layer chromatography on silica gel showed a single spot when developed by two solvent mixtures: chloroform–ethyl acetate (3:2) and chloroform–acetone (9:1). Glpc indicated at least 95% purity.

Methyl *trans*-2-Decalone-3-carboxylate (17).—An ethereal solution of diazomethane, prepared as before from N-methyl-N′-nitro-N-nitrosoguanidine (13.5 g, 91.8 mmol), was added to a solution of the crude keto acid **12** (13.6 g, 69.3 mmol) in diethyl ether (100 ml). The reaction mixture was stirred in an ice bath for 1 hr. The ethereal solution was then washed with water and saturated aqueous sodium chloride and filtered through anhydrous magnesium sulfate; the solvent was removed. The crude product was a yellow liquid, $n^{20}D$ 1.4999, yield 12.45 g (59.2 mmol, 85.4%). Distillation gave a colorless liquid: bp 96–97° (0.5 mm) [lit.[23] bp 126–129° (3 mm)]; $n^{20}D$ 1.5006; ir (CCl_4) 5.7, 5.82, 6.02, and 6.19 μ [lit.[15] ir ($CHCl_3$) 5.75, 5.85, 6.04, and 6.21 μ]: nmr 715 cps (enolic proton) (lit.[15] 724 cps in $CDCl_3$). The product solidified in white needles upon storage at 3°.

Methyl *trans*-2*a*-Decalol-3*e*-carboxylate (18).—The keto ester **17** (3.1 g, 14.8 mmol) was dissolved in absolute ethanol (40 ml) and mixed with platinum oxide catalyst (Engelhard Industries, Newark, N. J., 0.5 g, 85.48%). The mixture was hydrogenated in a Parr shaker at 25°. The calculated amount of hydrogen was absorbed in 30 min. Removal of the catalyst by filtration through Celite followed by evaporation of the solvent *in vacuo* afforded the hydroxy ester **18** as a white, crystalline solid in a quantitative yield of 3.3 g, mp 91–93° from carbon tetrachloride (lit.[14] mp 95–96° from acetone).

Methyl 2*a*-Acetoxy-*trans*-decalin-3*e*-carboxylate (5).—The crude hydroxy ester **18** (3.3 g, 14.8 mmol) was acetylated with acetic anhydride in dry pyridine as described above. Purification of the product obtained as an oil, by vacuum distillation and by chromatography (both column and gas phase), was unsuccessful. However, **5** separated as crystals upon prolonged standing. It was recrystallized from petroleum ether (bp 30–60°), giving white prisms: mp 62.5–63.5°; nmr δ 5.35 (pyramid, $W_{1/2}$ = 7 cps) and 2.45 (multiplet).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.40; H, 8.62.

Methyl *trans*-Δ^2-Octalin-3-carboxylate (7).—The free acid[20] (64 mg, 0.355 mmol) was esterified with diazomethane generated from N-methyl-N′-nitro-N-nitrosoguanidine (76 mg, 0.517 mmol) by the usual procedure. The crude product was a colorless liquid: yield 41.2 mg (0.212 mmol, 60%); $n^{25.3}D$ 1.4953 (lit.[20] $n^{25.5}D$ 1.4963); ir ($CHCl_3$) 5.86 and 6.06 μ. Glpc showed that the crude product was slightly contaminated by one substance, probably the free acid.

1-Methyl-$\Delta^{1,9}$-octal-2-one[24] (19).—1-(2-Oxocyclohexyl)pentan-3-one[25] (5 g, 23 mmol) was cyclized in hydrochloric acid by the method of Shunk and Wilds.[24] The product was obtained as an oil and was distilled *in vacuo*, bp 80–82°(*ca* 0.1 mm) [lit.[25] bp 150–155° (18 mm)], yield 3.5 g (78%).

***trans-anti-trans*-2-Hydroxy-1-methyldecalin (20).**[18]—The ketone **19** (5.9 g, 36 mmol) was reduced with sodium in liquid ammonia by the method of Turner, *et al.*[18] The crude product was distilled *in vacuo*, bp 80–85° (1.5–2 mm). The material condensed as a white, crystalline solid in the receiver, mp 52–55° (lit.[18] mp 55–57°), yield 3.7 g (67%).

***anti-trans*-1-Methyl-2-decalone (21).**[18]—The alcohol **20** was oxidized with chromium trioxide in dilute acetic acid by the method of Turner.[18] The product (2.8 g, 80%) was a clear liquid whose infrared and nmr spectra were consistent with 1-methyl-2-decalone.

Methyl *anti-trans*-1-Methyl-2-decalone-3-carboxylate (22).[19]—To sodium hydride (8.0 g, 0.18 mol, 54% in mineral oil dispension) in dry dioxane (100 ml) was added dimethylcarbonate (23.4 g, 0.23 mol) in dry dioxane (60 ml). The mixture was stirred and heated to 80–85°, and to it was added 1-methyl-2-decalone (**21**, 8.3 g, 0.05 mol) in dioxane (75 ml) over a 1-hr period. The heating and stirring was continued overnight, and the mixture was then cooled in ice and dissolved in aqueous acetic acid. The solution was concentrated on a rotary evaporator and the residue was dissolved in 20 ml of water. The resulting mixture was extracted with ether and the ether extracts were washed with aqueous sodium bicarbonate and aqueous sodium chloride. Drying ($MgSO_4$) followed by removal of the ether left a yellow oil, bp 90–96° (60% yield), whose infrared spectrum was consistent with that expected for the keto ester.

Methyl 1*e*-Methyl-*trans*-2*a*-Decalol-3*e*-carboxylate (23).—To the keto ester **22** (2 g, 8.9 mmol) in redistilled ethanol (30 ml) was added platinum dioxide (0.63 g). The material was hydrogenated in a Parr shaker for 5.5 hr. The product was distilled, bp 134–135.8° (3 mm). The distillate crystallized on standing, mp 78–79° (30% yield of crystalline product). The infrared and nmr spectra were consistent for the hydroxy ester.

Methyl 1*e*-Methyl-2*a*-acetoxy-*trans*-decalin-3*e*-carboxylate (6).—To the hydroxy ester **23** (2 g, 8.9 mmol) in dry pyridine (7 ml) was added acetic anhydride (10 ml). The mixture was heated at 155–160° for 45 min. The acetate was isolated as described above. Vacuum distillation gave a clear oil, bp 140° (3.2 mm), which crystallized on standing in the cold: mp 47–48°; yield 25%; nmr δ 5.48 (pyramid, $W_{1/2}$ = 7 cps) and 2.82 (multiplet).

Anal. Calcd for **6**: C, 67.25; H, 8.96. Found: C, 67.48; H, 8.90.

Pyrolysis of the Acetates.—The conditions used in the pyrolysis of the acetonide in the shikimic acid synthesis (1) were employed. The acetates were placed separately in Pyrex tubes of 8-mm i.d., evacuated to pressures of *ca.* 3×10^{-4} mm, and sealed. The tubes were heated in an electric furnace at temperatures indicated in Table I, p 1354. The oily products were dissolved in reagent grade ethyl acetate, treated with anhydrous sodium carbonate powder, and filtered. The filtrates were analyzed by glpc. The presence of olefinic substances in the pyrolysates was confirmed by the sharp ir band near 6.05 μ, which was absent in the infrared spectra of the starting acetates.

Registry No.—**3**, 23757-87-1; **4**, 23757-89-3; **5**, 23757-88-2; **6**, 23757-90-6; **7**, 1204-87-1; **15**, 23757-92-8; **17**, 23757-93-9; **22**, 23757-94-0; **23**, 23757-95-1.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health, Grants GM-9254 and GM-07444. The authors wish to express their appreciation to Dr. Wyman R. Vaughan, The University of Connecticut, for a sample of *trans*-Δ^2-octalin-2-carboxylic acid.

(23) D. Chakvavarti and K. P. R. Chaudhuri, *J. Indian Chem. Soc.*, **38**, 391 (1962); *Sci. Cult.* (Calcutta), **28**, 81 (1962).

(24) C. H. Shunk and A. L. Wilds, *J. Amer. Chem. Soc.*, **71**, 3946 (1949).

(25) G. Stork, A. Brizzolara, H. Landman, J. Szmuskovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

Thiomethylation[1]

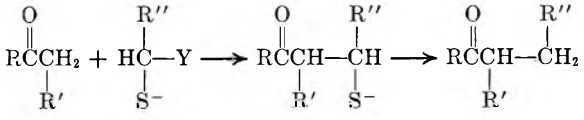
EDWARD E. SMISSMAN, JOHN R. J. SORENSON,[2] WILLIAM A. ALBRECHT,[2] AND MARY WEIR CREESE

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

Received November 13, 1969

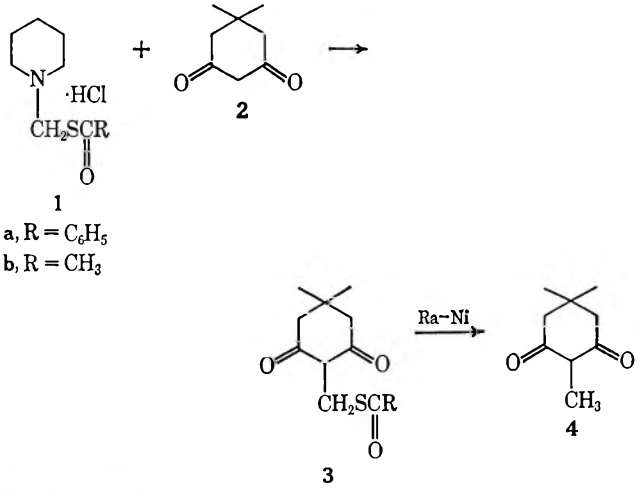
A method for the thiomethylation of active methylene compounds utilizing piperidinomethyl thiobenzoate hydrochloride (**1a**) and piperidinomethyl thioacetate hydrochloride (**1b**) is discussed. The scope and limitations of this reaction as a general alkylation method were investigated.

The common alkylation reactions involving active methylene type compounds usually involve modification of the system to be alkylated either by derivative formation (*e.g.*, eneamine) or by pretreatment with base. The utilization of an activated form of the alkylating agent which would require no modification of the compound to be alkylated and which could be used under very mild conditions appeared to be an attractive possibility. The ideal system would employ an activating group which could be removed during alkylation or which could be removed under neutral conditions after alkylation. A sulfur-containing system would meet these requirements since Raney nickel desulfurization following thioalkylation could be effected under mild conditions. The tentative scheme is given below.



Piperidinomethyl thiobenzoate hydrochloride (**1a**) was synthesized as a precursor for the preparation of "thioformaldehyde" in a thio-Prins reaction.[3] This compound was originally prepared[4] by the condensation of hydroxymethyl thiobenzoate with piperidine, and an alternate procedure was reported from these laboratories.[3]

When compound **1** was allowed to react with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**2**), utilizing an excess of the latter, methylenebisdimedone was obtained. When a 1:1 molar ratio of the alkylating agent **1a** and dimedone were warmed in dioxane, a monothiomethylated product, 2-benzoylthiomethyl-5,-5-dimethyl-1,3-cyclohexanedione (**3a**), formed as piperidine hydrochloride precipitated from the reaction solution. This compound was desulfurized to yield 2,5,5-trimethyl-1,3-cyclohexanedione (**4**).



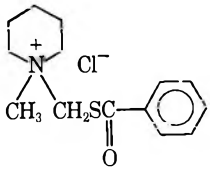
This method was utilized with a series of compounds (Chart I). In all cases, C-thioalkylation occurred with no O-alkylation being detectable. Proof of C-thioalkylation was obtained by desulfurization to the various methyl-alkylated systems. The use of benzenesulfonamide in this procedure yielded the N-thiomethylation product.

Attempts to thiomethylate cyclohexanone, malonic ester, phenol, and phloroglucinol under the conditions utilized for the successful alkylation of β-keto esters and β diketones failed to give the desired products. When the reaction time and/or the temperature were increased, the alkylating reagent, **1**, decomposed.[3]

An attempt at dialkylation by treating 3-benzoylthiomethyl-2,4-pentanedione (Chart I, eq 3) with 1 equiv of piperidinomethylthioacetate hydrochloride (**1b**) gave only starting material. Other modifications of the reagent and conditions were made in the hope of aiding in the elucidation of the mechanism. When the reagent **1** was utilized as the free base in the reaction with dimedone, no alkylated product was obtained.

The solvent utilized for the reaction does not appear to be critical. Dimedone was thiomethylated with **1** in refluxing dioxane, ethanol, chloroform, and dimethylformamide. The optimum reaction conditions were those utilizing the reagent **1** and dioxane. Under these conditions piperidine hydrochloride precipitates as **1** reacts with the material to be alkylated. A minor disadvantage in utilizing the thioacetate **1b** is its insolubility in dioxane. When other solvents are employed, formation of piperidine hydrochloride can not be observed since it is soluble.

In order to determine if the stability and reactivity of the alkylating agent could be increased, various changes were made in the reagent. N-Methylpiperidine was allowed to react with chloromethyl thiobenzoate to produce piperidinomethyl thiobenzoate methochloride (**5**). This compound was utilized, under the conditions specified for the alkylating agent **1** with dihydroresorcinol and acetylacetone, for periods



5

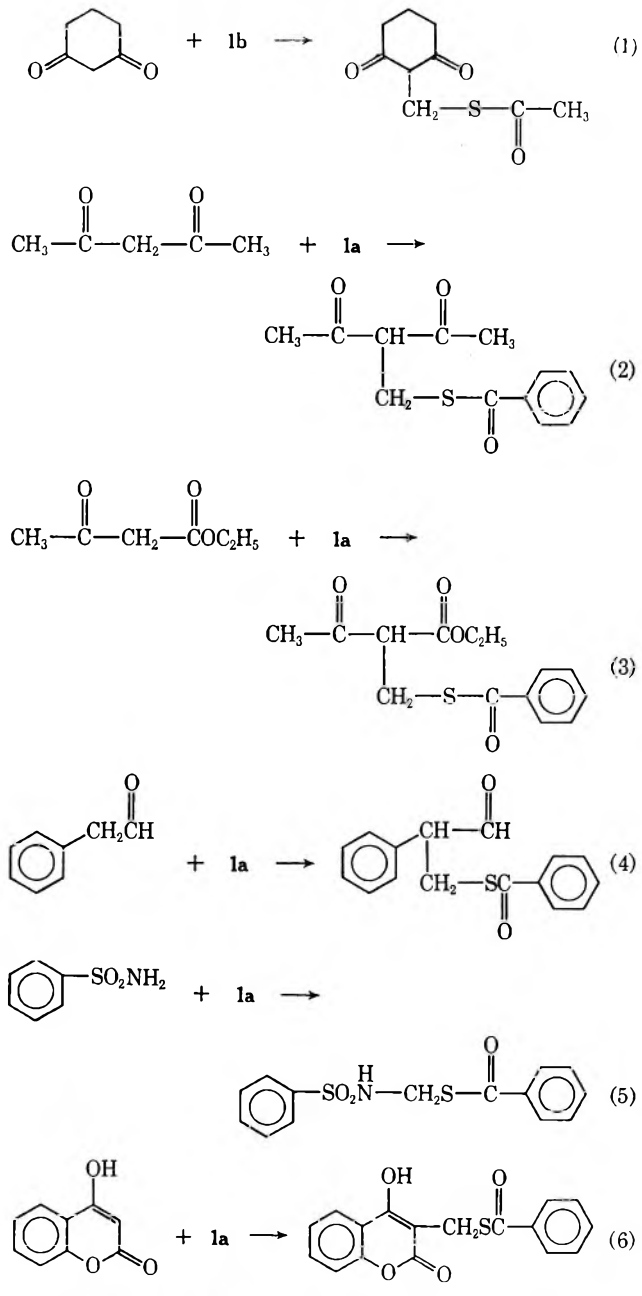
(1) Presented in part before the 1st Midwest Regional American Chemical Society Meeting, Kansas City, Mo., Nov. 4–5, 1965.

(2) Taken in part from the dissertations presented by J. R. J. Sorenson in Jan. 1965 and W. A. Albrecht in Dec 1965 to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(3) E. E. Smissman and J. R. J. Sorenson, *J. Org. Chem.*, **30**, 300 (1965).

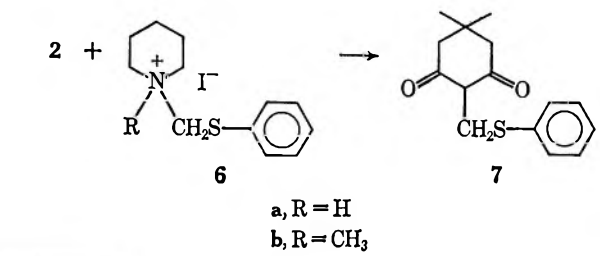
(4) H. Böhme, E. Nurnberg, and W. Schlephack, *Arch. Pharm.* (Weinheim), **292**, 585 (1959).

CHART I



up to 30 hr, but only starting material could be recovered.

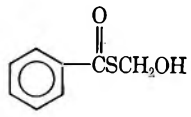
N-(Phenylthiomethyl)piperidine hydrochloride (**6a**) was prepared using the procedure of Grillot.[5] When it was refluxed with 1 equiv of dimedone in dioxane, an 89% yield of 2-phenylthiomethyldimedone (**7**) was obtained. Piperidine hydrochloride was observed in the reaction mixture within 2 min after mixing. However, N-(phenylthiomethyl)piperidine methiodide (**6b**) failed to alkylate dimedone.



6 **7**

a, R = H
b, R = CH_3

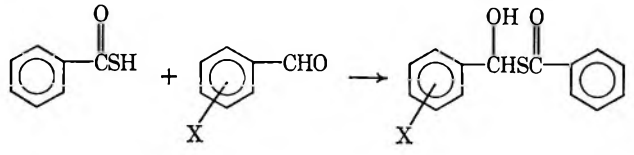
The thioalkylation of dimedone with hydroxymethyl thiobenzoate (**8**) in the presence of sulfuric acid has been reported.[6] In order to produce a more sensitive



8

reagent which could be utilized under essentially neutral conditions and to study the possibility of extending the reaction beyond thiomethylation, it was decided to make derivatives of the alcoholic function.

Because of the ease of displacement of the tosyl group, it was selected as the derivative of choice of the hydroxymethyl thiobenzoate (**8**). Four other α-arylmethyl thiobenzoates (**9**) were prepared utilizing thiobenzoic acid and substituted benzaldehyde. The ease of condensation varied with the nature of the substituent on the aldehyde, the order for decreasing ease of condensation being *p*-NO_2 > *p*-Cl > *o*-Cl > *o*-Me > H. All attempts to prepare tosylate de-

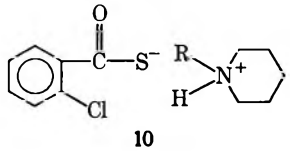


9

a, X = *p*-NO_2 **c**, X = *o*-Cl
b, X = *p*-Cl **d**, X = *o*-Me

rivatives of these thiobenzoates **9** failed. The condensation with α-naphthylisocyanate to give the corresponding α-naphthylurethans was successful; however, the latter compounds were unstable and tended to decompose to di-α-naphthylurea on recrystallization, on heating, or on standing at room temperature for 2–3 days.

Treatment of the α-hydroxy-α-arylmethyl thiobenzoates **9** with secondary amines resulted in the degradation of the benzoates to the corresponding aldehydes, and, in the case of the α-hydroxy-α-(chlorophenyl)methyl thiobenzoates, to the salt **10**.



10

Since the formation of derivatives of the substituted thiomethyl alcohols failed, several attempts at condensing substituted α-hydroxymethyl thiobenzoates with diketones were made under both basic and acid conditions. In general, under the conditions used, the thiobenzoate reverts to the parent aldehyde and thiobenzoic acid.

(5) G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Amer. Chem. Soc.*, **76**, 3969 (1954).

(6) H. Böhme, H. Bezzenberger, M. Clement, A. Dick, E. Nürnberg, and W. Schlephack, *Ann.*, **623**, 92 (1959).

Experimental Section[7]

Hydroxymethyl Thiobenzoate.—The literature procedure[6] was modified in the following manner. Thiobenzoic acid, 138 g (1.0 mol), and paraformaldehyde, 30 g (1.0 mol), were allowed to react at 100° for 2 hr under an atmosphere of nitrogen. The hot reaction mixture was filtered, and the filtrate solidified on cooling. The solid was recrystallized [ether–petroleum ether (bp 63–68°)] to give 135 g (80%) of product, mp 45–46° (lit.[6] mp 46°). The nmr spectrum showed peaks at 4.55, singlet, 1 H (–OH); 5.36, singlet, 2 H (–SCH_2O); 7.60, multiplet, 3 H (*meta* and *para* protons); 8.08, multiplet, 2 H (*ortho* protons).

Hydroxymethyl Thioacetate.—The above procedure was followed except that purification was accomplished by distillation, bp 30–35° (15 mm) [lit.[6] bp 68–70° (20 mm)], yield 109 g (80%).

Piperidinomethyl Thiobenzoate Hydrochloride (1a).—Piperidine, 25.2 g (0.29 mol), was dissolved in ether and treated with a large excess of anhydrous magnesium sulfate. The mixture was cooled in an ice bath, and an ethereal solution of hydroxymethyl thiobenzoate, 50.0 g (0.296 mol), was added slowly with stirring. After the addition was complete, the mixture was stirred for an additional 15 min and filtered into 300 ml of ether saturated with 13.0 g (0.36 mol) of hydrogen chloride gas. The white solid was filtered and air-dried, yield 60.0 g (75%), mp 173–176° (lit.[4] mp 173°). The nmr and ir are in agreement with the structure.

The hydrochloride was converted to the hydriodide *via* ion exchange. The white crystalline material, mp 189–191°, was stable to air drying.

Anal. Calcd for $C_{13}H_{18}INOS$: C, 42.98; H, 4.99; N, 3.86. Found: C, 42.81; H, 4.98; N, 3.68.

Piperidinomethyl Thioacetate Hydrochloride (1b).—The above procedure was followed utilizing 4.7 g (0.056 mol) of piperidine and 6.0 g (0.056 mol) of hydroxymethyl thioacetate. The white precipitate was filtered and air-dried, mp 185°, yield 7.5 g (65%).

Piperidinomethyl Thiobenzoate Methiodide and Methochloride (5).—Piperidine, 5.0 g (0.06 mol), was dissolved in 50 ml of ether containing 10 g of anhydrous magnesium sulfate. An ethereal solution of 10.0 g (0.006 mol) of hydroxymethyl thiobenzoate was added, dropwise, to the amine solution with stirring. After removal of the magnesium sulfate by filtration, 10 ml (0.16 mol) of methyl iodide was added and the solution was allowed to stand for several days. The white crystalline solid was collected by filtration and recrystallized (methanol–ethyl acetate), yield 2.5 g, mp 163–164°.

Anal. Calcd for $C_{14}H_{20}INOS$: C, 44.57; H, 5.34; I, 33.64; N, 3.71. Found: C, 44.30; H, 5.31; I, 33.82; N, 3.52.

N-Methylpiperidine, 3.6 g (0.036 mol), and chloromethyl thiobenzoate, 6.7 g (0.036 mol), were dissolved in 50 ml of dry benzene. After refluxing for 18 hr, 2.4 g of product was isolated: mp 184–186°; nmr (D_2O) 1.95 (broad singlet, 6 H, $(CH_2)_3$); 3.47 (singlet, 3 H, NCH_3); 3.91 (broad singlet, 4 H, $-CH_2N-CH_2-$); 4.92 (singlet, 2 H); 5.76 (singlet, 2 H, SCH_2N); 7.73 and 8.15 (two multiplets, 5 H, aromatic).

N-Phenylthiomethylpiperidine (6a).—The procedure of Grillot[5] was used and 78.8 g (76%) of product was obtained by distillation, bp 112–114° (1.0 mm) [lit.[5] bp 138–141° (5–6 mm)].

An ethereal solution of 58 g (0.28 mol) of N-phenylthiomethylpiperidine was treated with hydrogen chloride at 0°. The ether was decanted and the semisolid product was washed with ethyl acetate to yield a white hygroscopic solid 116–118°. The nmr and ir spectra were as expected. All attempts to recrystallize the product caused decomposition. Because of its hygroscopicity, the elemental analysis was not obtained.

N-Phenylthiomethylpiperidine Methiodide (6b).—An ether solution of 19.5 g (0.095 mol) of N-phenylthiomethylpiperidine (**6b**) and 9.4 ml (0.15 mol) of methyl iodide was allowed to stand for 1 week in a stoppered flask at room temperature. The solid was filtered and recrystallized (methanol–ethyl acetate) to give 24 g (72%) of product, mp 179–180°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{13}H_{20}INS$: C, 44.70; H, 5.77; N, 4.01. Found: C, 44.77; H, 5.69; N, 3.96.

(7) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data (μ) were recorded on Beckman IR-8 and IR-10 spectrometers. Nmr data (ppm, δ) were recorded on Varian Associates Model A-60 and A-60A spectrometers (TMS). Microanalyses were conducted by Huffman Laboratories, Inc., Wheatridge, Colo., and on an F & M Model 185 analyzer, University of Kansas.

2-Benzoylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione.—Dimedone, 2.8 g (0.02 mol), was added to a refluxing solution of piperidinomethyl thiobenzoate hydrochloride, 5.4 g (0.02 mol), dissolved in 100 ml of *p*-dioxane. Almost immediately solid material precipitated, and after 14 min the reaction mixture was cooled and filtered. The residue weighed 2.4 g and was identified as piperidine hydrochloride, mp 244°. The dioxane solution was treated with twice its volume of ether and 5.0 g (86%) of product was collected by filtration and recrystallized from chloroform–carbon tetrachloride, mp 170–171°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 65.72; H, 6.40.

3-Benzoylthiomethyl-2,4-pentanedione.—Acetylacetone, 1.0 g (0.01 mol), was dissolved in 25 ml of *p*-dioxane and the solution was heated to reflux. Piperidinomethyl thiobenzoate hydrochloride, 2.7 g (0.01 mol), was added to the solution with stirring and heating for 5 min. Piperidine hydrochloride, 1.2 g, was collected by filtration, and the filtrate was reduced in volume to 5 ml. The oil was crystallized from ethanol–water to yield 1.3 g (52%) of product, mp 61–62°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.37; H, 5.64. Found: C, 62.29; H, 5.63.

2-Benzoylthiomethyl-2-phenylacetaldehyde.—Piperidinomethyl thiobenzoate hydrochloride, 5.44 g (0.02 mol), was dissolved in 70 ml of refluxing *p*-dioxane. A solution of 2.4 g (0.02 mol) of freshly distilled phenylacetaldehyde dissolved in 10 ml of *p*-dioxane was added, and the reaction mixture was heated at reflux for 10 min. After cooling, 2.39 g of piperidine hydrochloride was collected by filtration. The filtrate was concentrated to about 5 ml and chromatographed on 40 g of silica gel. Elution was accomplished with carbon tetrachloride followed with dichloromethane. Upon evaporation of the latter solvent, 2.8 g of an orange oil was obtained. The nmr and ir spectra were as expected. The product was analyzed as its 2,4-DNP derivative, mp 161–162°.

Anal. Calcd for $C_{22}H_{18}N_4O_5S$: C, 58.66; H, 4.03; N, 12.44. Found: C, 59.06; H, 4.27; N, 12.30.

N-Benzoylthiomethylbenzenesulfonamide.—Piperidinomethyl thiobenzoate hydrochloride, 2.72 g (0.01 mol), was dissolved in 30 ml of refluxing dioxane. Benzenesulfonamide, 1.57 g (0.01 mol), was added, the reaction mixture was cooled, and 1.2 g (theoretical amount 1.2 g) of piperidine hydrochloride was collected by filtration, mp 244°. The filtrate was poured into 100 ml of ice water and the white precipitate was filtered and air-dried. Recrystallization from carbon tetrachloride gave 1.6 g (52%) of product, mp 84°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.70; H, 4.35; N, 4.54.

3-Benzoylthiomethyl-4-hydroxycoumarin.—To 5.44 g (0.02 mol) of piperidinomethyl thiobenzoate hydrochloride dissolved in 100 ml of refluxing *p*-dioxane was added 3.4 g (0.02 mol) of 4-hydroxycoumarin. The reaction mixture was refluxed for 10 min. After cooling, 2.35 g of piperidine hydrochloride was collected by filtration. The filtrate was poured into 150 ml of ice water, and the resulting precipitate was filtered and crystallized from acetone–water to yield 5.4 g (87%) of product, mp 166–167°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{17}H_{12}O_4S$: C, 65.37; H, 3.87. Found: C, 65.61; H, 4.04.

2-Acetylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione. A.—To a solution of 3.08 g (0.0147 mol) of piperidinomethyl thioacetate hydrochloride dissolved in 35 ml of dimethylformamide (DMF) was added 2.065 g (0.0147 mol) of dimedone. The solution was stirred and heated at 100° for 2 hr. On cooling, piperidine hydrochloride, 1.65 g, precipitated. Evaporation of the filtrate gave, after recrystallization from carbon tetrachloride, 2.9 g (86%) of 2-acetylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione, mp 135°. The nmr and ir spectra were as expected.

B.—Dimedone, 1.4 g (0.01 mol), and piperidinomethyl thioacetate hydrochloride, 2.1 g (0.01 mol); were dissolved in 25 ml of chloroform and refluxed for 1 hr. Carbon tetrachloride, 25 ml, was added to the solution and the chloroform was removed by heating the open flask on a steam bath. The hot carbon tetrachloride was filtered to remove 1.3 g of piperidine hydrochloride. The product crystallized, after cooling the filtrate, to give 1.76 g (78%), mp 134–135°.

2-Acetylthiomethyl-1,3-cyclohexanedione.—A solution of 1.1 g (0.01 mol) dihydroresorcinol and 2.1 g (0.01 mol) piperidinomethyl thioacetate hydrochloride dissolved in 50 ml of chloroform was refluxed for 1 hr. The chloroform solution was reduced to half its volume, and 100 ml of ether was added to precipitate piperidine hydrochloride, 1.55 g (100%). The solvent was removed to give an orange semisolid which was recrystallized from dichloromethane–petroleum ether (bp 63–68°) to yield 1.1 g (55%) of product, mp 132°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_9H_{12}O_3S$: C, 54.00; H, 6.04. Found: C, 53.72; H, 5.94.

2-Phenylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione.—To 25 ml of refluxing *p*-dioxane was added 2.4 g (0.01 mol) of N-phenylthiomethylpiperidine hydrochloride. Dimedone, 1.4 g (0.01 mol), was then added to the refluxing solution. Within 2 min, a white precipitate was observed. After cooling the reaction mixture, 1.1 g of piperidine hydrochloride was collected by filtration. The filtrate was poured into 100 ml of ice water and allowed to stand overnight. The precipitate was filtered and air-dried to yield 2.3 g (89%) of product. The solid was recrystallized from acetone–petroleum ether (bp 63–68°), mp 139°. The nmr and ir spectra were as expected.

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91. Found: C, 68.65; H, 6.90.

Desulfurization Procedure.—Raney nickel, the catalyst, was prepared by the method of Pavlic and Adkins.[8] Examples of the general procedure follow.

2,5,5-Trimethyl-1,3-cyclohexanedione.—2-Benzoylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione, 2.9 g (0.01 mol), was dissolved in 125 ml of ethyl acetate at 65–70°. About 20 g (wet weight) of Raney nickel was added to the solution with stirring and heated for 1 hr. The reaction mixture was filtered while hot and the residue was washed with three 50-ml portions of hot ethyl acetate. The washings and original filtrate were combined, and the solvent was removed to yield 0.96 g (62%) of product melting at 163–165° (lit.[9] mp 163°). An authentic sample was prepared by the method of Desai.[9] The melting point and infrared spectra were identical with those of the desulfurized product.

3-Methyl-4-hydroxycoumarin.—The above procedure was followed to desulfurate 2.1 g (0.0067 mol) of 3-benzoylthiomethyl-4-hydroxycoumarin dissolved in 80 ml of ethyl acetate using 14 g (wet weight) of Raney nickel. Upon removal of the solvent, 0.86 g (74%) of product was isolated and recrystallized from chloroform–carbon tetrachloride, mp 225–228° (lit.[10] mp 231°).

(8) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

Registry No.—Hydroxymethyl thiobenzoate, 23853-33-0; **1a** (HI), 23853-34-1; **1b** (HCl), 876-24-4; **5** (methiodide), 23853-36-3; **5** (methochloride), 23853-37-4; **6b**, 23853-38-5; 2-benzoylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione, 23853-39-6; 3-benzoylthiomethyl-2,4-pentanedione, 23853-40-9; 2-benzoylthiomethyl-2-phenylacetaldehyde (2,4-DNP), 23853-41-0; N-benzoylthiomethylbenzenesulfonamide, 23853-42-1; 3-benzoylthiomethyl-4-hydroxycoumarin, 23853-43-2; 2-acetylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione, 23853-44-3; 2-acetylthiomethyl-1,3-cyclohexanedione, 23853-45-4; 2-phenylthiomethyl-5,5-dimethyl-1,3-cyclohexanedione, 23853-46-5.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grants GM-9254 and GM-14,467.

(9) R. G. Desai, *J. Chem. Soc.*, 1079 (1932).
(10) K. Sen and P. Bagchi, *J. Org. Chem.*, **24**, 316 (1959).

Additions to Bicyclic Olefins. II. A Convenient Synthesis of Apobornene and Apocamphor[1]

HERBERT C. BROWN, JAMES H. KAWAKAMI,[1] AND SOICHI MISUMI[2]

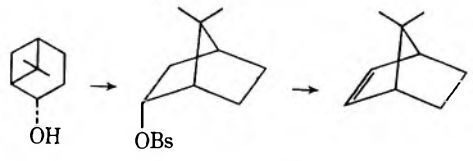
Richard B. Wetherill Laboratory, Purdue University, Lafayette, Indiana 47907

Received September 16, 1969

A convenient five-step synthesis of apobornene (7,7-dimethylnorbornene) from the readily available camphenilone (3,3-dimethylnorcamphor) has been developed in an overall yield of 30%. This procedure makes possible the synthesis of apobornene in relatively large quantities in purities of 98% or better. Through minor modifications the synthesis can be directed to the preparation of apocamphor.

A considerable quantity of pure apobornene (7,7-dimethylnorbornene) was required for our studies of the stereochemical aspects of additions to bicyclic systems.[3] The synthesis of apobornene has been described previously.[4,5] However, the procedures do not lend themselves to the preparation of apobornene in appreciable quantity or in the desired purity. Consequently, we undertook to develop a more satisfactory procedure.

The most direct procedure would be the Diels–Alder reaction of 5,5-dimethylcyclopentadiene with ethylene. However, the synthesis of the diene appeared to offer severe difficulties.[6] Another possibility was the conversion of β-nopinol into apobornyl brosylate,[7] followed by an elimination (eq 1). However, β-nopinol is not



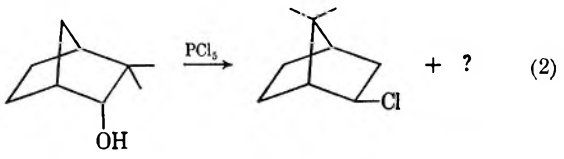
(1)

easily synthesized.[8] Solvolytic methods can be used to obtain apoisoborneol as a mixture with isomeric alcohols.[9] However, we observed that the isolation of pure alcohol on a large scale was quite time consuming.

After examining a number of such approaches we decided that the most convenient procedure appeared

(1) Graduate research assistant on grants (G 19878 and GP 6492 X) supported by the National Science Foundation.
(2) Postdoctorate research associate on Grant GM 10937 from the National Institutes of Health.
(3) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 1990 (1970).
(4) (a) G. Komppa and T. Hasselstrom, *Ann. Acad. Sci. Fenn. Ser. A9*, **24**, 3 (1925); (b) G. Komppa and T. Hasselstrom, *Ann.*, **497**, 116 (1932); (c) G. Komppa and R. H. Roschier, *ibid.*, **429**, 175 (1922).
(5) P. Lipp and J. Daniels, *Ber.*, **69**, 586, 2251 (1936).
(6) (a) C. F. Wilcox, Jr. and M. Mesirov, *J. Org. Chem.*, **25**, 1841 (1960); (b) R. S. Rouse and W. E. Tyler, *ibid.*, **26**, 3525 (1961).
(7) P. von R. Schleyer, W. E. Watts, and C. Cupas, *J. Amer. Chem. Soc.*, **86**, 2722 (1964).
(8) S. Winstein and N. J. Holness, *ibid.*, **77**, 3054 (1955).
(9) (a) See ref 8; (b) S. Beckmann and R. Bamberger, *Ann.*, **574**, 73 (1951); (c) Y. Chretien-Bessiere and J. P. Monthiard, *Compt. Rend.*, **258**, 937 (1964).

to be E2 elimination of the mixture of chlorides, presumably largely apoisobornyl chloride, produced in the reaction of phosphorus pentachloride with *endo*-camphenilol[9b] (eq 2). We hoped that we might then

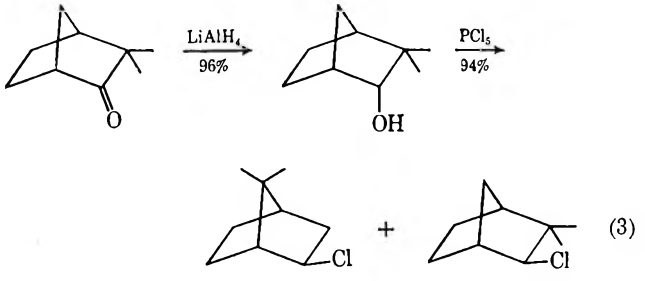


(2)

readily separate the desired olefin from the reaction mixture by fractional distillation or preparative gas chromatography. Although we encountered unexpected difficulties in this separation and isolation, we were able to solve the problems and achieve a convenient synthesis of apobornene in high purity and quantity. At the same time we developed a convenient procedure for the synthesis of apocamphor.

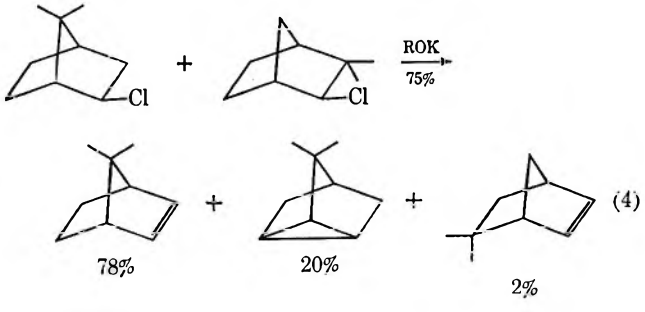
Results and Discussion

The present synthesis begins with camphenilone,[10] a compound readily available from the oxidation of camphene.[11] Reduction of camphenilone with lithium aluminum hydride gave a 96% yield of *endo*-camphenilol. The alcohol was treated with phosphorus pentachloride to produce a mixture of 64% apoisobornyl and 36% *exo*-camphenilyl chlorides in a yield of 94% (eq 3).



(3)

Experiments indicated that elimination with the potassium salt of 2-cyclohexylcyclohexanol in excess alcohol provided a highly satisfactory procedure. There was obtained a 75% yield of a mixture of apobornene (78%), apocyclene (20%), and 5,5-dimethylnorbornene (2%) (eq 4).



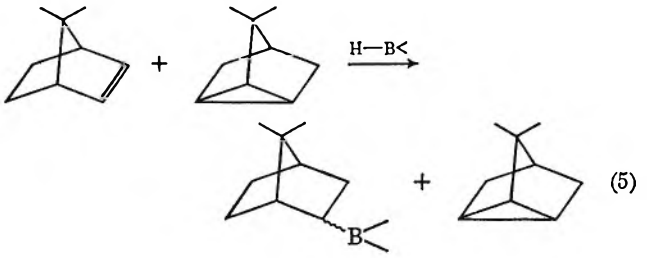
(4)

(10) The camphenilone was purchased in kilogram quantities from the Shawnee Chemicals Co., Springfield, Ohio.

(11) (a) W. Hückel, *Suomen Kemist.*, **B31**, 13 (1958); (b) P. S. Bailey, *Chem. Ber.*, **88**, 795 (1955); (c) P. D. Bartlett, E. R. Webster, E. E. Dills, H. G. Richey, Jr., *Ann.*, **623**, 217 (1959).

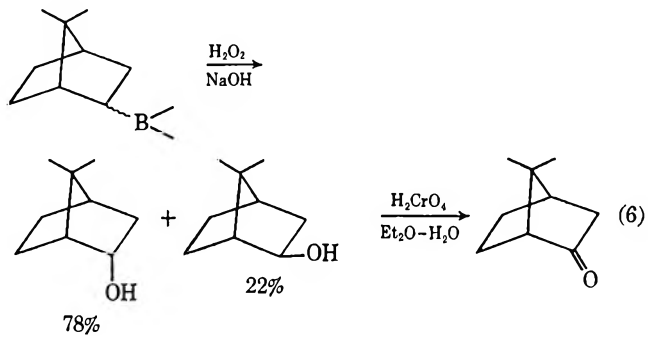
Here we encountered a major difficulty. The two hydrocarbons could not be separated by fractional distillation. Moreover, they could not be separated on a large number of preparative glpc columns examined. Surprisingly, even a silver nitrate column failed to achieve separation. Evidently the 7,7-dimethyl substituents block silver ion complexation from the *exo* direction, and complexation from the *endo* direction does not occur.[12]

Hydroboration of the reaction mixture[13] did achieve a selective reaction with apobornene and the apocyclene could be distilled away from the organoborane (eq 5).



(5)

Oxidation of the organoborane with alkaline hydrogen peroxide yielded a mixture of 78% apobornyl alcohol and 22% apoisobornyl alcohol,[4] free of any isomeric compounds. Oxidation of this mixture with chromic acid by the convenient two-phase procedure[14] gave pure apocamphor (eq 6).



(6)

We considered using the displacement reaction[15] as a means of regenerating the desired apobornene from the organoborane. However, a suggestion from Professor T. G. Traylor led us to try oxymercuration–deoxymercuration.[13] Fortunately, under the conditions employed, apocyclene does not undergo mercuration.[17] Consequently, reaction of the mixture with mercuric acetate in acetic acid, followed by dilution with aqueous

(12) A detailed study of this interesting feature was made and will be reported later.

(13) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

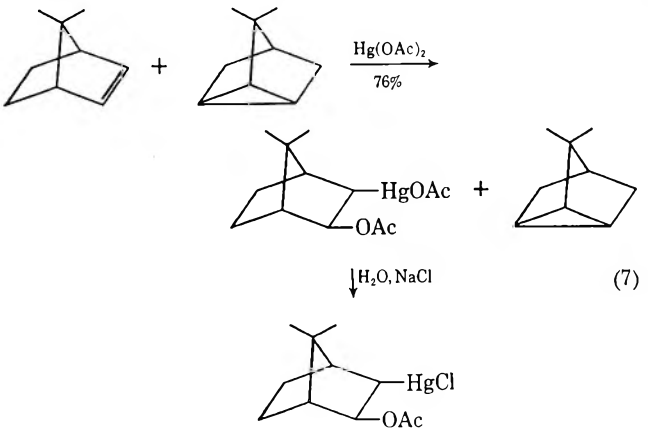
(14) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

(15) H. C. Brown, M. V. Bhatt, T. Munekata, and G. Zweifel, *ibid.*, **89**, 567 (1967).

(16) T. G. Traylor and S. Winstein, the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, Abstracts, O-82.

(17) Cyclopropanes do undergo oxymercuration and in some cases the reaction is quite facile. For example, it has been reported that bicyclo[2.1.0]pentane reacts with mercuric acetate in water to form the 1,3-addition compound: R. Y. Levina, V. N. Kostin, D. G. Kim, and T. K. Ustynyuk, *Zh. Obshch. Khim.*, **29**, 1956 (1959).

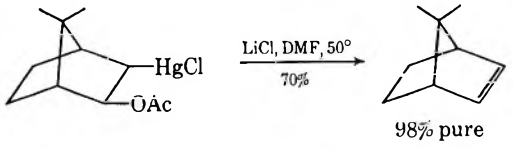
sodium chloride, precipitates the desired mercurichloride, free of apocyclene (eq 7).



(7)

We were anxious to avoid acidic deoxymercuration procedures,[18,19] to avoid possible isomerization of the product. Both lithium aluminum hydride and halide salts have been used to effect demercuration of such adducts.[16] Indeed, we observed that the use of lithium aluminum hydride in large excess does give good yields of apobornene along with a small amount of alcohol. However, although satisfactory for small-scale preparations, we considered the procedure hazardous for large-scale synthesis.

Consequently, we turned to demercuration with halide ion. A number of considerations led us to the use of lithium chloride in dimethylformamide. This worked ideally and provided apobornene in high purity (eq 8).

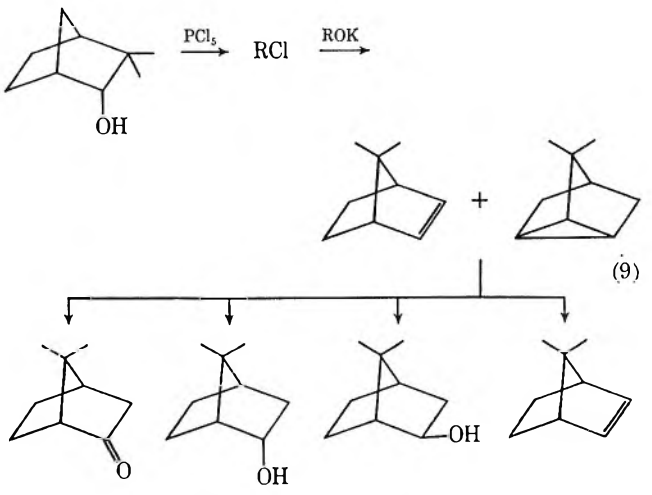


(8)

98% pure

Conclusions

The reaction of *endo*-camphenilol with phosphorus pentachloride, followed by elimination with the potassium salt of 2-cyclohexylcyclohexanol, provided a convenient route to an 80:20 mixture of apobornene and apocyclene. Oxymercuration–deoxymercuration provides pure apobornene. Oxymercuration–demercuration of the mixture provides pure apoisoborneol.[20] Finally, hydroboration oxidation provides a mixture of 78% apoborneol[21] and 22% apoisoborneol, with further oxidation yielding pure apocamphor (eq 9). Consequently, these procedures should greatly enhance the availability of these interesting intermediates.



(9)

Experimental Section

Purification of Camphenilone.—To a 500-ml flask fitted with a magnetic stirring bar and a 40 × 1 cm Vigreux column was added 333 g of 88% pure camphenilone[10] (12% camphene). Distillation at 223° until camphene was distilled out gave 247 g (74%) of 99% camphenilone, mp 41–43° (lit.[22] mp 38–39°). Analysis was on the Perkin–Elmer 154, 6 ft × 0.25 in. Carbowax 20M on 60–80 Chromosorb P, at 100°.

Preparation of *endo*-Camphenilol.—To a three-necked 3000-ml flask equipped with a mechanical stirrer and a reflux condenser was added 24.7 g (0.65 mol) of lithium aluminum hydride and 800 ml of anhydrous diethyl ether. With stirring, 247.3 g (1.79 mol) of camphenilone dissolved in 625 ml of ether was added from a pressure-equalized dropping funnel at such a rate to maintain a gentle reflux. After the addition was complete, the mixture was kept at reflux temperatures for a total reaction time of 4 hr. The excess hydride was destroyed with water at 0°, and 10% sodium hydroxide was added until the aluminum salts precipitated. The ether solution was decanted, and the ether was evaporated on the rotatory evaporator to give 224.5 g (90%) of camphenilol (predominantly *endo*-). In another preparation 100 g of camphenilone was converted into 97 g (96%) of camphenilol, mp 71–74.5° (lit.[22] mp 75–77°).

Conversion of *endo*-Camphenilol to a Mixture of Chlorides with Phosphorus Pentachloride.—To a 500 ml three-necked flask fitted with a mechanical stirrer, a pressure-equalized addition funnel (with tube leading to a sodium hydroxide solution to trap the generated hydrogen chloride), and a thermometer, was added 50.1 g (0.24 mol) of phosphorus pentachloride (Baker Analyzed), and 150 ml of petroleum ether (bp 35–37°). To this stirred slurry was added 28.2 g (0.202 mol) of *endo*-camphenilol dissolved in 200 ml of petroleum ether, at such a rate to keep the temperature between −5 to 0°. The addition time was about 45 min when a Dry Ice–acetone bath at −10° was employed. After the addition was completed, the reaction mixture was stirred vigorously for 5 min. The petroleum ether solution was decanted into a 2-l separatory funnel containing 300 g of crushed ice. Care was taken so that the unreacted phosphorus pentachloride (yellow solid) was not transferred. The flask was rinsed with 50 ml of petroleum ether, and the rinse was added to the funnel. (It is important that the temperature be kept near 0° or else the chlorides will isomerize. The presence of crushed ice in the separatory funnel during the work-up ensures this.) The aqueous layer was separated and the cloudy petroleum ether solution was washed twice with 500-ml portions of ice-cold water. Then the petroleum ether layer was washed with at least two 500-ml portions of ice-cold 2 *N* aqueous hydrochloric acid. (Vigorous shaking is necessary.) The washing was continued until no gas was evolved and the petroleum ether layer was clear and colorless. Then the organic layer was washed three times with a dilute solution of ice-cold potassium carbonate. Since it was difficult to remove all of the acid, the organic layer was dried over anhydrous potassium carbonate with stirring overnight at room temperature. The drying agent was filtered off and the solvent was removed at room temperature on the rotary evap-

(18) (a) M. M. Kreevoy and M. A. Turner, *J. Org. Chem.*, **29**, 1639 (1964); (b) M. M. Kreevoy, R. A. Kretchmer, G. E. Stokker, and A. K. Ahmed, *ibid.*, **28**, 3184 (1963).

(19) M. J. Abercrombie, A. Rodgman, K. R. Bharucha, and G. F. Wright, *Can. J. Chem.*, **37**, 1328 (1959).

(20) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, **89**, 1525 (1967).

(21) Although we did not attempt to separate these compounds, it is known that one can isolate the less reactive component of such mixtures (*i.e.*, isoborneol) through partial hydrolysis of the tosylates.

(22) W. Hückel, *Ann.*, **549**, 186 (1941).

orator (water aspirator vacuum) to give 30 g (94%) of a semisolid mixture of chlorides. The structures were assigned from their nmr spectrum in carbon tetrachloride. The proton adjacent to the chlorine exhibited a quartet at δ 3.9 ppm for 7,7-dimethyl-2-*exo*-norbornyl chloride (64%). The methyl resonances were at δ 1.0 and 1.33 ppm. In the minor isomer, the α-methine proton gave a doublet at δ 2.52 and methyl resonances at 1.06 and 1.1 ppm. These are consistent with 3,3-dimethyl-2-*exo*-norbornyl chloride (36%).[23]

Dehydrohalogenation of the Chlorides.—To a 200-ml one-necked flask fitted with a magnetic stirring bar and reflux condenser was added 100 g of 2-cyclohexylcyclohexanol (Dow Chemical Co.) and 11.7 g (0.3 g-atom) of potassium metal under a static pressure of nitrogen. The mixture was heated with stirring to 200° in 1 hr. The potassium reacts completely in 2 hr. (A powerful magnetic stirrer should be used.) The reaction mixture was cooled to 50° (solidification occurs), and then 30 g (0.189 mol) of chlorides was added (no solvent was used for the transfer). The reflux condenser was replaced with a Vigreux column (40 × 1 cm) maintained at 120° with a heating tape. A hot-water-heated condenser was connected to the Vigreux column, and an adapter (no narrow inside tube) was connected to the condenser. A three-necked flask fitted with a reflux condenser was used to collect the product. The mixture was then heated with stirring to 170° in about 1 hr. Initially some solvent remaining in the chloride distilled over. This can be removed with a pipet. At about 170° (oil-bath temperature), the apobornene and apocyclene starts to distil over. Within 2–3 hr (bath temperature 250°), there was obtained 17.3 g (75%) of a white semisolid. Analysis on the Perkin-Elmer Model 226 gas chromatograph on a 150 ft × 0.01 in. Golay column with Ucon LB 550X at 70° indicated 2% 5,5-dimethylnorbornene, 78% apobornene, and 20% apocyclene, in the order of increasing retention time.

Oxymercuration of Apobornene.—To a 100-ml round-bottom flask equipped with a magnetic stirring bar was added 15.9 g (50 mmol) of mercuric acetate and 50 ml of glacial acetic acid. To this stirred slurry was added 7.65 g of the apobornene–apocyclene mixture or 6.1 g (50 mmol) of apobornene. The mercuric acetate dissolves very quickly to form a pale yellow solution. After 3 hr at room temperature, the reaction mixture was poured into a stirred 200 ml of 1 *M* sodium chloride solution at room temperature. A white precipitate forms immediately. (If an oil forms, scratching with a glass rod induces crystallization.) After stirring for about 30 min, the product was filtered, crushed, washed well with cold water and pentane, and dried under vacuum at 1 mm overnight to give 18.7 g of the adduct (90%), mp 109–112°. Recrystallization by dissolving 15 g of the mercurial in 40 ml of hot absolute ethanol gave 12.6 g (84%) of pure mercurial, mp 121–121.5°. *Anal.* Calcd for $C_{11}H_{17}O_2HgCl$: C, 31.64; H, 4.11. Found: C, 31.41; H, 3.94.

(23) J. C. Davis, Jr., and T. V. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965), and references cited therein.

Deoxymercuration of the Apobornene Adduct.—To a 200-ml flask equipped with a magnetic stirring bar was added 20.9 g (50 mmol) of the mercurial and 100 ml of anhydrous dimethylformamide. The reaction mixture was warmed to 50° under nitrogen and 9.5 g (0.22 mol) of lithium chloride was added. After 6 hr at 50°, the reaction mixture was cooled, 25 ml of petroleum ether (bp 35–37°) was added, and the mixture was stirred well. Then the mixture was transferred to a separatory funnel containing 250 ml of water and shaken vigorously. Some emulsion and solid were separated, and the organic layer was washed twice with water and dried over magnesium sulfate. The solvent was distilled off through a 40 × 1 cm Vigreux column until some apobornylene started to distil. There was obtained 4.3 g (70%) of 98% apobornene and 2% 5,5-dimethylnorbornene, which had mp 46–47° (lit.[5d] mp 38°). The pmr spectrum in carbon tetrachloride exhibited a vinyl triplet at δ 5.9 (J = 1.5 Hz) and methyl protons at 0.90 and δ 0.95 ppm. *Anal.* Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.27; H, 11.52.

Apocyclene and Apobornene.—Apocyclene was prepared from the hydrazone of camphenilone, mp 40–41° (lit.[5b] mp 41–42°). The pmr spectrum displayed a methyl singlet at δ 0.90 ppm. 5,5-Dimethylnorbornene was obtained from Professor D. E. McGreer[24] who prepared it by the method of Berson.[25]

Synthesis of Apocamphor *via* Hydroboration.—To 11.2 ml (75 mol of hydride) solution of 1.13 *M* borane in tetrahydrofuran at 0° was added 4.88 g (40 mol) of 78% pure apobornene (20% apocyclene and 2% 5,5-dimethylnorbornene). The reaction mixture was stirred overnight under nitrogen at 25°. Decomposition of the excess hydride with water and oxidation with 10 ml of 30% hydrogen peroxide and 10 ml of 3 *M* sodium hydroxide at 40° in 2 hr gave 5.88 g (105%) of alcohol after the solvent and apocyclene were removed under vacuum. Oxidation by chromic acid, using the convenient ethyl ether–water two-phase method,[14] at 25° [20 ml of chromic acid solution prepared from 4.0 g (13.4 mol) of sodium dichromate dihydrate and 3 ml of 96% sulfuric acid] for 2 hr gave a 61% yield of apocamphor[26] by glpc, mp 108–110° (lit.[27] mp 109–110°).

Registry No.—*endo*-Camphenilol, 640-54-0; 7,7-dimethyl-2-*exo*-norbornyl chloride, 23758-28-3; 3,3-dimethyl-2-*exo*-norbornyl chloride, 22768-97-4; apobornene, 6541-60-2; mercurial, 23758-30-7; apocamphor, 10218-05-0.

(24) D. E. McGreer, *Can. J. Chem.*, **40**, 1554 (1962).

(25) J. A. Berson, *et al.*, *J. Amer. Chem. Soc.*, **83**, 3986 (1961).

(26) A modified procedure by using 100% excess of chromic acid at 0° for 15 min with vigorous stirring gave 80% isolation yield of apocamphor. A detailed discussion of this modified procedure will be reported in a manuscript now in preparation.

(27) G. Komppa and S. V. Hintikka, *Ber.*, **47**, 936 (1914).

Application of the Hofmann Elimination Reaction to α-, β-, γ-, and δ-Skytanthine[1a]

E. J. EISENBRAUN, H. AUDA, K. S. SCHORNO, AND G. R. WALLER[1b]

Departments of Chemistry and Biochemistry, Oklahoma State University, Stillwater, Oklahoma 74074

H. H. APPEL

Departmento de Quimica, Universidad Tecnica Federico Santa Maria, Valparaiso, Chile

Received November 25, 1968

The four isomers of skytanthine (1α, 1β, 1γ, and 1δ) were converted into quaternary ammonium salts and these were subjected to Hofmann β-elimination reactions. The pronounced differences in product composition are correlated with differences in stereochemistry of the reactants. Conformational differences appear to be important in determining the extent and direction of elimination *vs.* regeneration of tertiary amine. Gas chromatography using on-column reactions permitted study of a few milligrams of sample.

Of the *Skytanthus* alkaloids, β-skytanthine was the first to be subjected to the Hofmann degradation.[2] Later, α-, β-, γ-, and δ-skytanthine were prepared from the corresponding nepetalinic acids, and at least three skytanthine isomers were shown to be present in natural *Skytanthus* oil.[3]

Each quaternary salt derived from a skytanthine isomer can undergo either β elimination to form two possible methines or regeneration of the original amine. The double bond of the methine may appear in an isopropenyl group (*cf.* **3** and **5**) or in the junction of the methylene group to the cyclopentane ring (*cf.* **4** and **6**). However, only four methines result as shown in Scheme I. These studies were greatly facilitated by effecting the elimination reaction directly on a glpc column on a milligram scale.[4a] A second-stage Hofmann degradation readily removes nitrogen from these methines and provides dienes.[4a]

Scheme I shows a dramatic difference between 2α and 2β in direction of elimination. For 2α, only 5% 2-(*S*)-isopropenyl-N,N,5-(*S*)-trimethylcyclopentane-1-(*R*)-methylamine (**3**) resulted, and the main reaction product was N,N-dimethyl-2-*R*-[3-(*S*)-methyl-2-methylene-1-(*R*)-cyclopentane]propylamine (**4**), but 1α was also found. Care was taken to remove any 1α from the starting material 2′α by extraction with ether before conversion to the quaternary hydroxide for pyrolysis. When the Hofmann reaction was applied to 2β, a complete change in olefin proportions to favor an isopropenyl group rather than a methylene group was observed in the formation of 2-(*S*)-isopropenyl-N,N,5-(*S*)-trimethylcyclopentane-1-(*S*)-methylamine (**5**) and N,N-dimethyl-2-(*S*)-[3-(*S*)-methyl-2-methylene-1-(*R*)-cyclopentane]propylamine (**6**). The change in ratio was 65:0.2 (**5**:**6**) compared with 5:72 (**3**:**4**).

These changes in product composition prompted our including γ- and δ-skytanthine (1γ and 1δ) in the study. Pure α- and β-skytanthine (1α and 1β) were obtained from the natural oil. The γ and δ isomers were not available and were synthesized, along with a further supply of 1α, by reducing the appropriate nepetalinic acid to the diol, converting the diol to the ditosylate, and cyclizing this to the corresponding skytanthine isomer by heating with excess methylamine at 100° for 18 hr.[3a] The presence of δ-skytanthine in the natural oil was confirmed by glpc and mass spectroscopic studies, but the γ isomer was absent.[3,4b] These findings are of interest in the biogenesis of the methylcyclopentane monoterpenoid alkaloids.[4a]

The drastic change in methine yield in comparing 2α and 2β with 2γ and 2δ is notable. Regeneration of the starting skytanthine is the major outcome of the Hofmann reaction with 2γ and 2δ; the consequent scarcity of methines **3** and **6** necessitated study of these products exclusively by instrumental methods. Pyrolysis of methiodides 2′γ and 2′δ also led to low yields of methines and high yields of regenerated 1γ and 1δ. Other attempts to suppress regeneration of skytanthine isomers by substitution of other strong bases (NaH, $NaOCH_3$) and varying the pyrolysis temperature failed to alter the yield and ratio of products from 2γ and 2δ, even though it is known (and currently confirmed) that, in the Hofmann reaction of 1,2,3,4-tetrahydroquinoline, β elimination *vs.* regeneration of the tertiary amine can be altered by changing the reaction temperature.[5]

The different outcome of the pyrolysis of quaternary hydroxides 2α, 2β, 2γ, and 2δ may be rationalized with the aid of Dreiding models which show differences in both the preferred conformations and the resulting torsional angles of protons β to nitrogen. Newman projections are shown in Table I.

The chair models for 2α with *cis* ring junctions show both A_1 and B_1 to be reasonable ground-state conformations. Form A_1, with an equatorial C-4 methyl group and axial C-4 proton, does not present a favorable torsional angle for *anti* elimination[6a] to **3**. In contrast,

(1) (a) Supported by NIH Grant GM-11144 and NSF Grant GB-5607. (b) In part.

(2) (a) C. Djerassi, J. P. Kutney, and M. Shamma, *Chem. Ind.* (London), 210 (1961); (b) *Tetrahedron*, **18**, 183 (1962); (c) C. G. Casinovi, J. A. Garbarino, and G. B. Marini-Bettòlo, *ibid.*, **17**, 253 (1961).

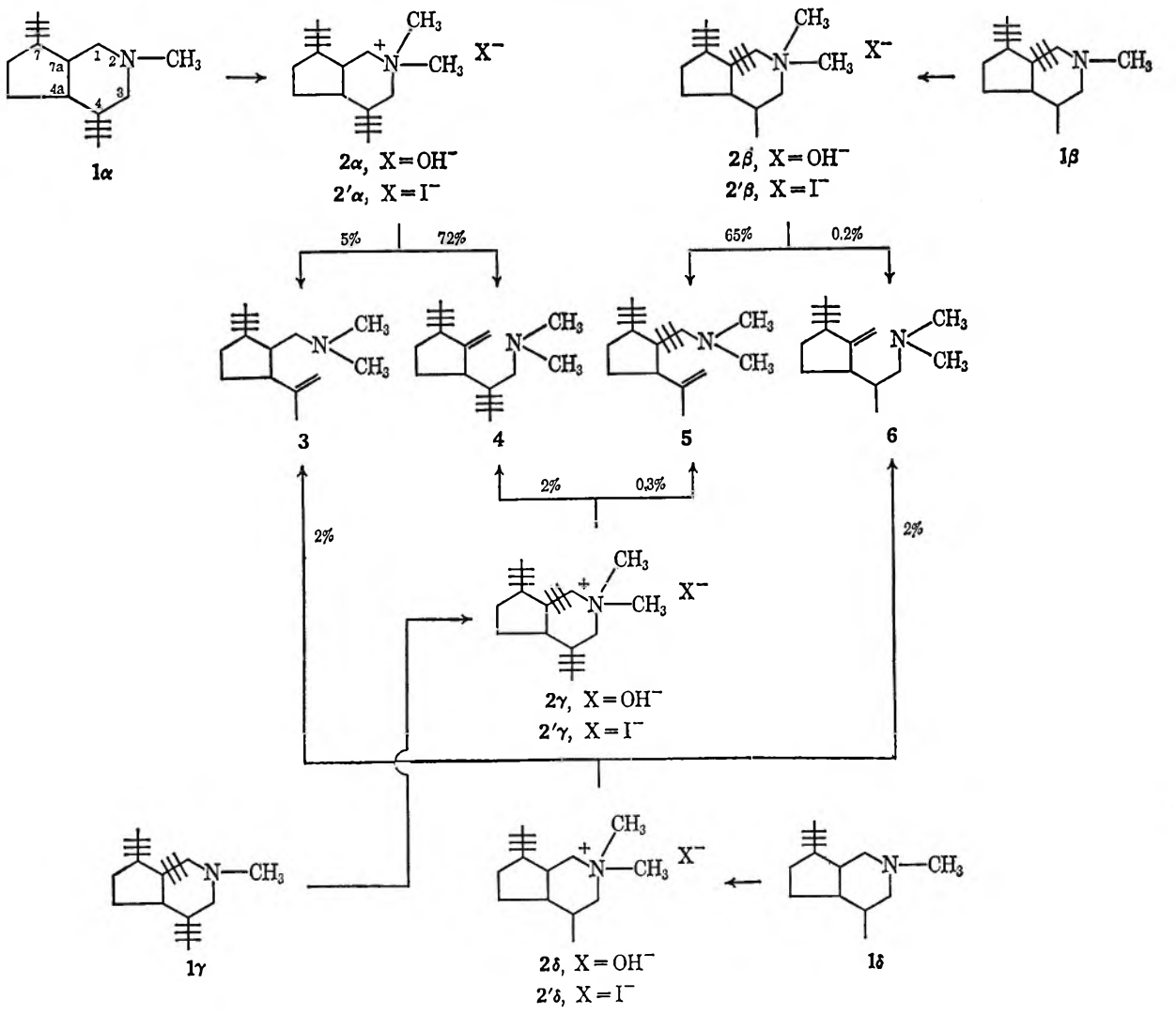
(3) (a) E. J. Eisenbraun, A. Bright, and H. H. Appel, *Chem. Ind.* (London), 1242 (1962). (b) C. G. Casinovi, F. Delle Monache, G. B. Marini-Bettòlo, E. Bianchi, and J. A. Garbarino, *Rend. Ist. Super. Sanita* (Ital. Ed.), **25**, 487 (1962).

(4) (a) H. Auda, H. R. Juneja, E. J. Eisenbraun, G. R. Waller, W. R. Kays, and H. H. Appel, *J. Amer. Chem. Soc.*, **89**, 2476 (1967). (b) Comparison of gas chromatography records for synthetic 1δ, the natural oil, and this oil enriched with 1δ showed the 1δ isomer as a small peak immediately following that for 1β in the gas chromatogram of the natural oil. The mass spectrum of natural 1δ was identical with that of synthetic 1δ.

(5) (a) A. C. Cope, *Org. React.*, **11**, 317 (1960); (b) J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.*, **1**, 225 (1962); (c) D. J. Cram, F. D. Greene, and C. H. Depuy, *J. Amer. Chem. Soc.*, **78**, 790 (1956).

(6) (a) The most favorable situation for *anti*-elimination reactions is a planar four-center transition state with an 180° torsional angle between the β proton and the departing nitrogen atom. (b) For favorable *syn*-elimination reactions, this torsional angle should be near zero. (c) J. Závoda and J. Sicher, *Collect. Czech. Chem. Commun.* **32**, 3701 (1967); (d) M. Pankova, J. Závoda, and J. Sicher, *Chem. Commun.*, 1142 (1968); (e) J. L. Coke, M. P. Cooke, Jr., and M. C. Mourning, *Tetrahedron Lett.*, 2247 (1968); (f) D. S. Bailey and W. H. Saunders, Jr., *Chem. Commun.*, 1598 (1968); (g) D. H. Froemsdorf and H. R. Pinnick, Jr., *ibid.*, 1600 (1968); (h) G. G. Ayerst and K. Schofield, *J. Chem. Soc.*, 3445 (1960).

SCHEME I



the equatorial C-7 a proton of form A_1 provides an *anti* orientation to yield **4** as the observed major product. Yields of methine products are shown in Scheme I. Since **4** is the major product from 2α, form A_1 apparently resembles the most likely transition-state conformation for β elimination despite the unfavorable 1,3 interaction between the N-methyl and C-7 proton. A transition state leading from form B_1 to **3** would suffer from a severe *syn*-axial interaction of the methyl groups at C-4 and on nitrogen, and, in fact, **3** is found only to the extent of 5%. Form B_1, with an axial methyl group and equatorial proton at C-4, has a favorable (near 180°) torsional angle for β elimination from *cis*-2α to give methine **3**. The C-7a proton is considerably more hindered in form B_1 compared with form A_1.

It is pertinent that Hofmann degradation was reported to yield the methines **7a**, **7b**, **7c**, and **7d** from the corresponding piperidines and none of the isomeric methine with a methylene group attached to the ring.[6h] These results emphasize the importance of steric effects introduced by the presence of C-methyl substituents in the examples of Scheme I and Table I.

Similar analysis of the boat forms for 2α shows unfavorable torsional angles or severe steric hindrance so that these conformations are less likely.

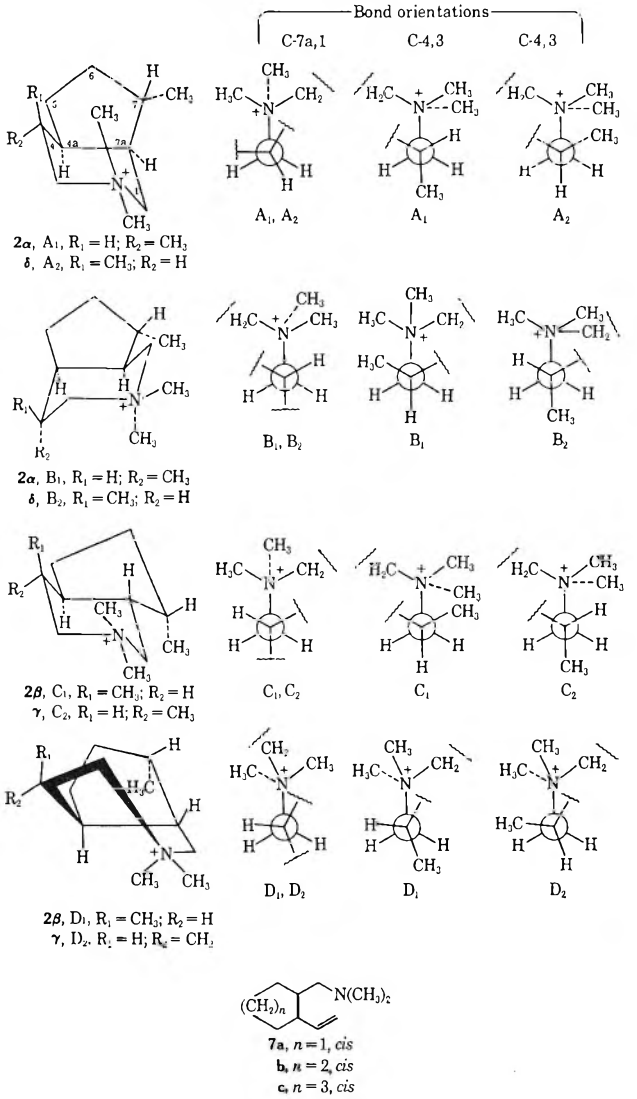
In 2β, form C_1 represents a chair model with a *trans* ring junction, and since a favorable torsional angle (180°)[6a] is observed for the equatorial C-4, a high yield (65%) of β elimination to **5** seems reasonable. *syn* elimination of the C-7a proton is considered unlikely owing to an unfavorable (*ca.* 60°) torsional angle,[6b] whereas relief of the 1,3-*syn*-axial C-4 methyl and N-methyl interaction in form C_1 facilitates formation of **5**.

Form D_1, a twisted boat, represents another model of 2β and shows a *ca.* 90° torsional angle for C–4 proton and approximately the same angle for the C-7a proton. Neither of these is favorable for β elimination.[6a,b]

The 2γ isomer with a *trans* ring junction is shown as the chair form C_2. This form may be compared to form C_1 of 2β, the two differing only in the configurations of C-4. However, inversion at this point destroys the stereochemistry favorable for *anti* elimination toward **5**. There results a change in ratio of products 2:0.3 (**4**:**5**) from 2γ compared with that of 0.2:65 (**6**:**5**) from 2β. Even more marked is the large drop in yield (to 2.3%) of *both* elimination products **4** and **5**, the formation of neither of which is now conformationally favored as an *anti* elimination, so that the major product from 2γ is the regenerated tertiary amine 1γ. A boat model (form D_2) does not appear to give better torsional angles[6a] for the elimination of a proton from C-4 or C-7a.

TABLE I

CONFORMATIONS AND NEWMAN PROJECTIONS FOR HYDROXIDES 2α, 2β, 2γ, AND 2δ



7a, $n = 1$, *cis*
b, $n = 2$, *cis*
c, $n = 3$, *cis*
d, $n = 3$, *trans*

The 2δ isomer is related to 2α by inversion of the methyl group at C-4 to give form A_2 or B_2. The model for form A_2 shows severe *syn*-axial interactions between N-methyl and axial C-4 methyl as well as the C-7 methine group. Thus, though the torsional angles for the equatorial C-4 proton (*ca.* 180°) and the C-7a proton in form A_2 are favorable and would be expected to give the observed 1:1 ratio (3:6) of olefins, the total yield of olefins is understandably low because a transition state corresponding in conformation to A_2 is disfavored by steric interactions. An arrangement with equatorial C-4 methyl (form B_2) is stable but for this conformation the torsional angles for both β-protons become unfavorable for elimination (*ca.* 80–120°),[6a,b] and the corresponding transition state leads to regeneration of tertiary amine **1δ**, which is, in fact, the main product of the reaction, olefins **3** and **6** being obtained in only 2% yield each.

Several eliminations from quaternary ammonium salts previously thought to proceed exclusively through an *anti* mechanism are now known to yield products which must arise through a *syn* mechanism.[6c-g] However, no studies demonstrating that a hetero quaternary nitrogen participates in *syn*-β elimination have appeared, and our results appear to favor the *anti* process. A *syn* process cannot be conclusively ruled out, but it would require acceptance of considerable deviation from the necessary eclipsing to permit elimination to olefin.

Experimental Section

Preparation of α-, β-, γ-, and δ-Skytanthine (1α, 1β, 1γ, and 1δ). A.—Isolation of 1α and 1β.—These were isolated by preparative gas chromatography of the steam-volatile oil from *Skytanthus acutus*[3] on a 15 ft × 0.5 in. column containing base-washed 80–100 mesh Chromosorb W coated with 15% Carbowax 20M heated at 130°. The retention times were 10 and 15 min, respectively, and the peak ratio was 1:9.

B.—Preparation of 1γ and 1δ.—These were prepared as previously reported.[3a] Their retention times were 26 min for 1γ and 25 min for 1δ.[7] The mass spectra[8] for 1α, 1β, 1γ, and 1δ are represented in Table II.

TABLE II

MASS FRAGMENTATIONS[a] OF 1α, 1β, 1γ, 1δ, 3, 4, 5, AND 6

	% ionization							
m/e	1α	1β	1γ	1δ	3	4	5	6
43	18	19	3	19				
44					10	12	24	6
58[b]	81	100	75	72	100	100	100	100
67	10	13	6	11				
81	9	13	5	1				
82					4	2	4	6
84	13	14	6	18				
98					6	1	16	13
110	1	12	15	12	4	1	3	8
124					3	2	2	2
138					3	1	2	1
152	20	22	20	23	3	1	5	1
166	100	100	100	100	6	3	11	3
167[c]	50	50	85	47				
181[c]					8	2	5	4

[a] See ref 8. [b] $[CH_2 \cdots N(CH_3)_2]^+$. [c] Parent ion.

α-, β-, γ-, and δ-Skytanthine Methiodides (2′α, 2′β, 2′γ, and 2′δ).—These were prepared in yields comparable to those previously reported[2a,b,4] and were purified by crystallization from ethanol and washed with ether before further use (Table III).

TABLE III

		Found[a]	
	Mp, °C	% C	% H
2′α	237–239	46.42	7.84
2′β	. . .[b,c]	46.23[d]	7.68[d]
2′γ	308–310	46.90	8.02
2′δ	303–305	46.84	8.25

[a] Calcd for $C_{12}H_{24}NI$: C, 46.60; H, 7.82; N, 4.56. [b] Lit.[2a,b] 296–298°. [c] Lit.[4] 293–295°. [d] Found: N, 4.45.

Conversion of 2′α, 2′β, 2′γ, and 2′δ to the Hydroxides 2α, 2β, 2γ, and 2δ.—The methiodides 2′α, 2′β, 2′γ, and 2′δ were converted to 2α, 2β, 2γ, and 2δ as described[2a,b,4a] except that water was removed by lyophilization. The methohydroxide concentrates were used as such.

Pyrolysis of 2α, 2β, 2γ, and 2δ to Methines 3, 4, 5, and 6.—The concentrates of 2α, 2β, 2γ, and 2δ were pyrolyzed at 180°

(7) A 0.25 in. × 10 ft glass column packed with base-washed 60–80 mesh Chromosorb P coated with 15% Carbowax 20M was used. The temperatures of the column, injector, and detector were 130, 210, and 280°, respectively.

(8) (a) The column,[7] separator, injector, and ion source of a prototype of the LKB-900 mass spectrometer–gas chromatograph were kept at 130–140, 250, 210, and 290°, respectively. (b) For the mass spectrum of **1β**, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, "Alkaloids," Holden-Day, Inc., San Francisco, Calif., 1964, pp 225, 226.

(1 mm) in small round-bottomed flasks[2a,b] or inside the injection port of the gas chromatograph.[4] Relative yields of **3**, **4**, **5**, and **6** were determined by planimeter measurement of glpc peak areas and are reported in Scheme I. The yields of recovered **1α**, **1β**, **1γ**, and **1δ** relative to total methine were 23, 35, 98, and 96%, respectively, and their retention times were 19, 25, 25, and 26 min on the 10 ft × 0.25 in. Carbowax 20M column.[7] Under the same conditions, **3**, **4**, **5**, and **6** showed 18, 22, 20, and 19 min retention, respectively. Samples of **4** and **5** were purified by preparative gas chromatography.[7] Some spectral properties follow.

Methine **4**: ir (liquid film) 2950, 2850, 2775, 2750, 1460, 1380, 1260, 1040, 880, 845 cm^{-1}; $[\alpha]^{23}D$ +139° (*c* 0.2, $CHCl_3$); nmr[9] (neat) δ 4.8 (m, 2), 2.1 (s, 6), 2.0 (s, 2), 1.0 (d, 3, J = 6 Hz), and 0.7 (d, 3, J = 6 Hz). *Anal.* Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79. Found: C, 79.17; H, 12.82.

(9) The nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The infrared spectra were determined with a Beckman IR-5a spectrometer.

5:[2a,b] ir (liquid film) 2950, 2850, 2775, 2750, 1650 (6.05 μ),[2b,4a] 1460, 1380, 1270, 1050, 1030, 885 (11.30 μ);[2b,4a] nmr (CCl_4) δ 4.7 (m, 2), 2.1 (s, 6), 1.65 (m, 3), 0.85 (d, 3, J = 6 Hz).[10]

Peaks from the mass spectra of **3**, **4**, **5**, and **6** are reported in Table II.

Registry No.—**1α**, 2065-32-9; **1β**, 2232-27-1; **1γ**, 23912-39-2; **1δ**, 2883-89-8; **2′α**, 23912-41-6; **2′γ**, 23912-42-7; **2′δ**, 23912-43-8; **3**, 23912-44-9; **4**, 23912-45-0; **5**, 23912-46-1; **6**, 23912-47-2.

Acknowledgment.—We thank Dr. E. L. Eliel for his advice and many helpful suggestions, and Dr. O. C. Dermer, who also read the manuscript. The partial support of the National Research Foundation through GB-5607 and the American Petroleum Institute through API Research Project 58A is gratefully acknowledged.

(10) We acknowledge a prior nmr determination by H. R. Juneja.

Bufadienolides. 1. Introduction and Base-Catalyzed Condensation of Methyl Ketones with Glyoxylic Acid[1]

GEORGE R. PETTIT[2]

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

BRIAN GREEN AND GEORGE L. DUNN

Department of Chemistry, University of Maine, Orono, Maine 04473

Received February 11, 1969

Introduction to a series of contributions pertaining to syntheses of isocardenolides, cardenolides, isobufadienolides, and bufadienolides is presented. A comprehensive study of an aldol condensation between glyoxylic acid and various methyl ketones is described. At high hydroxyl ion concentration, methyl β-naphthyl ketone gives bis(β-naphthacyl)acetic acid (**11a**), but by careful control of pH the condensation can be directed to yield the γ-ketoacrylic acid **16a** and/or a mixture of α-hydroxy-γ-oxobutyric acid (**15a**) and α-methoxy-γ-oxobutyric acid (**17a**). The reaction is applied to methyl cyclopentyl ketone, 2,5-dimethoxyacetophenone, 2,4-dimethylacetophenone, pinonic acid (**18**), and the steroidal ketones, 3β-hydroxy-20-oxo-5-pregnene (**7a**) and 3β-hydroxy-20-oxo-5α-pregnane (**24a**).

Ch'an su, the dried venom of a common Chinese toad, and extracts of the Mediterranean plant *Scilla maritima* (white squill) have received varied application in primitive medical practice for at least several millennia. The latter has been used from *ca.* 3500 B.C.[3] in the form of active glycoside extracts, principally for its diuretic and heart effects, but by the middle ages applications of the drug had gradually subsided. The heart effects were rediscovered in the early 18th century, but, with introduction of digitalis glycosides about 1785,[4] the plant was again gradually abandoned. The pioneering chemical investigations of Stoll[5] with the squill glycosides and Wieland[6] with extracts from the European toad *Bufo vulgaris* led, respectively, to structures for scillaren A,[7] bufotalin[8] (**1a**), and bufalin[9] (**1b**). The aglycones proved to be steroids bearing an α-pyrone ring at position 17 (*cf.* **1a**).[10,11]

Characteristic chemical and physiological[12] features of the plant and toad steroidal α-pyrones appear in bufalin (**1b**). In 1957, when the present study was initiated, neither bufalin nor any naturally occurring bufadienolide had yielded to total synthesis, and indeed no method was available for preparing even simpler 5-substituted 2-pyrones, such as **3**. Since then a preliminary account of the synthesis of a steroidal α-pyrone of the bufadienolide type has been reported,[13] and recently Sondheimer described a synthesis of

(1) Steroids and Related Natural Products. XLVIII. For the preceding contribution, see J. C. Knight and G. R. Pettit, *Phytochemistry*, **8**, 477 (1969). This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-06 and CA-10115-01 to CA-10115-02 from the National Cancer Institute, and is based, in part, on the Ph.D. dissertation submitted in June 1962 by G. L. Dunn to the University of Maine.

(2) To whom correspondence should be addressed.

(3) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., 1963.

(4) A. Stoll, *Chem. Ind.* (London), 1558 (1959).

(5) A. Stoll, E. Suter, W. Kreis, B. B. Bussemaker, and A. Hofmann, *Helv. Chim. Acta*, **16**, 703 (1933).

(6) H. Wieland and F. J. Weil, *Chem. Ber.*, **46**, 3315 (1913).

(7) A. Stoll and J. Renz, *Helv. Chim. Acta*, **24**, 1380 (1941).

(8) For leading references, see K. Meyer, *ibid.*, **32**, 1993 (1949).

(9) Isolation and structural determination of bufalin was reported by K. Kuwada [*J. Chem. Soc. Jap.*, **60**, 335 (1939); *Chem. Abstr.*, **34**, 1031 (1940)] and was confirmed by K. Meyer [*Helv. Chim. Acta*, **32**, 1238 (1949)].

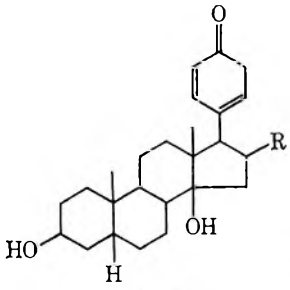
(10) In the case of hellebrigenin, the same aglycone has been found in both a plant extract and toad venom. For this and other interesting facets of bufadienolide chemistry, see ref 3 and other reviews cited therein.

(11) Subsequent extensive studies of Ch'an su, particularly by K. Meyer and colleagues, has led to location and identification of a number of related bufadienolides in this material, the most recent being 19-oxocinobufagin and 19-oxocinobufotalin: K. Meyer, *ibid.*, **52**, 1097 (1969).

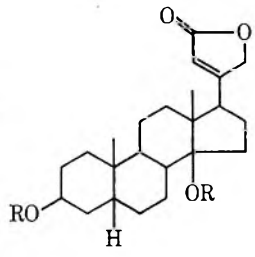
(12) The cardiac action of bufalin has been found almost equal to that of digitoxigenin (**2**) and in respect to local anesthetic potency on the rabbit cornea, *ca.* 90 times that of cocaine; see M. Okada, F. Sakai, and T. Suga, *Itsuu Kenkyusho Nempo*, **67**, 75 (1960); *Chem. Abstr.*, **55**, 16798 (1961). The bufadienolides generally display digitalis-like activity; *e.g.*, see K. K. Chen and A. Kovařikova, *J. Pharm. Sci.*, **56**, 1535 (1967); H. Murase, *Jap. J. Pharmacol.*, **15**, 72 (1965); *Chem. Abstr.*, **63**, 7517 (1965); W. Foerster, *Acta Biol. Med. Ger.*, **9**, 341 (1962); *Chem. Abstr.*, **58**, 11846 (1963).

(13) D. Bertin, L. Nedelec, and J. Mathieu, *Compt. Rend.*, **253**, 1219 (1961).

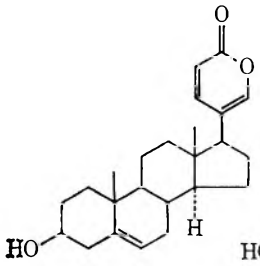
bufalin and resibufogenin.[14] With the objective of making bufadienolides more readily available for biological evaluation,[15] we decided to develop a practical synthesis of bufadienolides (*cf.* **3**) and complete a total synthesis of bufalin (**1b**). For reasons already apparent, the bufadienolide intermediates were also to be employed whenever appropriate for construction of cardenolide-type[4,16] lactones.



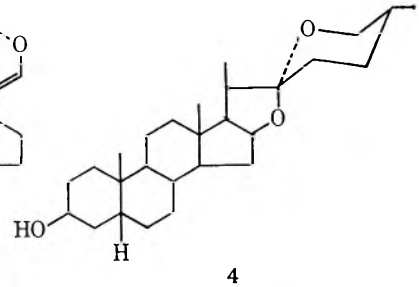
1a, R = $COOCH_3$
b, R = H



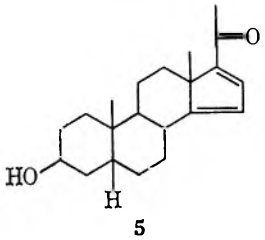
2



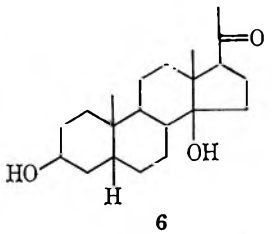
3



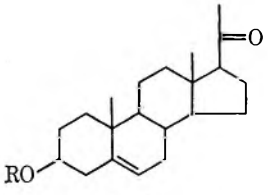
4



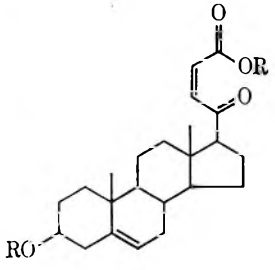
5



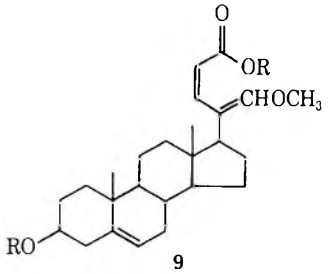
6



7a, R = H
b, R = $COCH_3$
c, R = $(C_6H_5)_3C$
d, R = CH_3OCH_2
e, R =



8



9

As originally conceived, smilagenin (**4**) was to serve as relay for obtaining diene **5** (alternatively prepared by a total synthetic sequence) and then 20-oxopregnane **6**. Simultaneously, pregnenolone (**7a**) was to be used to develop a general synthesis of bufadienolides which could be applied to bufalin intermediate **6**. Degradation of smilagenin to diene **5** was readily accomplished,[17] and, with completion of a total synthetic route to the steroidal sapogenins by Sondheimer and colleagues, formal total synthesis in turn of diene **5** was at hand. Experiments in progress to convert diene **5** into 14β alcohol **6** were discontinued when the Meister[18] and Sondheimer[19] synthesis of digitoxigenin (**2**) presented the possibility of using the glycoside digitoxin as a starting point for total synthesis of bufalin. Meanwhile, transformation of pregnenolone to γ-ketoacrylic acid **8** was being explored as summarized below, with the object of entering ketone **8** in a Wittig reaction leading to vinyl ether **9**, as noted in part 4.[20] An acidification sequence was then expected to provide the corresponding α-pyrone. Before a satisfactory procedure was uncovered for obtaining **9**, the isobufadienolide and bufadienolide syntheses described in parts 6 and 7 were completed.[21] Reduction of ketone **8** to isocardanolide and isocardenolide systems did proceed as planned and culminated in the lactone syntheses described in parts 2 and 3.[22]

The pressing requirement for an efficient route to 20-oxo-21-nor-22-cholenic acids suggested the exploration of an aldol condensation between methyl ketones and glyoxylic acid, despite the fact that no practical one-step conversion of this type had been reported. Shortly afterward, Newman[23] described the base-catalyzed condensation of a glyoxylate with the cyclic ketone α-tetralone to give an analogous product.[24] Later, Noltes and Kögl[25] found that heating the diethyl

(14) F. Sondheimer, W. McCrae, and W. J. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969). A review of 2-pyrone syntheses has been prepared: N. P. Shusherina, N. D. Dmitrieva, E. A. Luk'yanets, and R. Y. Levina, *Russ. Chem. Rev.*, **36**, 175 (1967).

(15) Our interest in 1957 was strongly motivated by reports that certain α,β-unsaturated lactones inhibit cell growth: L. J. Haynes, *Quart. Rev.* (London), **2**, 46 (1948). Since then, antitumor properties have been attributed to cardenolides [S. M. Kupchan, M. Mokotoff, R. S. Sandhu, and L. E. Hokin, *J. Med. Chem.*, **10**, 1025 (1967)], bufadienolides [S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *Tetrahedron Lett.*, 149 (1968)], and other lactones [S. M. Kupchan, R. W. Doskotch, P. Bollinger, A. T. McPhail, G. A. Sim, and J. A. Saenz Renauld, *J. Amer. Chem. Soc.*, **87**, 5805 (1965); J. E. Pike, J. E. Grady, J. S. Evans, and C. G. Smith, *J. Med. Chem.*, **7**, 348 (1964)].

(16) T. Reichstein, *Naturwissenschaften*, **54**, 53 (1967).

(17) G. R. Pettit and D. M. Piatak, *Can. J. Chem.*, **44**, 844 (1966). Results of an analogous study have recently been reported: G. Bach, J. Capitaine, and C. R. Engel, *ibid.*, **46**, 733 (1968); R. Bouchard and R. Engel, *ibid.*, **46**, 2201 (1968).

(18) P. D. Meister and H. C. Murray, U. S. Patent 2,968,596 (1961); *Chem. Abstr.*, **55**, 11,466 (1961).

(19) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966).

(20) G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, **35**, 1385 (1970).

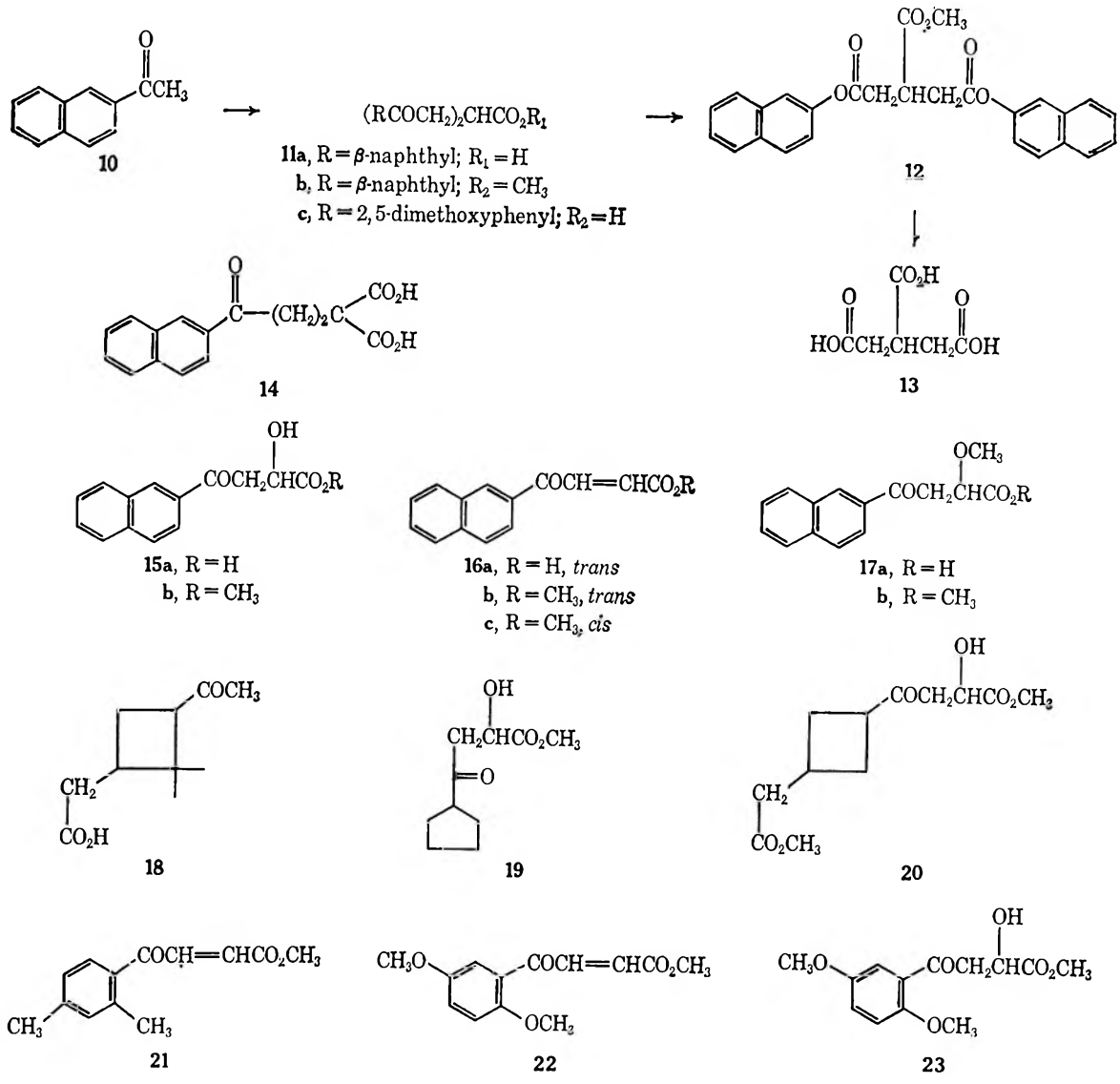
(21) (a) G. R. Pettit, J. C. Knight, and C. L. Herald, *ibid.*, **35**, 1393 (1970); (b) G. R. Pettit, D. Fessler, K. Paull, P. Hofer, and J. C. Knight, *ibid.*, **35**, 1398 (1970).

(22) (a) G. R. Pettit, B. Green, and G. L. Dunn, *ibid.*, **35**, 1377 (1970); (b) G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *ibid.*, **35**, 1381 (1970).

(23) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *ibid.*, **23**, 1832 (1953).

(24) A study of the condensation of aqueous glyoxylic acid with 17-oxo-androstanes has been made: P. Kurath and W. Cole, *ibid.*, **26**, 1939 (1961). We wish to thank Dr. Kurath for allowing us to review this manuscript prior to publication.

(25) A. W. Noltes and F. Kögl, *Rec. Trav. Chim. Pays-Bas*, **80**, 1334 (1961); see also P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 4592 (1961).



acetal of ethyl glyoxylate with a variety of ketones yielded α-hydroxy-γ-oxobutyric acid esters which could be dehydrated to the corresponding acrylic acids. Early attempts to condense glyoxylic acid with methyl ketones of the acetophenone type had yielded, instead of acrylic acid derivatives, bis(phenacyl)acetic acids,[26] presumably by Michael condensation of the initially formed acrylic acid with a second molecule of methyl ketone.

To determine whether a normal aldol condensation could occur, a number of reactions utilizing methyl β-naphthyl ketone[27] and glyoxylic acid or a glyoxylate were evaluated. Prior to appearance of the Newman procedure,[23] glyoxylic acid and aqueous solutions of the acid were prepared by treating barium glyoxylate with sulfuric acid. Concurrently, the more readily characterizable butyl glyoxylate (from lead tetraacetate cleavage of di-*n*-butyl tartrate) was also employed. Among a variety of acid-[28] and base-catalyzed[29] aldol conditions studied, only those reactions employing butyl glyoxylate and methyl β-naphthyl ketone, in ethyl alcohol containing 10% aqueous sodium hydroxide, gave reasonable amounts of acidic condensation products. The colorless carboxylic acid $C_{26}H_{20}O_4$ obtained was the product (**11a**) arising from Michael addition[26] of ketone **10** to the initially formed γ-ketoacrylic acid, and conclusive evidence for the bis(β-naphthacyl)acetic acid structure was obtained as follows. Acid **11a** was methylated with diazomethane and ester **11b** was treated with peroxytrifluoroacetic acid.[30] The resulting triester **12** was saponified and, following acidification, both β-naphthol and tricarballylic acid (**13**) were isolated. Assignment **11a** was further supported by an unequivocal synthesis in which diethyl malonate was condensed with ω-bromo-2-acetonaphthone and the product was saponified to provide the disubstituted malonic acid **14**, which on partial decarboxylation gave acetic acid derivative **11a**.[31]

Repeating the aldol route to acid **11a** in aqueous tetrahydrofuran–methanol at pH 14 using glyoxylic acid prepared[23] *in situ* from tartaric acid afforded bis(β-

(26) M. J. Bougault, *Compt. Rend.*, **148**, 1270 (1909).

(27) Structure of the acrylic acid **16** which would be obtained from this ketone was firmly established: G. Baddeley, G. Holt, S. M. Maker, and M. G. Ivinson, *J. Chem. Soc.*, 3605 (1952); M. Goldman and E. I. Becker, *Nature*, **170**, 35 (1952); *Chem. Abstr.*, **48**, 116 (1954).

(28) Z. Csuros, J. Petro, and P. Konig, *Acta Chim. Acad. Sci. Hung.*, **17**, 419 (1958); *Chem. Abstr.*, **53**, 17,053 (1959).

(29) For a comprehensive review of the aldol condensation, see A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

(30) W. D. Emmons and G. D. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

(31) An analogous sequence has been used to prepare bis(phenacyl)-acetic acid: W. Kues and C. Paal, *Chem. Ber.*, **19**, 3144 (1886).

naphthacyl)acetic acid in 65% yield. Under these strongly alkaline conditions, 2,5-dimethoxyacetophenone was easily transformed into acetic acid derivative **11c**. Application of conditions similar to those of Newman,[23] *i.e.*, lower pH, gave α-hydroxy-β-(2-naphthoyl)propionic acid (**15a**, 23%) accompanied by a lesser quantity of β-(2-naphthoyl)acrylic acid (**16a**). Heating the α-hydroxy acid in acetic anhydride with potassium hydrogen sulfate[25] gave acrylic acid **16a** in 33% yield.

Meanwhile, attempts were being made to condense aqueous glyoxylic acid obtained by the Newman method[23] with methyl ketones of the 20-oxopregnane type at various pH levels as noted below, and values (pH meter) of 13.25–13.65 were found most useful in effecting only the aldol condensation and avoiding further reaction to disubstituted acetic acids. Best conversion into acidic products was obtained at pH 13.65 (meter) in tetrahydrofuran–methanol containing 8% aqueous potassium hydroxide for 3 days at room temperature. By this means ketone **10** was transformed in up to 90% conversion into a mixture of three acids, which were esterified and separated by chromatography to give methyl esters **16b** (17%), **17b** (57%), and **15b** (10%). The unexpected ester **17b** exhibited strong infrared absorption at 1130 cm^{-1} characteristic of the carbon–oxygen bond in aliphatic ethers[32] and was deduced to be the product of addition of methanol to acrylic acid **16a**. Elemental analyses gave further support, and alternate preparation by methylation of α-hydroxy ester **15b** using diazomethane–boron trifluoride provided the necessary confirmation.[33]

Extension of the aldol condensation with glyoxylic acid to methyl cyclopentyl ketone and pinonic acid (**18**) gave comparable results, but only the α-hydroxy esters were characterized. Following methylation (diazomethane), the acid(s) from methyl cyclopentyl ketone and pinonic acid yielded α-hydroxy esters **19** (52%) and **20** (72%), respectively, as oils.

The principle objective, efficient conversion of ketone **10** into acrylic acid **16a**, was eventually achieved by allowing the aldol condensation to proceed for 12 hr at reflux temperature. The acidic products obtained in this way from β-naphthyl ketone, 2,4-dimethylacetophenone, and 2,5-dimethoxyacetophenone were methylated to furnish acrylates **16b**, **21**, and **22** in yields of 56–59%. The relative proportions of both aldol intermediates and methanol addition products were considerably smaller, as shown by careful investigation of the products from 2,5-dimethoxyacetophenone, which led to isolation of methyl α-hydroxy-β-(2,5-dimethoxybenzoyl)propionate (**23**) in 9% yield. Thin layer chromatography indicated the presence of a very small amount of the α-methoxy ester.

Shortly after the glyoxylic acid reaction with methyl ketones had reached a practical state of development, Bestmann reported[34] a valuable synthesis of γ-keto acrylic acids based on the condensation of an α-bromo ketone with carbomethoxymethylenetriphenylphosphorane. Application of this reaction to ω-bromo-2-acetonaphthone gave *trans*-methyl acrylate **16b** in 38% conversion. Irradiation of a solution of this yellow[35] product gave the colorless *cis* isomer **16c**. Side-chain olefin protons of the yellow isomer exhibited a coupling constant of 15 cps whereas the colorless isomer gave in the same region $J = 11$ cps, consistent with the assigned configurations.[36] While this general study of aldol-type reactions involving methyl ketones and glyoxylic acid was being undertaken, the model experiments now summarized were also being conducted.

Aldol condensation between benzaldehyde and 20-oxopregnenes using, *e.g.*, sodium methoxide in methanol, follows the predicted course and presents no problem.[37] However, a considerable number of experiments directed at condensing butyl glyoxylate or glyoxylic acid with 20-oxopregnanes **24a** or **7a** were quite unrewarding, leading in most cases to almost complete recovery of starting material. When the more general study of methyl ketones began to focus on aqueous glyoxylic acid prepared from tartaric acid,[23,24] it was decided to apply this method to suitable 5α- and Δ^5-20-oxopregnanes, which were chosen as models for the less readily available 3β-hydroxy-20-oxo-5β-pregnanes. It was originally deemed advisable to protect the 3β-hydroxyl group with a base-stable, acid-labile group, and those evaluated will now be discussed.

Triphenylmethyl chloride in pyridine solution generally favors reaction with a primary alcohol, but substitution of triphenylmethyl bromide can provide, in the case of secondary alcohols, greater than 80% yields of trityl ethers.[38] Modification (24-hr reaction period) of the Stegerhock procedure[38] with secondary alcohol **24a** and triphenylmethyl bromide gave reasonable conversion (53%) into ether[39] **24c**. Similarly, trityl ethers **7c** and **25b** were obtained in comparable yields, but low solubility of the trityl ethers in water–methanol–tetrahydrofuran mixtures caused rejection of this protecting group. In the expectation of a solubility increase in such protic solvent mixtures for a methoxymethyl ether,[40] a specimen of **7d** was obtained (18% yield) by treating pregnenolone (**7a**) with chloromethyl ether in the presence of silver oxide.[41] The

(32) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958.

(33) Alcohol **15a** may represent that portion of the aldol intermediate which did not undergo dehydration, although addition of water to the α,β-unsaturated carbonyl system after dehydration would still be expected to give the α- rather than the β-hydroxy acid. Hydrolysis of methyl β-(*p*-bromobenzoyl)crotonate in hot aqueous methanolic potassium hydroxide solution has been shown to yield α-hydroxy-β-(*p*-bromobenzoyl)butyric acid: W. Koenigs and E. Wagstaffe, *Chem. Ber.*, **26**, 554 (1893). Later experiments of a similar nature with methanol gave comparable results. See, *e.g.*, E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 236 (1950).

(34) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 620 (1961). Experimental details of the reaction were kindly provided by Professor Bestmann prior to publication. Later a full report and review of this useful reaction were made available: H. J. Bestmann, *Angew. Chem. Int. Ed. Engl.*, **4**, 583 (1965).

(35) Previous study of *cis–trans* isomers in β-aroylacrylic acids suggested that the yellow geometrical isomer of acid **7a** could be assigned the *trans* configuration. For a pertinent summary, refer to ref 27 (M. Goldman, *et al.*).

(36) A preliminary account of these stereochemical assignments has been summarized: G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964).

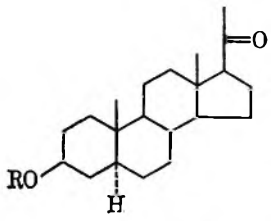
(37) I. Dory and G. Lanyi, *Acta Chim. Acad. Sci. Hung.*, **30**, 71 (1962); *Chem. Abstr.*, **58**, 564 (1963).

(38) L. J. Stegerhock and P. E. Verkade, *Rec. Trav. Chim. Pays-Bas*, **75**, 143 (1956).

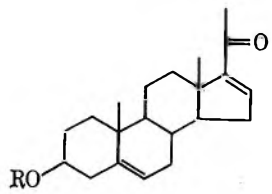
(39) For a related example, see. H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(40) R. Stern, J. English, Jr., and H. G. Cassidy, *J. Amer. Chem. Soc.*, **79**, 5797 (1957). A steroid 11-methoxymethyl ether has been prepared using formaldehyde, methanol, and hydrochloric acid: R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

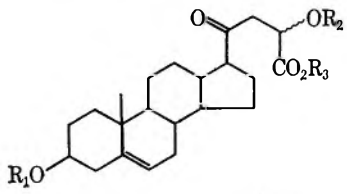
(41) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4553 (1961).



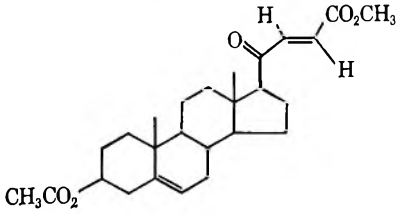
24a, R = H
b, R = $COCH_3$
c, R = $(C_6H_5)_3C$
d, R = 



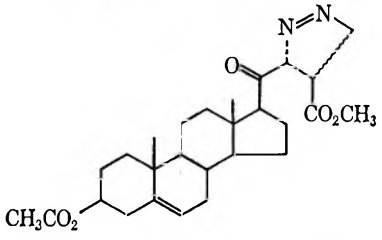
25a, R = H
b, R = $(C_6H_5)_3C$



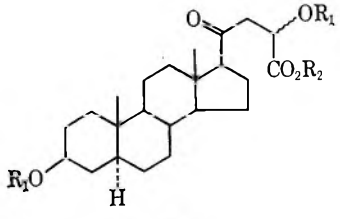
26a, $R_1 = COCH_3$; $R_2 = R_3 = CH_3$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_2 = COCH_3$; $R_3 = CH_3$
d, $R_1 = R_2 =$  ; $R_3 = CH_3$



27



28



29a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = COCH_3$; $R_2 = CH_3$

solubility of ether **7d** and the more efficiently prepared tetrahydropyranyl ethers **24d** and **7e** proved quite favorable, but protecting-group studies were discontinued when use of blocked alcohols in the aldol reactions proved unnecessary.

Meanwhile, effects of potassium hydroxide concentration on the total yield of acidic material from reaction between pregnenolone and aqueous glyoxylic acid at various pH levels were being evaluated. The yield of acidic products increased substantially from 25% at a pH reading of 13.25 to 45% at 13.48 to 81% at 13.65. The procedure involved adding 8% aqueous potassium hydroxide to a solution composed of methanol, tetrahydrofuran, pregnenolone, glyoxylic acid, and water until the required pH scale reading was reached. The acidic product from a reaction at pH 13.48 was methylated with diazomethane and the crude mixture of methyl esters was separated by chromatography. A fraction eluted by benzene–chloroform was acetylated and rechromatographed to give methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 20%), presumably arising by a Michael-type addition of methanol to the aldol condensation product. In addition to elemental composition and spectral data, the structure of ether **26a** was assigned using evidence already reviewed for the analogous product obtained from methyl β-naphthyl ketone.

A fraction eluted with chloroform gave methyl 3β-23-dihydroxy-20-oxo-21-nor-5-cholenate (**26b**, 30%), which was converted into both diacetate **26c** and bistetrahydropyranyl ether **26d**. Formation of these derivatives, combined with information already compiled for the aldol intermediate from methyl β-naphthyl ketone, provided structural evidence for diol **26b**.

The aldol reaction with pregnenolone and glyoxylic acid was repeated at a pH meter reading of 13.65 (optimal base concentration) and studied with respect to time and temperature. After 28 hr at room temperature, the acidic product was isolated, methylated, acetylated, and purified by column chromatography to give methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**27**),[42] methyl ether **26a**, diacetate **26c**, and an oily substance tentatively assigned pyrazoline structure **28** (formed by a 1,3-dipolar cycloaddition of diazomethane to the α,β-unsaturated ketone system).[43] Yields of the first three compounds amounted to, respectively, 5, 11, and 15%.

Extending the condensation to 72 hr increased the total yield of acidic products from 52 to 72%, and, following methylation, acetylation, and purification, olefin **27**, methyl ether **26a**, and diacetate **26c** were obtained in 8, 14, and 19% conversion, respectively. Adjusted for recovered pregnenolone, the respective yields were 15, 18, and 25% accompanied by 6% of the crude pyrazoline. It is apparent that increasing the reaction time increased the total yield of acidic products, but did not markedly affect the proportion of each constituent. Application of this procedure to 3β-acetoxy-20-oxo-5α-pregnane (**24b**) led to 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanic acid (**29a**) as major product, whose structure was confirmed by preparation of the methyl ester (**29b**) and diacetate (**29c**) derivatives; no attempt was made to characterize the minor reaction constituents, which were presumably analogous to those obtained from ketone **7a**. Some indication of the necessity of controlling the base concentration was obtained by treating alcohol **29b** with 5% potassium hydroxide in methanol for a 2-hr period at reflux, at which time *ca.* 25% of the alcohol had undergone reverse aldol condensation.

(42) Evidence for the structure and stereochemistry of olefin **5** has been summarized in a preliminary communication: G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964). A more complete summary is presented in part III.[22b]

(43) Similar reaction products have been investigated: See E. R. H. Jones, *et al.*, ref 33.

The parallel survey of reactions between glyoxylic acid and methyl β-naphthyl ketone by this time had shown that heating the aldol reaction mixture at reflux would increase acrylic acid formation. When pregnenolone was analogously condensed with glyoxylic acid, followed by methylation and acetylation, the yield of methyl ether **26a** and diacetate **26c** fell to, respectively, 1 and 8%. Substituting dimethoxypropane[44] for diazomethane in the methylation step allowed isolation of olefin **27** in *ca.* 20% yield.

Upon reaching this more promising stage for synthesis of γ-keto acrylic acid **27** by an aldol sequence, we were able to meet requirements for this compound by application of the then newly discovered Bestmann reaction.[34] However, the carefully defined experimental conditions reported herein for condensing glyoxylic acid with methyl ketones should prove of value where the α-halo ketone required for the Bestmann procedure cannot easily be obtained or where an aldol intermediate such as diol **29a** is required.

Experimental Section

Ligroin refers to a fraction boiling at 65–70°. Benzene and dihydropyran were redistilled from sodium; pyridine was redistilled from potassium hydroxide. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate or magnesium sulfate. Acetylation reactions were conducted using 1:1 acetic anhydride–pyridine at room temperature for 14–20-hr periods. The basic (Alcoa grade F-20), neutral (E. Merck, Darmstadt), and acid-washed (Merck, Rahway, N. J.) aluminas were used as supplied. Melting points reported for analytical specimens were observed using a Kofler melting point apparatus. All other melting points were determined in open capillaries in a silicone oil bath and are uncorrected. The thin layer chromatograms were prepared on silica gel G (developed with concentrated sulfuric acid) or silica gel HF_{254} (both from E. Merck). All analytical specimens were checked for purity by thin layer chromatography. A Beckman zeromatic pH meter equipped with a Beckmann E-2 glass electrode and a calomel reference electrode was used for pH measurements.

Ultraviolet, infrared (potassium bromide pellets unless noted differently), and nuclear magnetic resonance (Varian A-60 spectrometer) spectra were recorded by Dr. R. A. Hill, University of Maine. The nuclear magnetic resonance data are expressed in parts per million (δ) downfield from tetramethylsilane. The microanalyses were provided by Dr. A. Bernhardt, Max Planck Institute, Mülheim, Germany, and by the laboratory of Dr. C. Janssen, Beerse, Belgium. Optical rotation measurements (chloroform solution) were provided by Dr. Weiler and Dr. Strauss, Oxford, England.

Glyoxylic Acid.—Unless otherwise stated, glyoxylic acid was prepared in the following manner and used immediately without further purification or isolation. To a cooled solution of tartaric acid (5.7 g, 0.038 mol) in water (9 ml) at 0° was added a solution of paraperiodic acid (8.6 g, 0.038 mol) in water (18 ml). Before this glyoxylic acid solution was used, the cleavage reaction was allowed to proceed for 12 min.

Bis(β-naphthacyl)acetic acid (11a). Method A.—To a solution of methyl β-naphtyl ketone (**10**, 2 g, 0.012 mol) in ethyl alcohol (10 ml, 95%) was added *n*-butyl glyoxylate[45] (2 g, 0.015 mol) followed by aqueous sodium hydroxide (10%, 16 ml, 0.04 mol). The mixture was heated for 6 hr at 65–70°, cooled, diluted to 100 ml with water, and extracted with diethyl ether. Acidification of the aqueous layer gave a pale yellow solid, mp 195–198°. Recrystallization from dioxane–water gave colorless plates (1.5 g, 63%), mp 198–199°. Three crystallizations from dioxane–water afforded the analytical specimen: mp 199–200°; ν_{max} 3400–2600 (carboxylic acid), 1700 (carboxyl group), and 1685 cm^{-1} (ketones).

Anal. Calcd for $C_{26}H_{20}O_4$ (mol wt, 396): C, 78.79; H, 5.10. Found: C, 78.23; H, 5.29; neut equiv, 374, 385.

Method B.—A rapidly stirred solution of methyl β-naphthyl ketone (**10**, 3.4 g, 0.02 mol) in tetrahydrofuran (35 ml)–methanol (50 ml) was treated successively with aqueous potassium hydroxide (12.6 g in 54 ml of water) and a solution of glyoxylic acid (0.02 mol) prepared by the general procedure described above. After addition of water (25 ml), a hydrogen ion measurement showed pH >14.0.

After 16 hr (with stirring) at room temperature, the solution phase was filtered to remove inorganic salts and evaporated *in vacuo* to the point of turbidity. Dilution with water (200 ml) and extraction with diethyl ether gave upon evaporation methyl β-naphthyl ketone (0.1 g). The aqueous suspension was acidified with concentrated hydrochloric acid and extracted with chloroform. Evaporation of the water-washed and dried extract gave the disubstituted acetic acid **11a** as a brown solid,[46] which crystallized from dioxane–water as leaflets (2.55 g, 65%), mp 192–193°.

Methyl Bis(β-naphthacyl)acetic Acid (11b).—To a solution of bis(β-naphthacyl)acetic acid (**11a**, 2.70 g) in dioxane (50 ml) was added excess ethereal diazomethane. The mixture was allowed to stand at room temperature for 6 hr. Diazomethane and ether were removed by warming and the remaining solution was diluted with water. The oil which separated crystallized upon trituration to yield a colorless solid (2.70 g), mp 95–97°. One recrystallization from dioxane–water raised the melting point to 116.5–117.5°. Recrystallization from the same solvent mixture gave an analytical specimen, mp 117.3–118°.

Anal. Calcd for $C_{27}H_{22}O_4$: C, 79.00; H, 5.40. Found: C, 79.05; H, 5.09.

Baeyer–Villiger Oxidation of Methyl Bis(β-naphthacyl)acetate (11b).—A solution of trifluoroperacetic acid prepared from trifluoracetic anhydride (1.7 ml, 0.012 mol) and hydrogen peroxide (90%, 0.27 ml, 0.010 mol) in methylene chloride (3 ml) was added with stirring during 15 min to a solution of methyl bis(β-naphthacyl)acetate (**11b**, 1 g, 0.0024 mol) in methylene chloride (15 ml) containing a suspension of dry disodium hydrogen phosphate (3.54 g, 0.005 mol). The yellow mixture was stirred at room temperature for 3 hr and at reflux for 7 hr. Filtration of the warm solution followed by evaporation furnished a yellow residue, which was dissolved in ethyl alcohol (95%, 5 ml) and heated at reflux for 3 hr with aqueous potassium hydroxide (20%, 4.5 ml, 0.015 mol). After evaporative removal of ethyl alcohol *in vacuo*, the aqueous solution was acidified with concentrated hydrochloric acid and the precipitated brown solid was collected (the filtrate was retained; see below) and washed with diethyl ether (two 10-ml portions). The ethereal extract was concentrated to a brown solid, mp 112–116°. One crystallization from water–methanol gave β-naphthol[46] as tan crystals (0.28 g, 40%), mp 119–121°.

The aqueous filtrate was evaporated to dryness and the residue was extracted with boiling chloroform (two 5-ml portions). Evaporation of the filtered chloroform solution furnished a tan solid (**13**, 0.10 g, 23%), mp 155–158°, which proved to be tricarballylic acid, mp 160–162°.

Alternate Synthesis of Bis(β-naphthacyl)acetic Acid (11a).—To a cooled (0°) solution of methyl β-naphthyl ketone (17 g, 0.10 mol) in dry diethyl ether (100 ml) was added, over 30 min, bromine (16 g, 0.10 mol). The brown ethereal solution was washed with water (four 75-ml portions), dried (sodium sulfate), and evaporated to a crystalline solid. Recrystallization from ethyl alcohol (95%) afforded plates (**14**, 14 g, 56%), mp 82–83°, of ω-bromo-2-acetonaphthone (lit.[47] mp 82.5–83.5°).

Absolute ethyl alcohol (38 ml) was added gradually to finely cut sodium (1.3 g, 0.057 mol). When hydrogen evolution was complete, diethyl malonate (9.1 g, 0.056 mol) was added to the vigorously stirred solution followed, during 20 min, by ω-bromo-β-acetonaphthone (14 g, 0.0562 mol) in hot absolute ethyl alcohol (100 ml). After a 2-hr period at reflux (with vigorous stirring), the ethyl alcohol was removed *in vacuo* and the oily brown residue was shaken with aqueous potassium carbonate (10%, 100 ml), followed by methyl alcohol (50 ml). The remaining residue was dissolved in hot benzene, filtered, and evaporated to a yellow oil which was heated at reflux for 2 hr with aqueous potassium hydroxide (20%, 50 ml). The mixture was cooled in ice and acidified with concentrated hydrochloric acid, and the acidic

(44) N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(45) Prepared by cleavage of di-*n*-butyl tartrate with lead tetraacetate according to the method of Vogel: A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1956, p 951.

(46) The structure was confirmed by mixture melting point determination and infrared spectral comparison with an authentic sample.

(47) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).

product was collected by filtration. The air-dried **bis(β-naphthacyl)malonic acid** (**14**, 0.70 g) melted at 137–140° with decomposition.

The crude dicarboxylic acid (0.70 g) was heated at 150° until evolution of gas ceased (15 min), and the dark residue was dissolved in benzene, filtered, and treated with ligroin (1 ml). The brown solid (0.5 g, 79%) which precipitated melted at 193–195° and was identical with the acid **11a**, obtained by condensing methyl β-naphthyl ketone with butyl glyoxylate.

Bis(2,5-dimethoxyphenacyl)acetic Acid (**11c**).—Using the procedure outlined above (method B), 2,5-dimethoxyacetophenone (3.6 g, 0.02 mol) was condensed with glyoxylic acid. The crude, dark solid (3.0 g, 71%), mp 110–115°, gave an analytical specimen after four recrystallizations from isopropyl ether–acetone as colorless rosettes of microneedles: mp 130–131° dec; ν_{max} 3400 (carboxylic acid), 1700 (carboxylic acid), and 1665 cm^{-1} (ketones).

Ancl. Calcd for $C_{22}H_{24}O_8$: C, 63.46; H, 5.81. Found: C, 63.38; H, 5.84.

α-Hydroxy-β-(2-naphthoyl)propionic Acid (**15a**) **and β-Naphthoylacrylic Acid** (**16a**).—To a cooled solution of glyoxylic acid (0.04 mol, 26 ml) was added methyl β-naphthyl ketone (3.4 g, 0.02 mol) in 95% ethyl alcohol (25 ml), followed by an aqueous solution of sodium hydroxide (3 g, 0.075 mol in 54 ml of water). A mixture of 95% ethyl alcohol (50 ml) and water (150 ml) was added to produce homogeneity. The reaction was allowed to proceed for 18 hr at room temperature and at 60° for 10 min. Next the yellow mixture was cooled, diluted with water, and extracted with diethyl ether (two 300-ml portions). The aqueous solution was cooled to 10°, acidified with concentrated hydrochloric acid, and extracted with diethyl ether to provide, after drying and evaporation, a yellow solid (1.5 g). The residue was extracted with hot benzene, and insoluble material (1.1 g, 23%) was crystallized from methanol–water to give colorless crystals of acid **15a**, mp 130–132°. Four recrystallizations from the same solvent mixture yielded a pure sample of **α-hydroxy-β-(2-naphthoyl)propionic acid** (**15a**): mp 132.5–133.5°; ν_{max} 1730 (carboxylic acid) and 1690 cm^{-1} (ketone).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.53; H, 5.01.

The benzene-soluble material consisted of a yellow acid (0.4 g, 9%), mp 148–152°. Four recrystallizations from benzene gave an analytical sample of **β-naphthoyl acrylic acid** (**16a**): mp 167–168°; $\nu_{max}^{CHCl_3}$ 1710 (carboxylic acid) and 1670 cm^{-1} (conjugated ketone).

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46. Found: C, 74.10; H, 4.56.

Dehydration of α-Hydroxy-β-(2-naphthoyl)propionic Acid (**15a**).—A solution of α-hydroxy-β-(2-naphthoyl)propionic acid (**15a**, 0.36 g) in acetic anhydride (10 ml) was heated at 100° for 3 hr with potassium hydrogen sulfate (0.40 g). The solution was cooled, filtered, and diluted with water (10 ml). After 6 hr at room temperature the solution was evaporated to dryness *in vacuo*. The yellow residue was dissolved in saturated aqueous sodium bicarbonate, treated with Norit A, and acidified at 10° with concentrated hydrochloric acid. Upon cooling, the yellow crystalline **β-naphthoylacrylic acid** (**16a**, 0.12 g, 33%),[46] mp 164–165°, was collected.

Condensation of Methyl Ketones with Glyoxylic Acid. General Procedure A (Ambient).—A rapidly stirred solution of the ketone (0.032 mol) in tetrahydrofuran (250 ml)–methanol (360 ml) was treated successively with aqueous potassium hydroxide (100 ml, 8%) and an aqueous solution of glyoxylic acid (0.076 mol, 27 ml). The pH of the solution was adjusted to 13.65 by gradual addition of 8% aqueous potassium hydroxide. Stirring was continued for 3 days at room temperature. At this point, the yellow mixture was filtered, concentrated to 1/4 volume *in vccuo* at 50°, diluted with water (100 ml), and extracted with diethyl ether. Acidification of the aqueous solution with concentrated hydrochloric acid and extraction with chloroform provided the acidic product. Washing the chloroform solution with saturated aqueous sodium bicarbonate solution removed the acidic components and left in the chloroform neutral products whose infrared spectra indicated presence of a lactone (1780 cm^{-1}). The neutral material was formed (*ca.* 10% of the product) in all cases investigated but was not further characterized.

With Methyl β-Naphthyl Ketone.—Methyl β-naphthyl ketone (**10**, 5.4 g, 0.032 mol) was condensed with glyoxylic acid by the general procedure A given above to yield acidic (6.5 g) and neutral products (0.7 g); no starting material was recovered. A portion (3.8 g) of the crude acid was dissolved in methanol (115 ml) and heated at reflux for 3 hr with Amberlite IR-120 (H) (3.8 g).[48] The yellow solution was filtered and concentrated *in vacuo* to a yellow oil, which was dissolved in diethyl ether and washed with saturated aqueous sodium bicarbonate (three 20-ml portions) and water (two 20-ml portions). Removal of solvent gave a mobile yellow oil (2.4 g). Acidification of the sodium bicarbonate wash solution and extraction with diethyl ether gave 0.9 g of recovered acid. Repeating the esterification procedure yielded another portion of ester (0.5 g); the total yield of ester was 2.9 g. A sample of the ester (1 g) was chromatographed on acid-washed alumina (30 g) and afforded three distinct products. Elution with 2:5 ligroin–benzene led to a yellow solid (0.17 g), mp 108–109°. The melting point was raised to 112–112.5° by four recrystallizations from methanol to afford a pure sample (characterized in the sequel) of **methyl *trans*-β-(2-naphthoyl)acrylate** (**16b**):[46] ν_{max} 1720 (methyl ester) and 1665 cm^{-1} (conjugated ketone). Continued elution with benzene gave a colorless, mobile oil (0.57 g): ν_{max}^{neat} 1754 (methyl ester), 1694 (ketone), and 1124 cm^{-1} (methoxyl). Distillation at 120° (0.01 mm) gave an analytical specimen of **methyl α-methoxy-β-(2-naphthoyl)propionate** (**17b**).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.92. Found: C, 70.95; H, 5.74.

Elution with 1:1 benzene–chloroform afforded a colorless oil (0.10 g): ν_{max}^{neat} 3571 (hydroxyl), 1748 (methyl ester), and 1690 cm^{-1} (ketone). Distillation at 170° (0.01 mm) gave an analytical specimen of **methyl α-hydroxy-β-(2-naphthoyl)propionate** (**15b**).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.46; H, 5.46.

When the preceding reaction sequence was repeated using 2,4-dimethylacetophenone or 2,5-dimethoxyacetophenone in place of methyl β-naphthyl ketone, examination by thin layer chromatography and infrared spectroscopy of the crude products indicated analogous results. In these examples the actual products were not further identified.

With Methyl Cyclopentyl Ketone.—The ketone (10.6 g, 0.095 mol) was condensed with glyoxylic acid by general procedure A to yield neutral (2.0 g of colorless oil) and acidic (10.0 g, 56%) fractions. Continuous (48 hr) diethyl ether extraction of the acidified reaction mixture was used to isolate the yellow, oily acidic product.[9] A portion (3 g) of the acid was treated with ethereal diazomethane at 0°. Excess diazomethane was destroyed with glacial acetic acid and solvent was removed *in vacuo*. The resulting yellow oil (3.0 g) was chromatographed on a column of acid-washed alumina (90 g) and **methyl α-hydroxy-β-cyclopentylcarbonylpropionate** (**19**) was eluted by benzene–chloroform mixtures as a colorless oil (2.7 g, 52%). Distillation at 100° (0.1 mm) afforded an analytical specimen: ν_{max} 3546 (hydroxyl), 1740 (methyl ester), and 1709 cm^{-1} (ketone).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.63; H, 7.96.

With Pinonic Acid.—Pinonic acid[49] (**18**, 5.8 g, 0.032 mol) in tetrahydrofuran (250 ml)–methanol (360 ml) was condensed with glyoxylic acid, employing general procedure A, to give a dark, oily, acidic product (8.0 g), which was isolated by continuous extraction using diethyl ether. A portion (4.0 g) of the acid was dissolved in diethyl ether containing some methanol and treated with ethereal diazomethane. Excess diazomethane was destroyed by adding a few drops of glacial acetic acid. Removal of solvent *in vacuo* furnished a dark-colored oil (4.0 g), which was chromatographed on a column of acid-washed alumina (120 g). The product (3.3 g, 72%), **methyl α-hydroxy-β-pinonoyl propionate** (**20**), was eluted by benzene–chloroform mixtures as a pale yellow oil which was purified by distillation: bp 170° (0.1 mm); ν_{max}^{neat} 3400 (hydroxyl), 1740 (methyl esters), and 1705 cm^{-1} (ketone).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.35; H, 7.65.

General Procedure B (Heating).—To a stirred solution of the ketone (0.013 mol) in tetrahydrofuran (100 ml)–methanol (150 ml) was added potassium hydroxide solution (30 ml, 8%), followed by aqueous glyoxylic acid (0.03 mole, 11 ml). The pH was adjusted as specified by addition of aqueous potassium hydroxide (8%) and the mixture was stirred for 60 min at room

(48) P. J. Mill and W. R. C. Crimmin, *Biochem. Biophys. Acta*, **23**, 432 (1957).

(49) J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, **24**, 1870 (1959). We wish to thank Dr. Hedrick for a generous supply of pinonic acid.

temperature followed by 12 hr at reflux. The acidic product(s) was isolated as summarized in general procedure A.

With Methyl β-Naphthyl Ketone.—Condensing methyl β-naphthyl ketone (**10**, 2.2 g, 0.013 mol) with glyoxylic acid using general procedure B (pH 13.20) led to 2.7 g of crude acidic product. A portion (0.5 g) of this material was dissolved in methanol (8 ml) and treated with 2,2-dimethoxypropane (Dow Chemical Co.) followed by concentrated hydrochloric acid (4 drops).[50] The yellow solution was heated to 50° and treated with four 1-ml portions of 2,2-dimethoxypropane at 1-hr intervals. The temperature was maintained at 50° for 17 hr, after which most of the solvent was removed *in vacuo* and water (50 ml) was added. Following extraction of the turbid aqueous mixture with chloroform and washing of the extract with saturated aqueous sodium bicarbonate and water, drying, and evaporating, a yellow oil (0.6 g) was obtained. Chromatography on a column of neutral alumina (18 g) and eluting with a series of hexane–benzene mixtures afforded a pale yellow solid (0.30 g, 57%): mp 108–109°; ν_{max} 1720 (methyl ester), 1665 (conjugated ketone), and 1630 cm^{-1} (double bond). Four recrystallizations from methanol gave an analytical specimen of **methyl *trans*-β-(2-naphthoyl)acrylate (15b)** as pale yellow needles: mp 112–112.5° (lit.[51] mp 112–113°); pmr (CCl_4) δ 3.74 (singlet, 3 methyl protons) and 6.61 and 6.88 (doublet, J = 15 cps, 1 proton, the second olefin proton was obscured by the aromatic proton region).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.04. Found: C, 74.64; H, 4.84.

With 2,4-Dimethylacetophenone.—A 1.9-g (0.013 mol) sample of 2,4-dimethylacetophenone was condensed with glyoxylic acid by general procedure B at pH 13.20 to give 2.2 g of acidic product. A portion (0.5 g) of the acidic fraction was esterified using methanol and 2,2-dimethoxypropane as described above for the preparation of methyl-β-(2-naphthoyl)-acrylate and provided a dark yellow oil (0.60 g). Column chromatography on neutral alumina (15 g) and elution with hexane yielded a yellow oil (0.30 g, 56%), ν_{max}^{neat} 1725 (methyl ester), 1670 (conjugated ketone), and 1630 cm^{-1} (double bond). The oil crystallized after 24 hr at 0°. Four recrystallizations from 2-propanol gave a yellow, crystalline, analytical specimen of **methyl β-(2,4-dimethylbenzoyl)acrylate (21)**, mp 50–50.2°.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.35; H, 6.44.

With 2,5-Dimethoxyacetophenone.—The acetophenone (2.3 g, 0.013 mol) was condensed with glyoxylic acid by general procedure B at pH 13.65 and the crude acidic product (2.9 g) was esterified by treatment for 3 hr with Amberlite IR-120 (H) (2.9 g) in boiling methanol (75 ml). The yellow solution was filtered and the solvent was removed *in vacuo* to yield a dark, oily residue which was dissolved in diethyl ether. The ethereal solution was washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to furnish a yellow oil (1.7 g). This residue was chromatographed on a column of acid-washed alumina (40 g). Elution with 1:1 hexane–benzene gave a yellow oil (1.0 g, 59%), which crystallized from 2-propanol in matted, yellow needles (0.9 g), mp 65–68°. Four recrystallizations from 2-propanol yielded an analytical specimen of **methyl β-(2,5-dimethoxybenzoyl)acrylate (22)**: mp 73–73.5° (lit.[52] mp 65°); ν_{max}^{Nujol} 1727 (methyl ester), 1672 (conjugated ketone), and 1636 cm^{-1} (double bond).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.65; H, 5.80.

Further elution of the column with chloroform gave a dark oil (0.15 g). Distillation at 170° (0.01 mm) afforded **methyl α-hydroxy-β-(2,5-dimethoxybenzoyl)propionate (23)** as a pale yellow oil, ν_{max}^{neat} 3570 (hydroxyl), 1754 (methyl ester), and 1677 cm^{-1} (ketone).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.53; H, 6.59.

Methylation of Methyl α-Hydroxy-β-(2-naphthoyl)propionate (15b).—To a solution of methyl α-hydroxy-β-(2-naphthoyl)-propionate (**15b**, 0.5 g) in diethyl ether (5 ml) at −10° was added 1 drop of boron trifluoride etherate followed dropwise by an ethereal solution of diazomethane from 1.2 g of nitrosomethylurea during 5 min.[53] Cooling was maintained until the yellow color had disappeared (15 min). A gelatinous precipitate was removed by filtration and the filtrate was washed with saturated aqueous sodium bicarbonate, dried, and concentrated to a colorless oil (0.2 g). The residue was chromatographed on acid-washed alumina (15 g), and **methyl α-methoxy-β-(2-naphthoyl)-propionate (15b**, 0.1 g, 18%) was obtained, eluted by benzene, as a colorless oil.

Alternate Synthesis of Methyl *trans*-β-(2-Naphthoyl)acrylate (16b).—To a stirred solution of ω-bromo-2-acetonaphthone (2.4 g, 0.01 mol) in dry tetrahydrofuran (20 ml) was added in one portion a warm solution of carbomethoxymethylenetriphenylphosphorane[54] (6.7 g, 0.02 mol) in dry tetrahydrofuran (30 ml). After 24 hr at room temperature the solution was filtered to remove carbomethoxymethyltriphenylphosphonium bromide (2.6 g, 64%). The filtrate was evaporated to a dark oil, which was diluted with dry benzene and treated with methyl iodide for 2 hr at 5°. Filtration and evaporation yielded a dark residue which was chromatographed (column) on acid-washed alumina (30 g). The hexane–benzene fractions yielded a yellow solid **16**,[46] which recrystallized from methanol as pale yellow plates (0.91 g, 38%), mp 110–111°.

Methyl *cis*-β-(2-Naphthoyl)acrylate (16b).—Methyl *trans*-β-(2-naphthoyl)acrylate (**16a**, 0.20 g) in benzene (10 ml) was irradiated with a sun lamp (GE 110–125 V) at a distance of 4 ft for 48 hr, at which time tlc examination showed almost complete conversion into the more polar *cis* isomer. Evaporation of solvent gave an orange oil which slowly crystallized on trituration with hexane. The crude product was heated with hexane and the hot solution was decanted from an oily by-product. The product, which crystallized upon cooling, was recrystallized three times from hexane to give cream-colored crystal clusters (0.06 g): mp 92–95°; pmr (CCl_4) δ 3.41 (singlet, 3 methyl protons) and 5.94, 6.13, 6.58, and 6.77 (quartet, J = 11 cps, 2 protons, *cis* isolated double bond).

3β-Triphenylmethoxy-20-oxo-5α-pregnane (24c).—A solution of 3β-hydroxy-20-oxo-5α-pregnane (**24a**, 3.6 g, 11 mmol) and triphenylmethyl bromide (5.4 g, 17 mmol) in dry pyridine (100 ml) was heated at 100° for 12 hr. The yellow reaction mixture was cooled and poured onto ice, and the resulting yellow precipitate was collected by extraction with chloroform. The chloroform extract was washed twice with water, dried, and evaporated to yield a yellow gum which solidified on trituration with diethyl ether. Filtration provided a cream-colored solid (3.87 g), mp 216–220°. Recrystallization from chloroform–methanol gave cream-colored needle clusters in two crops of 2.2 g, mp 222–225°, and 1.3 g, mp 218–223°. Recrystallization of the second crop from the same solvent mixture gave 1.19 g, mp 223–227°. Yield (of almost pure material) was 3.39 g (53%). An analytical specimen was prepared by three recrystallizations from the same solvent mixture: mp 227–230°; ν_{max} 1695 (ketone) and 1030–1050 cm^{-1} (ether); $[\alpha]^{22}D$ +39.2° (*c* 1.46).

Anal. Calcd for $C_{40}H_{48}O_2$: C, 85.66; H, 8.63. Found: C, 85.11; H, 8.26.

3β-Triphenylmethoxy-20-oxo-5-pregnene (7c).—Treatment of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 5.0 g, 16 mmol) with triphenylmethyl bromide in pyridine was performed exactly as described above for the 5α analog **24c** to yield a brown, glasslike crude product (11.4 g). A solution of the residue in 5:1 hexane–benzene was chromatographed on basic alumina (250 g). The benzene–hexane eluate gave a colorless solid which crystallized from chloroform–methanol as needles (4.7 g, 53%), mp 180–185°. An analytical specimen was prepared by trituration with boiling methanol followed by six recrystallizations of the insoluble material from chloroform–methanol: mp 188–191°; $[\alpha]^{22}D$ +23.2° (*c* 1.29); ν_{max} 1690 (ketone) and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{40}H_{46}O_2$: C, 85.98; H, 8.30. Found: C, 85.49; H, 8.05.

3β-Triphenylmethoxy-20-oxo-5,16-pregnadiene (25b).—A 5.0-g (16 mmol) sample of 3β-hydroxy-20-oxo-5,16-pregnadiene (**25a**) was treated with triphenylmethyl bromide in hot pyridine for 24 hr as described above for **24c**. The product was a dark, viscous oil (10 g). Column chromatography on basic alumina (250 g) and elution with hexane–benzene mixtures gave a colorless solid which crystallized from chloroform–methanol as glistening needles (4.5 g, 51%), mp 190–194°. Three recrystal-

(50) N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(51) R. H. Martin and P. Stoffyn, *Bull. Soc. Chim. Belg.*, **59**, 83 (1950); *Chem. Abstr.*, **45**, 594 (1951).

(52) K. P. Dave and K. S. Nargund, *J. Univ. Bombay*, **7**, Part 3, 191 (1938); *Chem. Abstr.*, **33**, 3779 (1939).

(53) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

(54) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

lizations from acetone gave an analytical sample: mp 195–197°; $[\alpha]^{22}D$ −21.4° (*c* 1.215); ν_{max} 1665 (conjugated ketone) and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{40}H_{44}O_2$: C, 86.27; H, 7.97. Found: C, 86.22; H, 7.98.

3β-Methoxymethyloxy-20-oxo-5-pregnene (7d).—A solution of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 7.5 g, 24 mmol) in refluxing chloromethyl methyl ether (75 ml, Eastman) containing suspended Drierite (20 g) was treated in portions with freshly prepared, dry silver oxide (17 g) during 90 min. Heating was continued for 4 hr. The solvent was reduced in volume and filtered, and the inorganic residue was washed well with chloroform. The residue (9.0 g) obtained upon removal of solvent *in vacuo* was chromatographed on basic alumina (200 g). Elution with benzene gave a colorless solid (1.5 g, 18%), mp 95–100°. Four recrystallizations from methanol gave a pure specimen as colorless microneedles: mp 103–104°; $[\alpha]^{22}D$ 0°; ν_{max} 1700 (ketone), 1150, 1100, and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{28}H_{36}O_3$: C, 76.64; H, 10.07. Found: C, 77.23; H, 9.94.

Elution of the column with chloroform yielded unreacted 3β-hydroxy-20-oxo-5-pregnene (5.5 g).

Condensation of 3β-Hydroxy-20-oxo-5-pregnene (7a) with Glyoxylic Acid at Readings of pH 13.25–13.48. Experiment A. pH 13.25.—A vigorously stirred solution of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 2.0 g, 6.3 mmol) in tetrahydrofuran (50 ml)–methanol (75 ml) was treated successively with potassium hydroxide solution (8% aqueous, 20 ml), and a solution of glyoxylic acid (23 mmol, 6 ml) prepared as described above. Potassium hydroxide (8% aqueous) was then gradually added until the pH meter scale reading was 13.25. Stirring was continued for 3 days at room temperature, and the solution was filtered, concentrated *in vacuo* to 1/5 volume, and diluted with water (100 ml). Extracting the basic mixture with chloroform followed by washing with water, drying, and concentration furnished unreacted 3β-hydroxy-20-oxo-5-pregnene (**7a**, 1.3 g).[46] Acidification of the aqueous solution with concentrated hydrochloric acid gave a gelatinous, acidic product which was collected by chloroform extraction to yield a colorless, amorphous, acidic product (0.63 g, 25%): mp 160–170° dec; ν_{max} 3400 (broad, acid) and 1750–1690 cm^{-1} (carboxylic acid and ketone).

Experiment B. pH 13.48.—Experiment A was repeated with ketone **7a** (3 g, 9.5 mmol) exactly as above except that the pH reading was adjusted to 13.48. The neutral extract gave starting material (1.3 g), and the acidic fraction yielded a colorless, amorphous solid (1.6 g, 45%), mp 155–175° dec.

Methyl 3β,23-Dihydroxy-20-oxo-21-nor-5-cholenate (26b).—Condensation of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) with glyoxylic acid was carried out at pH 13.48 exactly as described above (experiment B) to yield starting material (8.5 g) and amorphous acid (12.3 g, 50%), mp 155–175° dec. A portion (11 g) of the acidic material, dissolved in methanol, was treated with ethereal diazomethane at 0°. Excess diazomethane was decomposed immediately with a few drops of glacial acetic acid, and the solvent was removed *in vacuo*. The yellow, viscous oil (11.5 g) was chromatographed on acid-washed alumina (250 g). A pale yellow solid (4 g) was eluted by 1:1 benzene–chloroform; purification of this material will be described below (see **26a**). Elution with chloroform furnished a pale yellow solid (7 g, 30%), mp 154–164°, which was homogeneous as evidenced by thin layer chromatography. Four recrystallizations from isopropyl ether–methanol afforded an analytical sample of diol **26b** as colorless plates: mp 170–174°; $[\alpha]^{22}D$ +9.0°; ν_{max} 3400 (hydroxyl), 1740 (methyl ester), and 1700 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.18; H, 8.80.

A sample (2.3 g) of the diol was acetylated, and the crude diacetate (**26c**, 2.6 g) was decolorized by two treatments with Norit-A in methanol. Recrystallization from aqueous methanol gave the diacetate (2.2 g, 79%) as colorless plates, mp 105–107°. An analytical specimen of methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**) was prepared by five recrystallizations from aqueous methanol: mp 105–108°; $[\alpha]^{22}D$ +23.2° (*c* 1.242); ν_{max}^{Nujol} 1754 (sh, methyl ester), 1738 (acetates), 1709 (ketone) and 1250 cm^{-1} (acetates).

Anal. Calcd for $C_{28}H_{40}O_7$: C, 68.82; H, 8.25. Found: C, 68.90; H, 7.96.

Methyl 3β,23-Ditetrahydropyranyloxy-20-oxo-21-nor-5-cholenate (26d).—To a magnetically stirred suspension of 3β,23-dihydroxy-20-oxo-21-nor-5-cholenate (**26b**, 1.25 g) in dry benzene (40 ml) and dihydropyran (7.5 ml, distilled from sodium) was added *p*-toluenesulfonic acid monohydrate (75 mg). After 2 min the solution became homogeneous, and stirring was continued at room temperature for 30 min.[55] The pale yellow solution was washed with sodium hydroxide solution (1% in 1:1 methanol–water) and water. Removal of solvent gave a yellow oil (2.0 g) which was chromatographed on neutral alumina (30 g). Elution with 1:1 benzene–hexane gave a colorless oil (1.25 g, 70%) which solidified, mp 70–75° (vacuum dried) upon trituration with cold (ice-bath) methanol. An analytical sample was prepared by three recrystallizations from methanol, followed by two from aqueous acetone: mp 70–78°; ν_{max} 1750 (methyl ester), 1705 (ketone), and 1030 cm^{-1} (split, ethers).

Anal. Calcd for $C_{34}H_{52}O_7$: C, 71.29; H, 9.15. Found: C, 71.53; H, 9.10.

Methyl 3β-Acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (26a).—A portion (1.5 g) of the material (4 g) eluted in 1:1 benzene–chloroform (see **26a** above) during isolation of methyl 3β,23-dihydroxy-20-oxo-21-nor-5-cholenate (**26a**) was acetylated. The oily acetate (1.2 g) was chromatographed on acid-washed alumina (30 g). A 0.3-g quantity of 3β-acetoxy-20-oxo-5-pregnene (**7b**) was eluted by 1:1 benzene–hexane. Elution with benzene gave a colorless solid (0.7 g), mp 102–103°. Three recrystallizations from diethyl ether–hexane gave a pure specimen as colorless plates: mp 104–105°; $[\alpha]^{20}D$ +20.5° (*c* 2.879); ν_{max}^{Nujol} 1754 (methyl ester), 1733 (acetate), 1709 (ketone), 1250 (acetate), and 1136 cm^{-1} (methoxy); pmr δ 3.24 (3 methoxy protons) and 3.58 (3 methyl ester protons).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.76. Found: C, 70.80; H, 8.68.

Condensation between 3β-Hydroxy-20-oxo-5-pregnene (7a) and Glyoxylic Acid at pH 13.65. Method A. Room Temperature.—Reaction between 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) and glyoxylic acid at pH 13.65 was accomplished as described above (*cf.* **26b**). After 28 hr, half of the reaction mixture was taken for isolation studies and the other half was allowed to proceed for an additional 48 hr at room temperature. Isolation work with the first half was complicated by emulsion formation (during extraction of the basic solution with chloroform), and caused inefficient separation into neutral and acidic fractions. The neutral extract furnished 3β-hydroxy-20-oxo-5-pregnene (0.6 g, **7a**), and the acidic portion was obtained as a pale yellow foam (10 g). The acid (10 g) was dissolved in 10:1 chloroform–methanol and treated with ethereal diazomethane at ice-bath temperature. Excess diazomethane was destroyed at once with a few drops of glacial acetic acid. The solution was concentrated to a yellow oil (11 g). Acetylation gave a yellow, viscous oil (11.5 g) which was chromatographed on acid-washed alumina (300 g). Elution with 1:1 hexane–benzene gave **3β-acetoxy-20-oxo-5α-pregnane** (**7b**, 4.3 g), and benzene gave a mixture of two components, separable by crystallization from methanol, to give first the less soluble **methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate** (**27**, 0.60 g, 5%), mp 153–156°. Three recrystallizations from methanol gave long yellow needles: mp 157–158.5°; $[\alpha]^{20}D$ +37.5° (*c* 1.27); ν_{max} 1735 (methyl ester), 1730 (acetate), 1690 (conjugated ketone), and 1628 cm^{-1} (m, conjugated double band).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.34; H, 8.43.

The second component eluted by benzene was identical[46] with **methyl 3β-acetoxy-23-methoxy-20-oxo-5-cholenate** (**26a**, 1.6 g, 11%), mp 102–104°. Further elution of the column with 2:1 benzene–chloroform gave **methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate** (**26c**, 2.3 g, 15%),[46] mp 96–99°, and a pale yellow, viscous oil (1.0 g). An infrared spectrum suggested that the oil represented **pyrazoline 28:** ν_{max} 1745 (methyl ester), 1701 (ketone), and 1577 cm^{-1} (pyrazoline). Continued elution with 10:1 and 4:1 benzene–chloroform gave mixtures (shown by thin layer chromatography) of the 23-acetoxy (**26b**) and 23-methoxy (**26d**) esters.

After 72 hr the second half of the reaction product was methylated and acetylated in the same way to give 3β-hydroxy-20-oxo-5-pregnene (**7a**, 0.8 g) as the initial neutral fraction and a mixture of methyl esters (9.0 g) from the initial acid fraction. Chromatography of the methyl ester mixture as before gave 3β-

(55) Normal reaction time (3 hr) for tetrahydropyranyl ether formation produced a mixture of products. After several experiments over various periods, the 30-min procedure was found most satisfactory.

acetoxy-20-oxo-5-pregnene (**7b**, 1.6 g), methyl 3β-acetoxy-20-oxo-21-nor-5,22-choladienate (**27**, 1.0 g, 8%), methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 2.0 g, 14%), methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**, 3.0 g, 19%), and pyrazoline **28** (0.4 g).

Method B. Reflux Temperature.—Here, 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) was condensed with glyoxylic acid as described above at pH 13.65 except that the reaction was heated at reflux temperature (60°) for 8 hr. Despite an inefficient separation because of emulsification, 2.4 g of unreacted starting material and 19.5 g of acidic material (as a pale yellow foam) were isolated. Methylation (see method A) and acetylation gave a dark oil (20 g) which was chromatographed on acid-washed alumina (500 g). Elution with the same solvents as described in the preceding experiment gave 3β-acetoxy-20-oxo-5-pregnene (**7b**, 3.56 g), methyl 3β-acetoxy-20-oxo-21-nor-5,22-choladienate (**27**, 2.1 g, 8%), methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 0.3 g, 1%), methyl 3β-23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**, 2.8 g, 9%), and pyrazoline **28** (5.5 g).

In another experiment[56] a portion (17 g) of the acidic product prepared by method B (reflux, 8 hr) in methanol (170 ml) was treated with 2,2-dimethoxypropane (17 ml) and warmed to 50° with concentrated hydrochloric acid (5 ml). After 1 hr, more dimethoxypropane (17 ml) was added, and this operation was repeated twice more at hourly intervals. One day later the brown solution was filtered and concentrated *in vacuo*. Addition to water and extraction with chloroform furnished the crude product. Acetylation led to a pale yellow solid (17 g). Chromatography on acid-washed alumina (450 g) and elution with benzene gave methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**27**, 5.0 g),[46] mp 154–155°. In this case the other products were not isolated.

Condensation between 3β-Acetoxy-20-oxo-5α-pregnane (24a) and Glyoxylic Acid.—Using method A (see above with ketone **7a**, pH 13.65), 3β-acetoxy-20-oxo-5α-pregnane (**24a**, 10 g, 28 mmol) was condensed with glyoxylic acid. A period of 3 days at room temperature afforded starting material (5.1 g) after reacetylation and acidic product (4.82 g), mp 198–205° dec, collected by filtration. A sample of the acid was recrystallized five times from aqueous ethyl alcohol to give the analytical specimen of **3β,23-dihydroxy-20-oxo-21-nor-5α-cholanic acid (29a)** as colorless plates: mp 227–229° dec; ν_{max} 3350 (hydroxyl), 2700–2300 (w, carboxyl), 1730 (carboxyl), and 1698 cm^{-1} (ketone).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24; O, 20.38. Found: C, 70.80; H, 9.00; O, 20.20.

A solution of the crude acid (mp 198–205° dec, 4.8 g) in 1:1 chloroform–methanol (200 ml) was converted into the methyl ester with ethereal diazomethane. Excess reagent was quickly destroyed with acetic acid, and the solution was washed with saturated sodium bicarbonate solution followed by water. Removal of solvent furnished a yellow, oily residue. The crude ester was chromatographed on acid-washed alumina (140 g). Elution with 7:3 benzene–chloroform gave a yellow oil (1.1 g) which slowly solidified and showed two closely positioned spots on a thin layer chromatogram. Elution with 1:1 benzene–chloroform led to a colorless solid (2.0 g), mp 147–157°. Recrystallization from diethyl ether containing a trace of methanol gave colorless needles (1.0 g), mp 165–167°. Three recrystallizations from the same solvent gave **methyl 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanate (29b)** as needles: mp 177–179°; $[\alpha]^{20}D$ +91.8° (c 1.381); ν_{max} 3200, 3100 (hydroxyls), 1739 (methyl ester), and 1697 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 70.84; H, 9.24; O, 20.16.

Acetylation of a sample of the dihydroxymethyl ester (0.09 g), mp 174–176°, gave diacetate **29c** (0.12 g), mp 109–113°, and successive recrystallization from hexane and aqueous ethyl alcohol gave the analytical specimen of **methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate (29c)** as colorless plates: mp 113–114.5°; $[\alpha]^{21}D$ +71.1° (c 0.82); ν_{max} 1725–1750 (acetates and methyl ester) and 1695 cm^{-1} (ketone).

Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.52; H, 8.79; O, 22.92.

Conversion of Methyl 3β,23-Dihydroxy-20-oxo-21-nor-5α-cholanate (29b) into 3β-Hydroxy-20-oxo-5α-pregnane (24a).—A solution of methyl 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanate (**29b**, 0.1 g) in methanol (20 ml) containing potassium hydroxide (1 g) was heated at reflux for 2 hr. Concentration *in vacuo* to a small volume, followed by dilution with water, three extractions with chloroform, and evaporation of solvent gave a colorless, crystalline solid (25 mg) identical[46] with **3β-hydroxy-20-oxo-5α-pregnane (24a)**. Acidifying the alkaline solution provided a 0.072-g acid fraction.

Registry No.—Glyoxylic acid, 298-12-4; **7c**, 23328-04-3; **7d**, 23328-05-4; **11a**, 23349-18-0; **11b**, 23389-68-6; **11c**, 23349-19-1; **14**, 23349-20-4; **15a**, 23359-85-5; **15b**, 23349-21-5; **16a**, 23328-06-5; **16b**, 23328-07-6; **17b**, 23349-22-6; **19**, 23349-23-7; **20**, 23349-24-8; **21**, 23349-25-9; **22**, 23349-26-0; **23**, 23349-27-1; **24c**, 23328-08-7; **25b**, 23328-09-8; **26a**, 23328-10-1; **26b**, 23328-11-2; **26c**, 23328-12-3; **26d**, 23328-13-4; **27**, 23330-45-2; **28**, 23328-15-6; **29a**, 23328-16-7; **29b**, 23328-17-8; **29c**, 23328-18-9.

(56) Performed by Dr. A. K. Das Gupta.

Bufadienolides. 2. 20-Hydroxy-21-nor-5α-cholanic Acid γ-Lactones (24→20)[1]

GEORGE R. PETTIT[2]

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

BRIAN GREEN AND GEORGE L. DUNN

Department of Chemistry, University of Maine, Orono, Maine 04473

Received February 11, 1969

Sodium borohydride reduction of both methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (**1a**) and the corresponding 23-methyl ether **1b** was found to produce 3β,20-dihydroxy-21-nor-5-cholenic acid γ-lactone (24 → 20). Concomitant elimination of the 23 substituent (to yield lactone **2a**) again occurred with methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate (**3**) to give γ-lactone **4a**, which was also obtained by palladium-catalyzed hydrogenation of olefin **2a**. Hydrogenation of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**5**) gave 5α-cholanate **6a** as a major product accompanied by small quantities of 3-deoxycholanate **6b** and γ-lactone **4b**. Sodium borohydride reduction of ketone **6a** yielded γ-lactone **4b**, thereby confirming structures assigned to lactones **2** and **4**. Platinum-catalyzed hydrogenation of 23-methyl ether **1b** and of 23-acetate **3** led, respectively, to 23-substituted lactones **4c** and **4d**. A potentially useful lactone (3-oxo-4-ene, **8**) for biological evaluation was obtained by Oppenauer oxidation of alcohol **2a**.

Once experimental conditions had been devised for condensing glyoxylic acid with 20-oxopregnanes, a practical route to 23-substituted lactones of the isocardanolide type[1c] became the next objective. To this end, 23-acetoxy- (**1a**) and 23-methoxy- (**1b**) 20-oxo-cholenates[1a] were reduced by sodium borohydride[3] with the expectation of obtaining the corresponding γ-lactones, which are members of one of two possible groups of isocardanolides (*cf.* ref 1c).[4] Spectral data and microanalyses indicated that both ketones **1a** and **1b** had been converted into the same γ-lactone, namely, **2a**. A β-type elimination[5] of the oxygen substituent during reduction would have yielded an α,β-unsaturated lactone, but, if β elimination occurred in the presence of sufficient sodium borohydride, reduction of the olefin or a suitable intermediate might occur.[6] Also a direct deoxygenation reaction would seem plausible, in which the hydride ion displaces the oxygen substituent by a nucleophilic substitution mechanism.

Analogous reduction and saponification of the product from methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate (**3**) led to γ-lactone **4a**, again involving elimination of the 23-acetoxy group. The structural relationship of lactones **2a** and **4a** was readily established by palladium-catalyzed hydrogenation of the former to γ-lactone **4a**. Specimens of this lactone ranged in melting point from 237–241 to 248–253° with optical rotation values at the sodium D line of −72 to −102°, but all exhibited identical infrared spectral and thin layer chromatographic properties. The undefined melting-point and rotation values for lactone **4a** suggest epimeric mixtures at C-20.[7] Unequivocal support for the gross structure of lactones **2** and **4** was obtained as follows. Hydrogenation with palladium of *trans* 22 olefin **5** gave 20-oxo-5α-cholanate (**6a**) as the major product accompanied by methyl 20-oxo-21-nor-5α-cholanate[8] (**6b**) and lactone **4b** in very low yield. Application of the sodium borohydride procedure to ketone **6a** and extension of the reaction period to 72 hr gave lactone **4b**, which was identical with a sample obtained by acetylating lactone **4a**. Subsequently, by sodium borohydride reduction of ketone **4a** at 0°, a 56% yield of the 20-hydroxy methyl ester intermediate was isolated, which was readily converted into γ-lactone **4b** by absorption on a column of silica gel for 4 days.

For the main purpose of providing chemical evidence for the *trans* configuration assigned olefin **5**, reduction with sodium borohydride followed by saponification gave the *trans* hydroxy acid **7**, which failed to lactonize. As expected, palladium-catalyzed hydrogenation of this product followed by acetylation provided only lactone **4b**. Hydrogenation[9] of the *cis* geometrical isomer of olefin **5** in acetic acid containing platinum again provided lactone **4b**.

The platinum-catalyzed hydrogenation reaction of 23-methyl ether **1b** yielded 23-methoxy lactone **4c**, whose isolation was achieved by preparative layer chromatography; a proton magnetic resonance spectrum displayed a characteristic methyl ether signal at δ 3.46. Similarly, catalytic reduction of diacetate **3** led to 23-acetoxy lactone **4d**, whose pmr spectrum showed two sharp singlets at δ 1.96 and 2.09 from the 3β- and 23-acetate groups. Assuming that the lactone ring may have a preferred spatial orientation,

(1) (a) Part 1: G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **34**, 1267 (1970). (b) This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-06 and CA-10115-01 from the National Cancer Institute. (c) A preliminary account of the present study was presented in part in Dec 1963 at the VIth Pan-American Congress of Pharmacy and Biochemistry, Mexico City, Mexico; see G. R. Pettit, G. L. Dunn, and B. Green, *Chem. Ind.* (London), 1265 (1964).

(2) To whom correspondence should be addressed.

(3) A variety of δ-lactones have been obtained by sodium borohydride reduction of δ-oxovaleric acids, *e.g.*, R. Lukes, S. Dolezal, and K. Capek, *Collect. Czech. Chem. Commun.*, **27**, 2408 (1962); K. W. Rosenmund and H. Bach, *Chem. Ber.*, **94**, 2401 (1961).

(4) Examples of this type of lactone system have been obtained by synthesis [D. Bertin, French Patent 1,369,319; *Chem. Abstr.*, **62**, 1718 (1965)] and by degradative routes [D. Rosenthal, A. O. Niedermeyer, and J. Fried, *J. Org. Chem.*, **30**, 510 (1965); P. Crabbé, G. Ourisson, and T. Takahashi, *Tetrahedron*, **3**, 279 (1958)].

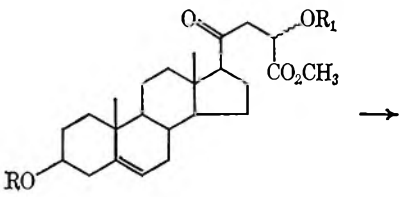
(5) For an example, see G. R. Pettit and T. H. Brown, *J. Chem. Soc., C*, 2024 (1967).

(6) (a) C. Djerassi and W. Rittel, *J. Amer. Chem. Soc.*, **79**, 3528 (1957); (b) G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *J. Org. Chem.*, **34**, 1381 (1970).

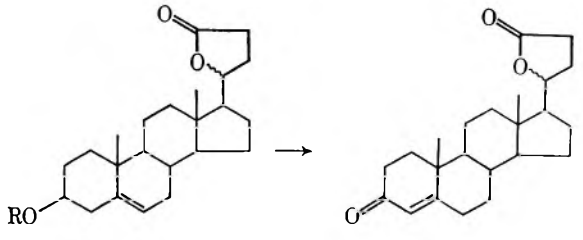
(7) Reduction of steroid 20 ketones using sodium borohydride generally gives 20β alcohols as major products: D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Amer. Chem. Soc.*, **81**, 3291 (1959). Assuming that reduction of ketones **1** and **3** follow a similar course, lactones **2** and **4** may consist mainly of the 20β epimer.

(8) Hydrogenolysis of the carbon–oxygen bond at C-3 has been observed with several other 3β-acetoxy-Δ⁵ steroids in our laboratory: G. R. Pettit, A. K. Das Gupta and R. L. Smith, *Can. J. Chem.*, **44**, 2023 (1966).

(9) *Cf.* P. Kurath, W. Cole, J. Tadanier, M. Freifelder, G. R. Stone, and E. V. Schuber, *J. Org. Chem.*, **28**, 2189 (1963).

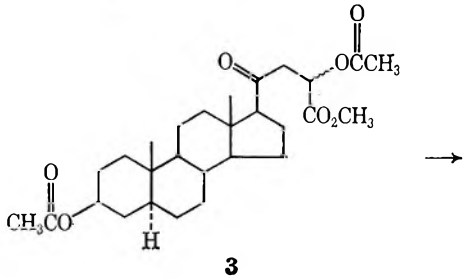


1a, R = R$_1$ = COCH$_3$
b, R = COCH$_3$; R$_1$ = CH$_3$

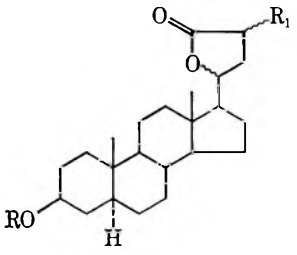


2a, R = H
b, R = COCH$_3$

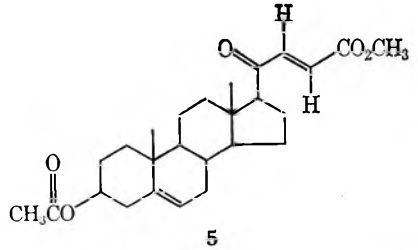
8



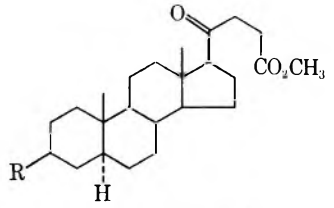
3



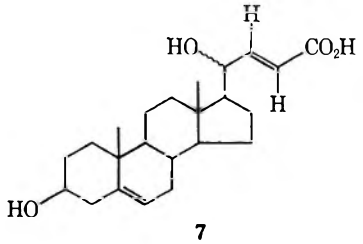
4a, R = R$_1$ = H
b, R = COCH$_3$; R$_1$ = H
c, R = COCH$_3$; R$_1$ = OCH$_3$
d, R = COCH$_3$; R$_1$ = OCOCH$_3$



5



6a, R = OCOCH$_3$
b, R = H



7

the sharp signals of the 23 substituents may reflect the presence of essentially one C_{23} epimer.

The terminal objective of the route to isocardanolides was synthesis of A-ring α,β-unsaturated ketone **8** for biological evaluation.[10] Oppenauer oxidation[11] of lactone **2a** yielded lactone **8**, which was isolated by preparative layer chromatography and showed a characteristic C-4 olefinic proton signal (pmr) at δ 5.46.[12]

Experimental Section

All solvents were redistilled. Acetylations were conducted using 1:1 acetic anhydride–pyridine at 25° for 12–15 hr. The combined extracts of aqueous solutions were dried over anhydrous magnesium or sodium sulfate. Acid-washed alumina (Merck, Rahway) and 0.05–0.20-mm-mesh silica gel (E. Merck, Darmstadt) were employed for column chromatography. Thin layer chromatograms were prepared using silica gel G (E. Merck) and visualized with concentrated sulfuric acid. Preparative layer chromatography employed 20 × 20 cm plates coated with a 1-mm layer of silica gel G. All analytical samples were colorless and displayed one spot on a thin layer chromatogram.

Melting points for analytical specimens were determined using a Kofler apparatus and all other melting points were observed in open capillaries (silicone oil bath) and are uncorrected. Physical measurements by Dr. R. Hill, University of Maine, comprised ultraviolet (Perkin-Elmer, Model 400 spectrophotometer), infrared (in potassium bromide unless otherwise indicated, Baird spectrophotometer), and pmr (deuteriochloroform solution with tetramethylsilane as internal standard, Varian A-60) spectra. Elemental microanalytical data was obtained in the laboratory of Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany, and optical rotations (chloroform solution at 20°) were provided by Dr. P. Demoen, Janssen Pharmaceutica, Beerse, Belgium.

3β,20-Dihydroxy-21-nor-5-cholenic Acid γ-Lactone (24 → 20) (2a). Route A.—To a solution of methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate[13a] (**1a**, 4.0 g, 8.2 mmol) in dimethylformamide (160 ml) was added dropwise during 15 min, with stirring, a solution of sodium borohydride (1.26 g, 32.8 mmol) in water (30 ml) at 15°. The mixture was stirred for 3 hr at room temperature, treated with 25% aqueous acetic acid (40 ml), and poured into water (500 ml). The aqueous mixture was saturated with sodium chloride and extracted with chloroform, and the combined extract was washed with saturated aqueous sodium bicarbonate and water. Evaporation of the dry solvent yielded an oil (3.2 g) which was dissolved in methanol containing 0.5 *N* potassium hydroxide (270 ml)–water (30 ml) and heated at reflux for 2 hr. Dilution with water (300 ml) and concentration to 75 ml *in vacuo* gave a turbid mixture. Following acidification with 3 *N* hydrochloric acid (600 ml), and a 12-hr period at room temperature, the precipitated gel was extracted with chloroform and the solvent was evaporated to a colorless foam (2.6 g), which was dissolved in benzene (0.68 g insoluble) and chromatographed on acid-washed alumina (60 g). Elution with 3:1 benzene–chloroform afforded a solid (1.1 g, 38%), mp 240–244°. Three recrystallizations from acetone furnished rods: mp 244–246°; $[\alpha]_D$ −83° (*c* 0.572); ν_{max} 3400 (hydroxyl) and 1745 cm^{-1} (γ lactone).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.07; H, 9.52; O, 13.19.

Route B.—Methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**1b**, 1.4 g, 3.05 mmol) was reduced with sodium borohydride (0.45 g, 12.2 mmol) in dimethylformamide–water as described in route A above to give, after saponification and acidification, a semicrystalline mass (0.97 g), which was dis-

(10) Endocrinological studies of the steroids described herein are being performed under the auspices of the National Cancer Institute, National Institutes of Health. Isocardanolide **4b** was found to be devoid of cardiac activity, being completely inactive in an ATPase test system at concentrations as high as 0.1 m*M*. We wish to thank Professor Repke for this information; *cf.* H. J. Portius and K. Repke, *Arzneim.-Forsch.*, **14**, 1073 (1964).

(11) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(12) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 90.

solved in 3:1 benzene–chloroform and chromatographed on acid-washed alumina (30 g) to yield 0.51 g, mp 215–240°. Four recrystallizations from chloroform–ether gave plates: mp 237–241°; $[\alpha]_D$ −72° (c 0.22); ν_{max}^{Nujol} 3400 (hydroxyl) and 1740 cm^{-1} (γ lactone). This sample was identical[13] with a sample prepared by route A.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.58; H, 9.34.

A portion (0.075 g) of the 3β,20-dihydroxy-21-nor-5-cholenic acid γ-lactone (24 → 20) (**2a**) was acetylated. Recrystallizing the product from methanol furnished **3β-acetoxy-20-hydroxy-21-nor-5-cholenic acid γ-lactone (24 → 20)** (**2b**, 0.06 g): mp 192–197°; ν_{max} 1770 (γ lactone), 1730, and 1250 cm^{-1} (acetate). Four recrystallizations from methanol gave shiny plates, mp 204–205°, $[\alpha]_D$ −64.3° (*c* 0.49).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.62; H, 9.24.

Route C.[14]—A 0.2-g specimen of 3β acetate **2b** was saponified overnight using 10% aqueous potassium carbonate (3 ml) in methanol (16 ml). An analytical sample of alcohol **2a** was obtained by repeated recrystallization from acetone as prisms: mp 248–253°; $[\alpha]_D$ −102° (*c* 0.19); ν_{max} 3400 and 1740 cm^{-1}; pmr δ 0.78 (CH_3-18), 1.02 (CH_3-19), 3.55 (multiplet, 1 proton, H-3α), 4.4 (multiplet, 1 proton, H-20), and 5.37 (multiplet, 1 proton, H-6).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.50, 76.55; H, 9.58, 9.48.

3β,20-Dihydroxy-21-nor-5α-cholanic Acid γ-Lactone (24 → 20) (4a). Route A.—Methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate[1a] (**3**, 1.0 g, 2.0 mmol) in dimethylformamide (40 ml) was reduced with sodium borohydride (0.32 g, 8.2 mmol) in water (8 ml) exactly as described above (*cf.* **2a**) for the unsaturated compound. After saponification and acidification, the colorless foam (0.70 g) was treated with boiling benzene (0.25 g, solid residue) and the filtrate was chromatographed on acid-washed alumina (15 g). Elution with 3:1 benzene–chloroform gave a solid (0.30 g), mp 241–244°, which after five recrystallizations from chloroform–hexane afforded an analytical specimen as rods: mp 246–248°; $[\alpha]_D$ −18.7° (*c* 0.643); ν_{max} 3400 (hydroxyl) and 1745 cm^{-1} (γ-lactone).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 77.07; H, 9.92.

Route B.—A sample (**2a**, 0.10 g) of 3β,20-dihydroxy-21-nor-5-cholenic acid γ-lactone (24 → 20) in tetrahydrofuran (30 ml) containing 1 drop of perchloric acid (70%) and suspended palladium on charcoal (25 mg, 10%) was shaken in an atmosphere of hydrogen for 2 hr. Filtration, dilution with chloroform, washing with saturated aqueous sodium bicarbonate, drying, and evaporation yielded a pale yellow oil (0.07 g). Repeated recrystallization from chloroform–hexane gave rods (0.02 g), mp 238–242°, identical with γ-lactone **4a** prepared by route A.

Hydrogenation of Methyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (5).—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate[6b] (**5**, 2.49 g) in ethyl acetate (150 ml) containing suspended palladium-on-charcoal catalyst (0.8 g, 10%) was shaken for 4 hr under hydrogen. Filtration and evaporation furnished a solid, which was chromatographed on acid-washed alumina (75 g) to yield the following products.

(1) A crystalline solid (0.12 g) was eluted by 3:1 hexane–benzene. Recrystallization from methanol gave slender needles (0.07 g), mp 173–177°. Two further recrystallizations from the same solvent gave an analytical specimen of **methyl 20-oxo-21-nor-5α-cholanate** (**6b**): mp 181–182°; $\nu_{max}^{CHCl_3}$ 1740 (methyl ester) and 1708 cm^{-1} (ketone), *no* absorption at 1250–1270 cm^{-1} (acetate); pmr δ 2.57 (multiplet, 4 protons, $-COCH_2CH_2CO_2-$) and 3.58 (singlet, 3 protons, methyl ester).

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.81; H, 10.17.

(2) A crystalline solid (1.63 g) was eluted by benzene. Recrystallization from methanol provided **methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate** (**6a**, 1.3 g), mp 126.5–128.5°. Further recrystallization gave an analytical specimen as blades: mp 128–129°; $[\alpha]_D$ +73.7° (c 1.49); pmr δ 1.97 (singlet, 3 acetate methyl protons), 2.56 (multiplet with strong central signal, 4 protons, $COCH_2CH_2CO_2$), and 3.57 (singlet, 3 methyl ester protons).

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; O, 18.49. Found: C, 72.20; H, 9.56; O, 18.41.

(3) A crystalline solid (0.22 g) was eluted by chloroform. Recrystallization from methanol gave 0.1 g, mp 198–203°, of **3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20) (4b).**—Another recrystallization from methanol gave an analytical sample as blades: mp 204–207°; $[\alpha]_D$ −25.3° (*c* 0.32); $\nu_{max}^{CHCl_3}$ 1760 (γ lactone) and 1720 cm^{-1} (3-acetate); pmr δ 0.72 (singlet, 3 protons, CH_3-18), 0.80 (singlet, 3 protons, CH_3-19), 1.94 (singlet, 3 acetyl methyl protons), and 4.3 (diffuse area, 2 protons, –COOCH).

3β-Acetoxy-20-hydroxy-21-nor-5α-cholanic Acid γ-Lactone (24 → 20) (4b). Method A.—To a solution of methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (**6a**, 0.25 g, 0.575 mmol) in dimethylformamide (13 ml) was added sodium borohydride (0.20 g, 5.57 mmol) in water (6 ml). After 72 hr at room temperature, isolation was achieved by dilution with water, treatment with 1 *N* hydrochloric acid, and filtration. The solid (0.22 g) was washed well with water, dried, and chromatographed in benzene on acid-washed alumina (10 g). The desired γ-lactone (**4b**, 0.17 g)[13] was eluted by 9:1 benzene–chloroform and recrystallized successively from methanol and isopropyl ether to give analytical specimen as blade clusters: mp 204–207°; $[\alpha]_D$ −13.5° (*c* 0.52); ν_{max}^{Nujol} 1770 (γ lactone) and 1735 cm^{-1} (acetate); pmr δ 0.72 (singlet, slight splitting, CH_3-18), 0.80 (singlet, 3 protons, CH_3-19), 1.94 (singlet, 3 protons, acetate), and 4–4.5 (unresolved region, 2 protons, –COOCH).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.60; H, 9.51; O, 15.90. Found: C, 74.38; H, 9.36; O, 16.37.

In another experiment[15] employing ketone **6a** (6.1 g, 14 mmol) in dimethylformamide (350 ml) and sodium borohydride (4.8 g, 127 mmol)–water (25 ml) at 0° for 17 hr, careful acidification (at 0° to congo red) and dilution with ice–water gave **methyl 3β-acetoxy-20ζ-hydroxy-21-nor-5α-cholanate.** Recrystallization from methanol–methylene chloride provided 3.4 g (56%) of crystals: mp 171–174°; ν_{max} 3500 (20-hydroxyl), 1725 (acetate and methyl ester), and 1260 cm^{-1}.

Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74; O, 18.41. Found: C, 71.99; H, 9.71; O, 18.28.

A sample (0.19 g) of the 20 alcohol in benzene was left on a column of silica gel (6 g) for 4 days. Elution with benzene–ethyl acetate mixtures and recrystallization of the product from methanol–methylene chloride afforded 0.11 g of lactone **4b**,[13] mp 204–207° (sintering from 195°).

Method B.—Methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**5**, 0.50 g, 1.2 mmol) was reduced during 2 hr with sodium borohydride (0.09 g, 2.4 mmol) in dimethylformamide (25 ml)–water (2.5 ml) as described above (method A). The same isolation procedure led to a colorless oil (0.5 g) which was saponified at reflux temperature during 2 hr in 0.5 *N* methanol–potassium hydroxide solution (20 ml). Dilution with water (50 ml), concentration *in vacuo* to 20 ml, acidification with 3 *N* hydrochloric acid, extraction with chloroform, and evaporation of solvent gave colorless acid **7** (0.2 g): mp *ca.* 220° dec; ν_{max}^{Nujol} 3000–3400 and 1726 cm^{-1} (carboxylic acid). A solution of acid **7** in tetrahydrofuran (40 ml) containing perchloric acid (1 drop, 70%) and suspended palladium-on-charcoal catalyst (50 mg, 10%) was hydrogenated at atmospheric pressure and room temperature for 2 hr. Filtration, concentration to 10 ml, dilution with chloroform, washing with sodium bicarbonate solution and water, drying, and evaporation yielded a discolored product (0.12 g). After acetylation a colorless solid (0.10 g), mp 192–197°, was isolated. Three recrystallizations from methanol gave crystals (0.02 g) of lactone **4b**:[13] mp 201–204°; ν_{max} 1770 (γ-lactone), 1730, and 1250 cm^{-1} (acetate).

Method C.—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (0.11 g)[6b] in acetic acid (20 ml) containing perchloric acid (2 drops) and suspended platinum from platinum oxide (0.05 g) was shaken in an atmosphere of hydrogen for 1 hr. Hydrogen adsorption was fast and essentially complete after 30 min. The solution was filtered, diluted with diethyl ether, and washed successively with saturated aqueous sodium bicarbonate and water. Removal of solvent furnished a viscous oil which crystallized slowly on standing. The product (0.12 g) was dissolved in 1:1 hexane–benzene and chromatographed on silica gel (3.5 g). Benzene eluted a colorless solid (0.045 g, essentially pure by thin layer chromatography). Recrystallization from

(13) The structure was confirmed by mixture melting point, thin layer chromatography, and ir spectral comparison with an authentic specimen.

(14) This experiment was performed by Dr. J. P. Yardley.

(15) By Dr. P. Sunder-Plassmann.

isopropyl ether gave lactone **4b**[13] as elongated prisms, mp 198–202°.

Method D.—A 7-mg sample of 3β,20-dihydroxy-21-nor-5-cholenic acid γ-lactone (**2a**) prepared by sodium borohydride reduction of methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**1b**) was acetylated. A solution of the crystalline acetate in ethyl acetate (10 ml) was hydrogenated with platinum oxide (10 mg) during 2 hr. Filtration and evaporation gave a solid residue. Following dissolution in methanol, filtration to remove flocculent material, and evaporation to small volume, lactone **4b**[13] crystallized as colorless needles (5 mg), mp 196–202°.

Method E.—Acetylation of 0.05 g of 3β,20-dihydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20) (**4a**) led to 0.04 g of solid acetate **4b**, mp 204–207°. Three recrystallizations from methanol gave plates: mp 208–209°; $[\alpha]D$ 0°; ν_{max} 1770 (γ lactone) and 1730 and 1250 cm^{-1} (acetate).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.20; H, 9.63.

Lactone **4b** obtained by this means was identical[13] in all respects with samples prepared by methods A–D.

3β-Acetoxy-23-methoxy-20-hydroxy-21-nor-5α-cholanic Acid γ-Lactone (24 → 20) (4c).—Methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**1b**, 0.16 g) in acetic acid (30 ml) containing perchloric acid (3 drops, 70%) was shaken in a slight positive pressure atmosphere of hydrogen with a catalyst from platinum oxide (0.075 g) for 2 hr. Filtration and addition to water gave a white precipitate (0.14 g), which was collected and water washed. Additional product (0.02 g) was obtained by extracting the filtrate with diethyl ether. The extract was successively washed with sodium bicarbonate solution and water. A solution of the crude material in benzene was chromatographed on silica gel (6 g). Two major fractions (0.12 g) were eluted by mixtures of 13:3 and 3:1 benzene and chloroform, but thin layer chromatograhy examination showed only partial separation. The total amount (0.12 g) was subjected to preparative thin layer chromatography on four plates each containing silica gel G (25 g). The solvent system was 1:1 hexane–ethyl acetate and bands were detected by water spraying. Components were isolated by chloroform extraction: lower band, 48 mg; center band, 26 mg; and upper band, 7 mg. The lower band crystallized from methanol as elongated prisms (25 mg): mp 228–232°; mixture melting point with 3β-acetoxy-20-hydroxy-5α-cholanic acid γ-lactone (**4b**) was depressed to 191–200°; $[\alpha]D$ 0°; $\nu_{max}^{CHCl_3}$ 1770 (γ lactone), 1720, 1255 (acetate), and 1135 cm^{-1} (methoxyl); pmr δ 0.71 (singlet, 3 protons, CH_3-18), 0.81 (singlet, 3 protons, CH_3-19), 1.96 (singlet, 3 protons, acetate), and 3.46 (singlet, 3 protons, methyl ether).

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.20; H, 9.32. Found: C, 72.05; H, 8.91.

3β,23-Diacetoxy-20-hydroxy-21-nor-5α-cholanic Acid γ-Lactone (24 → 20) (4d).—Methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate (**3**, 0.20 g) in acetic acid (40 ml) was hydrogenated for 1 hr using perchloric acid (4 drops, 70%) and platinum oxide (100 mg) essentially as noted above (*cf.* **4c**). The crude product (0.195 g) in benzene was chromatographed on silica gel (8 g) to yield in 9:1 → 3:1 benzene–chloroform mixtures a colorless solid (0.13 g, almost homogeneous by thin layer chromatography). Recrystallization from methanol gave needle clusters in two crops (0.06 g total), mp 197–202° and 204–208°. Recrystallization from the same solvent gave the analytical specimen as tiny crystals: mp 204–208°; $[\alpha]D$ −15.5° (c 0.32); $\nu_{max}^{CHCl_3}$ 1780 (γ lactone), 1740, and 1718 cm^{-1} (acetates); pmr δ 0.72, 0.74 (doublet, 3 protons, CH_3-18), 0.81 (singlet, 3 protons, CH_3-19), 1.96 (singlet, 3 protons, 3 acetate), and 2.09 (singlet, 3 protons, 23 acetate).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75; O, 20.84. Found: C, 70.59; H, 8.44; O, 20.83.

3-Oxo-20-hydroxy-21-nor-4-cholenic Acid γ-Lactone (24 → 20) (8). Procedure A.[16]—A solution of lactone **2a** in toluene (15 ml)–cyclohexanone (5 ml) was heated to reflux and 3 ml of toluene was removed by slow distillation to ensure dryness. To the hot solution was added aluminum isopropoxide (0.34 g, Matheson Coleman and Bell) in toluene (4 ml). The reaction mixture was heated at reflux with stirring for 25 min. Upon cooling, water (4 ml) was added. Following acidification with 2 *N* hydrochloric acid and extraction with diethyl ether, the ethereal extract was washed well with water. The residue obtained by removal of solvent was subjected to exhaustive steam distillation and the resulting crystalline residue was dissolved in chloroform and washed with water. Solvent was removed and the residue (0.22 g) was purified by preparative thin layer chromatography. Three plates were used and developed with 1:1 benzene–ethyl acetate. The product was recovered from the silica gel by repeated extraction with 19:1 chloroform–methanol. The 0.14-g sample of lactone **8** obtained in this manner was recrystallized from acetone–hexane to yield 0.12 g. The analytical sample was recrystallized from acetone: mp 220–223°; $[\alpha]D$ +78° (*c* 0.28); ν_{max} 1760 (γ lactone), 1673 (3 ketone), and 1612 cm^{-1} (4 olefin); pmr δ 0.79 (CH_3-18), 1.12 (CH_3-19), 4.25 (multiplet, 1 proton, H-20), and 5.48 (singlet, 1 proton, H-4).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.48; H, 9.05. Found: C, 77.52; H, 8.85.

Procedure B.—To a solution of 3β,20-dihydroxy-21-nor-5-cholenic acid γ-lactone **2a** (0.37 g) in toluene (15 ml)–cyclohexanone (2 ml) was added aluminum *t*-butoxide (0.40 g). The mixture was heated at reflux for 4 hr, and the resulting yellow suspension was cooled, diluted with diethyl ether (50 ml), and washed successively with hydrochloric acid (20%), saturated sodium bicarbonate, and water. Evaporation of solvent gave a colorless solid (0.40 g) which was chromatographed on acid-washed alumina (15 g). Elution with 5:1 benzene–chloroform gave a solid (0.23 g, 62%), mp 207–211°. Five crystallizations from chloroform–diethyl ether afforded microneedles: mp 210–211°; ν_{max}^{Nujol} 1740 (γ lactone), 1690 (3 ketone), and 1618 cm^{-1} (4 olefin); λ_{max}^{EtOH} 241 mμ (log ε 4.21).

Anal. Found: C, 77.93; H, 9.09.

Further elution with 5:1 benzene–chloroform returned starting material (0.06 g).

Registry No.—**2a**, 23330-63-4; **2b**, 23330-64-5; **4a**, 23330-65-6; **4b**, 23330-66-7; **4c**, 23367-50-2; **4d**, 23330-67-8; **6a**, 23330-48-5; **6b**, 23330-69-0; **8**, 23330-70-3; methyl 3β-acetoxy-20ζ-hydroxy-21-nor-5α-cholanate, 23330-71-4.

(16) Performed by Dr. J. P. Yardley.

Bufadienolides. 3. A Synthetic Route to Isocardenolides[1]

GEORGE R. PETTIT,[2a] BRIAN GREEN, ARUN K. DAS GUPTA,[2b]
PHILIP A. WHITEHOUSE, AND JOHN P. YARDLEY

Department of Chemistry, University of Maine, Orono, Maine 04473, and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received February 11, 1969

A Bestmann reaction employing 3β-acetoxy-20-oxo-21-iodo-5-pregnene (**2**) and carbomethoxymethylenetriphenylphosphorane was used to complete a synthesis of methyl 3β-acetoxy-2-oxo-21-nor-5-*trans*-22-choladienate (**1**), which upon irradiation in sunlight gave *cis* isomer **5**. Similarly, 3β-acetoxy-20-oxo-21-iodo-5,16-pregnadiene (**6**) was converted into *trans* side-chain olefin **7** and *cis* side-chain olefin **8**. Palladium-catalyzed hydrogenation of triene **8** resulted in methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (**9a**) accompanied by small amounts of the corresponding 3-deoxy derivative **9b** and 3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20). Subjecting triene **8** to sodium borohydride reduction in ethanol yielded isocardanolide **10**. The principal objective, synthesis of isocardenolide **11**, was realized by selective reduction of ketone **5** with sodium borohydride in dimethylformamide.

Although a variety of synthetic approaches[3] to cardenolides[4] have been described, only one example each of the two possible isocardenolides bearing an unsubstituted lactone ring have been recorded.[5] Synthesis of γ-keto acrylate **1** was considered the key stage in a systematic approach to bufadienolide[6] and isocardenolide systems. Condensation of pregnenolone with glyoxylic acid followed by methylation and acetylation steps was initially employed to obtain ketone **1**, but increasing demand for this compound led us to develop a more efficient synthesis.[7] The first steps comprised conversion of pregnenolone acetate into the 20-enol acetate followed by treatment with N-iodosuccinimide to provide 21-iodo-20 ketone **2**.[8a] Treatment of this compound with carbomethoxymethylenetriphenylphosphorane[9] in toluene provided *trans* olefin **1** in 43% yield.[10]

Some related experiments aimed at further simplifying conversion of a 20-oxopregnane into a γ-keto acrylate derivative were also explored, including the treatment of 3β-acetoxy-20-oxo-5α-pregnane with dioxane dibromide[11] to yield 21-bromo ketone **3**.[12,13] It is interesting to note here that direct halogenation of a 20-oxopregnane bearing a proton at C_{17} yields the 17α-halo derivative; however, bromination of a 20 ketal has been used for substitution at C_{21}.[14] To confirm the structural assignment **3**, diazo ketone **4a** was allowed to react with hydrogen bromide to give the 21 bromide, which was identical with the dioxane dibromide product. Conversion of 21 bromide **3** into the corresponding 21 iodide employing sodium iodide proved unsatisfactory, but application of the Bestmann reaction to the bromide afforded, in low yield, *trans* olefin **4b**.

Both the glyoxylic acid and iodo ketone synthetic routes to olefin **1** yielded the yellow *trans* geometrical isomer, whose pmr spectrum showed the 22- and 23-olefin proton signals as a pair of doublets at δ 6.28, 6.54, 6.82, and 7.04 with a coupling constant of 15 cps, characteristic of a *trans* configuration.[15] A minor constituent of the Bestmann reaction product was the colorless *cis* isomer **5**, showing a pair of doublets in the pmr spectrum at δ 5.81, 5.90, 6.17, and 6.36 with J = 11 cps, assignable to 22,23-*cis* protons. An infrared spectral comparison of the *cis* and *trans* isomers also supported these assignments. The conjugated double-bond absorption of the *trans* isomer appears at 1628 cm^{-1} and for the *cis* isomer at 1620 cm^{-1}

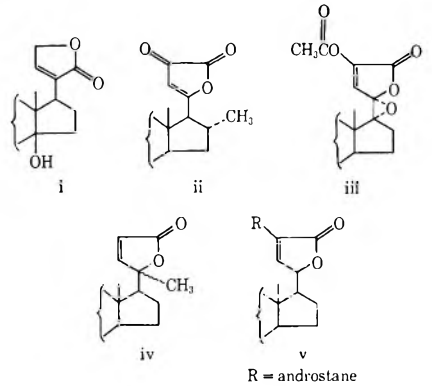
(1) (a) Part 2: G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **34**, 1377 (1969). (b) This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-07 and CA-10115-01 from the National Cancer Institute. (c) A preliminary report of the present study was summarized in part by G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964).

(2) (a) To whom correspondence should be addressed at Arizona State University; (b) Research Division, East India Pharmaceutical Works, Calcutta, India.

(3) For leading references, consult G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970); J. M. Ferland, Y. Lefebvre, and R. Deghenghi, *Tetrahedron Lett.*, 3617 (1966). The chemistry of butenolides has been reviewed: Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964). For more recent advances, see W. W. Epstein and A. C. Sonntag, *J. Org. Chem.*, **32**, 3390 (1967); P. E. Sonnet, *Chem. Ind.* (London), 1296 (1967).

(4) T. Reichstein, *Naturwissenschaften*, **54**, 53 (1967).

(5) The designation isocardenolide has been suggested (**1a**) as a means of designating cardenolide-type steroids where the butenolide ring has been substituted at positions 21 or 22 instead of 20. An example (**11**) of the parent 21 isomer was described in a prelimary report[1c] of the present study, and the 22 counterpart (i) has recently been reported (see Ferland, ref 3). Beginning in 1959, several lactone-substituted isocardenolides (ii–v) were synthesized; see, respectively, K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959); R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 353 (1962); B. Camerino and U. Valcavi, U. S. Patent 3,068,229 (1962); *Chem. Abstr.*, **58**, 9183 (1963); J. E. Baldwin, *Tetrahedron*, **20**, 2933 (1964).



(6) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(7) The phosphorane step we wish to designate as the Bestmann reaction; see ref 6, footnote 34, and ref 10.

(8) (a) C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **75**, 3493 (1953).

(9) O. Isler, H. Gutmann, N. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

(10) H. J. Bestmann, *Angew. Chem. Int. Ed. Engl.*, **4**, 583 (1965).

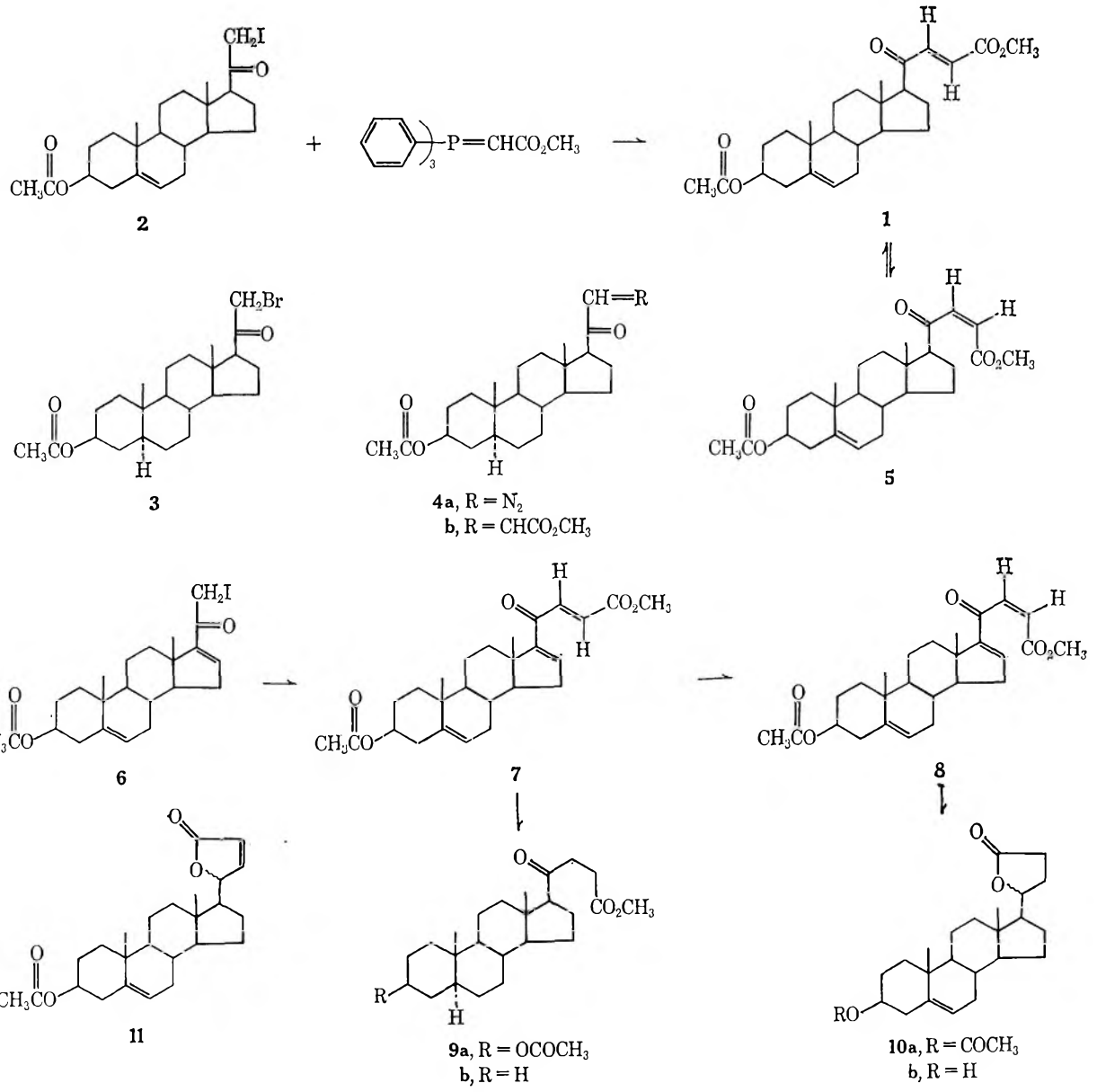
(11) N. N. Suvorov, L. V. Sokolava, Z. A. Yaroslavtseva, Z. D. Ovchinnikov, V. S. Murasheva, and F. Y. Leibel'man, *J. Gen. Chem. USSR*, **31**, 3469 (1961).

(12) We thank Dr. S. K. Sengupta for a rotatory dispersion curve of this compound.

(13) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Amer. Chem. Soc.*, **81**, 2383 (1959).

(14) A. Marquet and J. Jacques, *Bull. Soc. Chim. Fr.*, **90** (1962).

(15) K. L. Rinehart, C. E. Coverdale, and P. K. Martin, *J. Amer. Chem. Soc.*, **88**, 3150 (1966).



with increased intensity. To provide further material, *trans* olefin **1** in benzene was irradiated with a sun lamp to give, after 5 days, a high yield of the *cis* isomer, which could be reconverted into the *trans* form by mild acid treatment.

An indication of the general utility of the transformation **2** → **5** was obtained by converting 3β-acetoxy-20-oxo-5,16-pregnadiene into 21-iodo ketone[16a] **6** and thence to yellow *trans* olefin **7** and colorless *cis* olefin **8**. The pmr data for both isomers supported the assignments, and both *cis* and *trans* isomers displayed double-bond absorption at 1580 cm^{-1}; in this case absorption was more intense for the *trans* isomer. Palladium-catalyzed hydrogenation of *trans* olefin **7** led to saturated ester **9a**, previously obtained[1a] by hydrogenation of *trans* olefin **1**, together with small amounts of the corresponding 3-deoxy derivative **9b** and 3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (**24** → **20**) as observed earlier.[1a] A more selective reduction was achieved when an equilibrium mixture (1:6 *trans–cis*) was allowed to react with sodium borohydride in cold ethanol. Following a 4-hr period the previously obtained lactone **10a** was formed in reasonable yield. For purposes of evaluating the ease of reduction of the 16 double bond under these conditions, 3β-acetoxy-20-oxo-5,16-pregnadiene was treated in the same way to give as the major product, after reoxidation of the 20 alcohol with Jones reagent, pregnenolone acetate.[16b]

The route to isocardenolide **11** was satisfactorily completed by selective reduction of *cis* isomer **5** using sodium borohydride in dimethylformamide at room temperature. The pmr spectrum of lactone **11**, particularly the doublet centered at δ 7.25 (J = 5 cps) attributable to the C-23 olefinic proton, and the double doublet centered at δ 5.86 of the C-22 proton, confirmed the structural formulation. The C_{18} methyl signal was split, indicating, as with other borohydride reductions of the 20-keto group,[1a] that the product was a mixture of C-20 epimers. The reduction reaction was quite sensitive to experimental conditions and could be diverted, as already mentioned, with γ-keto acrylate **8** to yield lactone **10a**.

(16) (a) C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **76**, 1722 (1954). (b) *Cf.* D. Kupfer, *Tetrahedron*, **15**, 193 (1962).

Isocardenolide **11** was studied by Dr. K. Repke using an ATPase test system and found completely inactive up to concentrations as high as 0.1 m*M;* it therefore appeared devoid of any cardiac activity.[17]

General endocrinological evaluation of the steroids reported herein is being carried out under auspices of the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

Experimental Section[18]

Methyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (1).—To a refluxing solution of carbomethoxymethylenetriphenylphosphorane[9] (18.1 g, 54 mmol) in toluene (120 ml) was added in one portion under nitrogen, 3β-acetoxy-20-oxo-21-iodo-5-pregnene[8a] (12.5 g, 25.9 mmol) in toluene (60 ml). The solution quickly became straw colored and solid material began to separate after 5 min. After the solution had been heated at reflux for 4 hr and cooled, the solid phase (8.6 g) was collected and washed with toluene. The filtrate and washings were treated with methyl bromoacetate (3.8 ml), and heated at reflux for 2 hr to give a thick precipitate which was separated upon cooling (4.3 g). After standing at room temperature for 20 hr, the filtrate was concentrated to a dark brown residue (16 g) which was chromatographed on acid-washed alumina. Elution with benzene gave a yellow solid (6.02 g), which recrystallized from benzene–hexane as yellow needles (4.75 g, 43%): mp 156–158° (three recrystallizations from methanol did not change the melting point); $[\alpha]^{22}D$ +43.5° (c 0.8); ν_{max} 1730, 1250 (acetate), 1735 (methyl ester), 1690 (conjugated ketone), and 1628 cm^{-1} (conjugated double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.68 (singlet, 3 protons, methyl ester), 5.20 (multiplet, 1 proton, C-6 olefin H), and 6.28, 6.54, 6.82 and 7.04 (quartet, 2 protons, J = 15 cps, 22,23-*trans* protons).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47; O, 18.67. Found: C, 73.00; H, 8.39; O, 18.81.

3β-Acetoxy-20-oxo-21-bromo-5α-pregnane (3). Method A.—To purified dioxane (7 ml)–heptane (7 ml) at 0° was added, with occasional shaking, a cooled solution of bromine (14 g) in heptane (14 ml). The yellow precipitate which separated from the deep brown solution was collected, washed with heptane, and dried *in vacuo*. The dioxane dibromide slowly decomposed on storage. To a stirred solution of 3β-acetoxy-20-oxo-5α-pregnane (5.0 g, 14 mmol) in methanol (85 ml)–chloroform (15 ml) was added dioxane dibromide (3.5 g, 14.1 mmol) in methanol (15 ml) at 20°. Decolorization occurred after 90 min with simultaneous separation of a white solid. Stirring was continued for an additional 15 min and the mixture was diluted with chloroform (400 ml) and washed successively with 4% aqueous sodium hydroxide solution and water, followed by evaporation of the chloroform solution to yield a solid. Recrystallization from methanol–diethyl ether afforded crystals, mp 140–143° (3.8 g), mmp 115–129° with starting material. The analytical specimen[19] was obtained by two recrystallizations from methanol, mp 148–149.5°, $[\alpha]^{23}D$ +90.8° (c 0.091).

Anal. Calcd for $C_{23}H_{35}O_3Br$: C, 62.84; H, 8.03; Br, 18.19. Found: C, 63.04; H, 8.00; Br, 18.01.

Method B.[20]—Hydrogen bromide gas was bubbled slowly through the yellow solution of diazo ketone **4** (0.30 g, see part 7) in dry diethyl ether (50 ml) at room temperature. After 20 min the color disappeared, and evaporation of solvent gave a crystalline residue (0.35 g), mp 136–140°. One recrystallization from benzene–hexane yielded crystals, mp 143–146°, identical[21] with a specimen prepared by method A.

Methyl 3β-Acetoxy-20-oxo-21-nor-5α-chol-*trans*-22-enate (4b).—Bromo ketone **3** (4.4 g) was condensed with carbomethoxymethylenetriphenylphosphorane (6.8 g) in toluene (40 ml) as summarized for synthesis of olefin 1 (see above). Isolation and recrystallization from 95% ethanol gave 1.2 g of *trans* olefin **4b** as pale yellow prisms: mp 129–130°; ν_{max} 1730, 1680, 1658, and 1240 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.67; H, 9.00; O, 18.21.

Methyl 3β-Acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (5). Procedure A.—During the preparation of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (1), a 2.7-g fraction obtained by elution with benzene was crystallized from methanol to give yellow *trans* isomer 1 (1.8 g). Upon concentration, the mother liquors gave a sticky, colorless product (0.9 g). Three recrystallizations from methanol led to colorless plates (0.12 g), mp 172–176°. Two more recrystallizations from the same solvent gave an analytical specimen of *cis* isomer **5**: mp 177–179°; $[\alpha]D$ +33.7° (c 0.697); ν_{max} 1730 (acetate and methyl ester), 1690 (conjugated ketone), and 1620 cm^{-1} (conjugated double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.64 (singlet, 3 protons, methyl ester), 5.20 (multiplet, 1 proton, H-6), and 5.81, 5.90, 6.17, and 6.36 (2 doublets, 2 protons, J = 11 cps, 22,23-*cis* protons).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.92; H, 8.61.

Procedure B.—A sample (0.10 g) of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (1) in benzene was irradiated with a General Electric sun light for 5 days, during which time the yellow color gradually faded.

Progress of the reaction was followed by thin layer chromatography, the *cis* isomer having a lower R_f value than the *trans* isomer. Removal of solvent afforded a crystalline residue. Three recrystallizations from methanol gave a pure sample as colorless plates (0.075 g), mp 176–178°, identical[21] in all respects with material obtained by method A.

Conversion of Methyl 3β-Acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate to the *trans* Isomer (5 → 1).—Methyl 3β-acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (**5**, 50 mg) in methanol (3 ml)–diethyl ether (3 ml) was treated with 1 drop of 2 *N* hydrochloric acid at room temperature. After 20 hr the solution which had gradually developed a yellow color was diluted with diethyl ether and washed twice with water. Drying and evaporation furnished a pale yellow oil. The crude product crystallized and a thin layer chromatogram indicated largely *trans* isomer 1, a trace of *cis* isomer **5**, and a smaller amount of more polar material, a hydrolysis product.

Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (7).—A solution of 3β-acetoxy-20-oxo-21-iodo-5,16-pregnadiene[16a] (**6**, 6.5 g, 13.5 mmol) in dry toluene (30 ml) was added to a refluxing solution of carbomethoxymethylenetriphenylphosphorane (9.4 g, 28.07 mmol) in toluene (60 ml). The reaction was performed exactly as described above with 21-iodo pregnene **2** to yield a sticky solid (9.6 g). Chromatography on acid-washed alumina and elution with 2:1 benzene–hexane furnished a yellow solid (2.8 g), which recrystallized from acetone–methanol as silky, yellow needles, mp 153–154°. Further attempts to purify caused a drop in melting point and were not pursued: ν_{max} 1728 (methyl ester and acetate), 1661 (ketone), 1620 (conjugated double bond), and 1580 cm^{-1} (16 double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.68 (singlet, 3 protons, methyl ester), 5.20 (multiplet, C-6 olefin proton), 6.70 (multiplet, C-16 olefin proton), and 6.33, 6.60, 7.22, and 7.46 (2 doublets, 2 protons, J = 15 cps, 22,23-*trans* protons).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04; O, 18.70. Found: C, 73,13; H, 8.07; O, 18.87.

Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*cis*-22-cholatrienate (8).—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5,12-*trans*-22-cholatrienate (**7**, 0.27 g) in benzene (10 ml) was irradiated during 4 days[22] with a General Electric sun lamp at a distance of 4 ft. Removal of solvent *in vacuo* gave a very pale yellow oil which crystallized upon trituration with hexane. Recrystallization from hexane afforded nearly colorless crystals (0.22 g), mp 110–115°; a second crop (0.04 g) melted at 108–112°. Recrystalliza-

(17) We are grateful to Dr. K. Repke, Institute für Biochemie, Berlin, for this valuable information.

(18) Unless otherwise described, the infrared spectra were determined using potassium bromide pellets and optical rotation values were observed at 20° in chloroform solution. Proton magnetic resonance measurements (by Dr. R. A. Hill) were made in deuteriochloroform solution with tetramethylsilane as internal standard. Melting points were observed using a Kofler melting point apparatus. Other general experimental techniques, reagents, and chromatographic absorbents are summarized in the experimental introduction of part 2.[1a]

(19) Reference 12 reports a melting point of 142–143°; R. E. Marker and H. M. Crooks [U. S. Patent 2,369,065 (1945); *Chem. Abstr.*, **39**, 4197 (1945)] quote a melting point of 145–147°.

(20) We wish to thank David S. Blonda for assistance with this experiment.

(21) Mixture melting point determination and infrared spectral comparison supported this observation.

(22) The *cis/trans* ratio appeared by tlc to have reached an equilibrium value. A pmr spectrum of the equilibrium mixture indicated the *cis/trans* ratio to be 17:3.

tion of the first crop from hexane gave colorless prism clusters (0.18 g), mp 112–115°. A final recrystallization from hexane–isopropyl ether gave the analytical specimen as plate clusters: mp 113–115°; $[\alpha]_D$ −34.3° (c 0.58); ν_{max} 1728 (methyl ester and acetate), 1655 (ketone), 1638 (sh, conjugated double bond), and 1580 cm^{-1} (w, 16 double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.56 (singlet, 3 protons, methyl ester), *ca.* 5.2 (multiplet, C-6 olefin proton), *ca.* 6.2–6.3 (multiplet, C-16 olefin proton), 5.68, 5.87, and 6.24 (obscured), and 6.42 (2 doublets, J = 11 cps, 22,23-*cis* protons).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04; O, 18.76. Found: C, 72.92; H, 8.01; O, 19.20.

Hydrogenation of Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (7).—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (**7**, 0.45 g) in ethyl acetate (25 ml) was shaken under slightly positive pressure of hydrogen with palladium on charcoal catalyst (0.2 g, 10%) for 3 hr at room temperature. Filtration and evaporation of solvent gave a colorless solid whose thin layer chromatogram indicated **methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate** (**9a**) as major product, accompanied by small amounts of **methyl 20-oxo-21-nor-5α-cholanate** (**9b**) and **3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20)**.[1a,21] Recrystallization from methanol gave blades (0.25 g), mp 119–122°. Two more recrystallizations from methanol raised the melting point to 123–125°, but a thin layer chromatogram still suggested presence of a small amount of 3-deoxy derivative **9b**. Thus a sample (0.14 g) was chromatographed on acid-washed alumina (6 g) to give, on elution with benzene, methyl ester **9a**[21] (0.11 g), pure by tlc. Recrystallization from ethanol afforded blades, mp 126–128°, $[\alpha]_D$ +63° (*c* 0.78).

Sodium Borohydride Reduction of Methyl 3β-Acetoxy-20-oxo-21-nor-5,16,22-cholatrienate (8).—An equilibrium mixture (1.3 g) comprising *ca.* 85% *cis* olefin **8** and 15% *trans* olefin **7** in ethanol (40 ml) was cooled in an ice bath and treated dropwise with sodium borohydride (0.63 g) in ethyl alcohol (10 ml). The course of the reaction was monitored by thin layer chromatography, and after 4 hr essentially no starting material remained. The mixture was poured with stirring into ice–dilute hydrochloric acid and extracted with chloroform. The combined extract was washed with water and concentrated to dryness to give a residue which was chromatographed on acid-washed alumina (10 g). Elution with diethyl ether gave an oily solid fraction weighing 0.72 g, which was purified by preparative layer chromatography using six plates and 2:1 benzene–ethyl acetate as the mobile phase. The specimen of lactone **10a** obtained was crystallized from acetone–hexane to yield 0.46 g. A pure specimen recrystallized from methanol as plates, mp 226–229°.

In another experiment, 0.45 g of the *cis–trans* mixture in ethanol (40 ml) was reduced as described above with sodium borohydride (0.41 g) in ethanol (10 ml). Upon preparative layer chromatography, the less polar product (R_f 0.5–0.6) led to 0.26 g of lactone **10a**, and a more polar (R_f 0.3) fraction was found to be the 3β-hydroxy derivative **10b** (51 mg). Two recrystallizations of alcohol **10b** from acetone afforded 18 mg, mp 246–249°. Both specimens (**10a** and **10b**) were identical[21] with authentic samples.[1a]

Sodium Borohydride Reduction of 3β-Acetoxy-20-oxo-5,16-pregnadiene.—Reduction of 3β-acetoxy-20-oxo-5,16-pregnadiene (1.0 g) in ethanol (40 ml) using sodium borohydride (0.70 g) in ethanol (20 ml) was conducted as summarized for ketone **8** (see above). In this case, reduction appeared by tlc to be complete in 3 hr and 20 min at room temperature. A sample (0.28 g) of the crude product (1.0 g) in acetone (10 ml) was treated with an 8 *N* chromium trioxide reagent[23] until oxidant was present in slight excess (*ca.* 0.2 ml). After 2 min, isopropyl alcohol (0.2 ml) was added and the solution was diluted to 100 ml with water. Extraction with diethyl ether and purification by preparative layer chromatography (three plates using 2:1 benzene–ethyl acetate as mobile phase) and collection of the band with R_f 0.65–0.72 led to 0.16 g of pregnenolone acetate[21] estimated by pmr and ir measurements to be more than 90% pure. The minor contaminant appeared to be starting material.

3β-Acetoxy-20-hydroxy-21-nor-5,22-choladienic Acid γ-Lactone (24 → 20) (11).—To a solution of methyl 3β-acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (**5**, 0.30 g, 0.7 mmol) in dimethylformamide (21 ml) at room temperature was added sodium borohydride (0.14 g, 3.65 mmol) in water (2 ml) with magnetic stirring. After 7 hr the mixture was poured into water and acidified with 2 *N* hydrochloric acid to give a gelatinous precipitate which was collected by filtration and washed with water. A solution of the colorless solid (0.27 g) in 2:1 benzene–hexane was chromatographed on silica gel (10 g) to yield in 3:1 → 73:27 benzene–chloroform a solid (0.23 g). Recrystallization from diethyl ether or isopropyl ether gave crystals, mp 223–227°. The analytical specimen separated from isopropyl ether as blades: mp 225–227°; ν_{max} 1745 (unsaturated γ lactone) and 1720 cm^{-1} (acetate); $[\alpha]_D$ −51.8° (*c* −0.62); pmr 0.75, 0.83 (doublet, 3 protons, CH_3-18), 1.01 (singlet, 3 protons, CH_3-19), 1.97 (singlet, 3 protons, 3 acetate), 5.2 (multiplet, C-6 olefin proton), 5.86 (double doublet, J = 5 cps, C-22 olefin proton), and 7.2 and 7.3 (doublet, J = 5 cps, C-23 olefin proton).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.82; H, 8.71.

Registry No.—**1**, 2330-45-2; **4b**, 23330-46-3; **5**, 23367-42-2; **7**, 23330-47-4; **8**, 23367-43-3; **9a**, 23330-48-5; **11**, 23330-49-6.

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

Bufadienolides. 4. Reaction of 20-Oxo Steroids with Methoxymethylenetriphenylphosphorane[1]

GEORGE R. PETTIT,[2a] BRIAN GREEN,[2b] GEORGE L. DUNN,[2b] AND PAUL SUNDER-PLASSMANN[2c]

Department of Chemistry, University of Maine, Orono, Maine 04473, and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received February 11, 1969

Reaction of 20-oxo-5-pregnenes **1a–1c** with the ylide prepared from methoxymethyltriphenylphosphonium chloride was studied in detail. Vinyl ether **2a** was also obtained along with a comparable amount of 3β-acetoxy-26,27-bisnor-5,20(22)cholestadiene (**3a**), employing the mixture of phosphoranes from methoxymethyltri-*n*-butylphosphonium chloride. Acid-catalyzed hydrolysis of vinyl ether **2** afforded aldehyde **4**. Attempts to condense methoxymethylenetriphenylphosphorane with *trans* olefinic ketone **5a**, *cis* olefinic ketone **6a**, or saturated ketone **7a** led to extensive side reactions attributable to the methyl ester group. Use of the carboxylic acid (**7j**) or the *t*-butyl ester (**7b**) or amide (**7d**) eliminated side reactions but satisfactory involvement of the 20 ketone was not realized.

A potentially efficient method planned[3a] for transforming a 20-oxopregnane to a bufadienolide involved two key stages comprising (a) the condensation of the ketone with a glyoxylic acid derivative to yield a β-acyl acrylate (**1a** → **6a**) and (b) the condensation of the acrylate with methoxymethylenetriphenylphosphorane to afford an open-chain precursor[3b] (**6b**) of the 2-pyrone. Simultaneously with studies[3a,4] aimed at obtaining the necessary acrylic acids, model experiments needed for the vinyl ether step were also initiated and are summarized herein.

When the generation of a 21-aldehyde substituent *via* the methoxymethylene derivative of a 20 ketone was considered in 1957, Wittig-type reactions employing a methoxymethylenephosphorane had not been described, but condensation of methoxymethylenetriphenylphosphorane with tigogenone, a 3-oxo steroid, was reported in the following year[5] and, subsequently, Wittig[6] described an extensive investigation of this route to vinyl ethers and aldehydes, emphasizing the synthetic utility of such reactions. Consequently, experiments now described were limited to the required 20-oxo steroid model compounds.

Reaction between pregnenolone acetate (**1a**) and methoxymethylenetriphenylphosphorane was selected for detailed examination. The ylide which was prepared from the corresponding phosphonium chloride using either *n*-butyllithium or potassium *t*-butoxide[7] as base gave, after several days with pregnenolone acetate in ether, vinyl ether **2a** in 30% yield. The use of tetrahydrofuran as solvent and pregnenolone (**1b**) increased the yield to 42%, but to improve this still further the use of an aliphatic phosphorane[8] such as methoxymethylenetri(methoxymethyl)phosphorane was considered. In order to obtain the precursor phosphonium salt of this ylide, an organometallic derivative of chloromethyl methyl ether would have been required. At that time no workable procedure was available,[9] and so the more readily available phosphorane mixture derived from methoxymethyltri-*n*-butylphosphonium chloride[10] was employed, leading on reaction with pregnenolone (**1b**) to vinyl ether **2a** in 35% yield (after acetylation) accompanied by a similar quantity of olefin **3a**. Addition of *n*-butyllithium to pregnenolone and acid-catalyzed dehydration (following acetylation) of the resulting tertiary alcohol provided an authentic specimen of the latter. Location of the side-chain double bond was substantiated by appearance of two (C-6 and C-22) olefin proton signals at δ 5.1–5.5 in the pmr spectrum. Before it could be determined whether olefin **3a** arose from excess *n*-butyllithium accompanying the phosphorane reagent or whether preparation of vinyl ether **2a** could be substantially improved using methoxymethylenetri(methoxymethyl)-phosphorane a more convenient route was found and these points were not further pursued.

A survey[11] of the Wittig reaction with various keto steroids indicated that functional groups, *i.e.*, hydroxyl and acetoxy, decreased the yield but that the tetrahydropyranyl ether protecting group did not have this detrimental effect. Condensing pyranyl ether **1c** with methoxymethylenetriphenylphosphorane in tetrahydrofuran afforded vinyl ether **2c** in 47% yield, but replacing tetrahydrofuran by diethylene glycol dimethyl ether and heating the mixture at reflux for 7 hr raised conversion to 83%.[12] Treating vinyl ethers **2b** and **2c** with 70% perchloric acid–diethyl ether[5] resulted in ready hydrolysis to aldehyde **4**, previously obtained[13] by ozonolysis of stigmasterol. With good overall conversion of 20-oxopregnane **1c** into aldehyde **4** established, extension to 20-oxonorcholadienates **5a** and **6a** was next undertaken.

(1) (a) Preceding contribution: G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *J. Org. Chem.*, **35**, 1381 (1970). (b) This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-07 and CA-10115-01 from the National Cancer Institute.

(2) (a) Arizona State University; (b) University of Maine; (c) Farbenfabriken Bayer A. G., 509 Leverkusen, Germany.

(3) (a) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970). (b) Later we learned that analogous intermediates derived from isopropyl and cyclohexyl bromides have been hydrolyzed to the corresponding 5-substituted 2-pyrones: R. Nicoletti, *Ann. Chim.* (Rome), **51**, 1260 (1961).

(4) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1377 (1970).

(5) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958). We are indebted to Dr. Levine for providing us with his experimental procedure prior to publication.

(6) (a) G. Wittig and E. Kanuss, *Angew. Chem.*, **71**, 127 (1959); (b) G. Wittig, W. Böll, and K. H. Krück, *Chem. Ber.*, **95**, 2514 (1962).

(7) *Cf.* R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(8) S. Tripett and D. M. Walker, *Chem. Ind.* (London), 933 (1960); A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

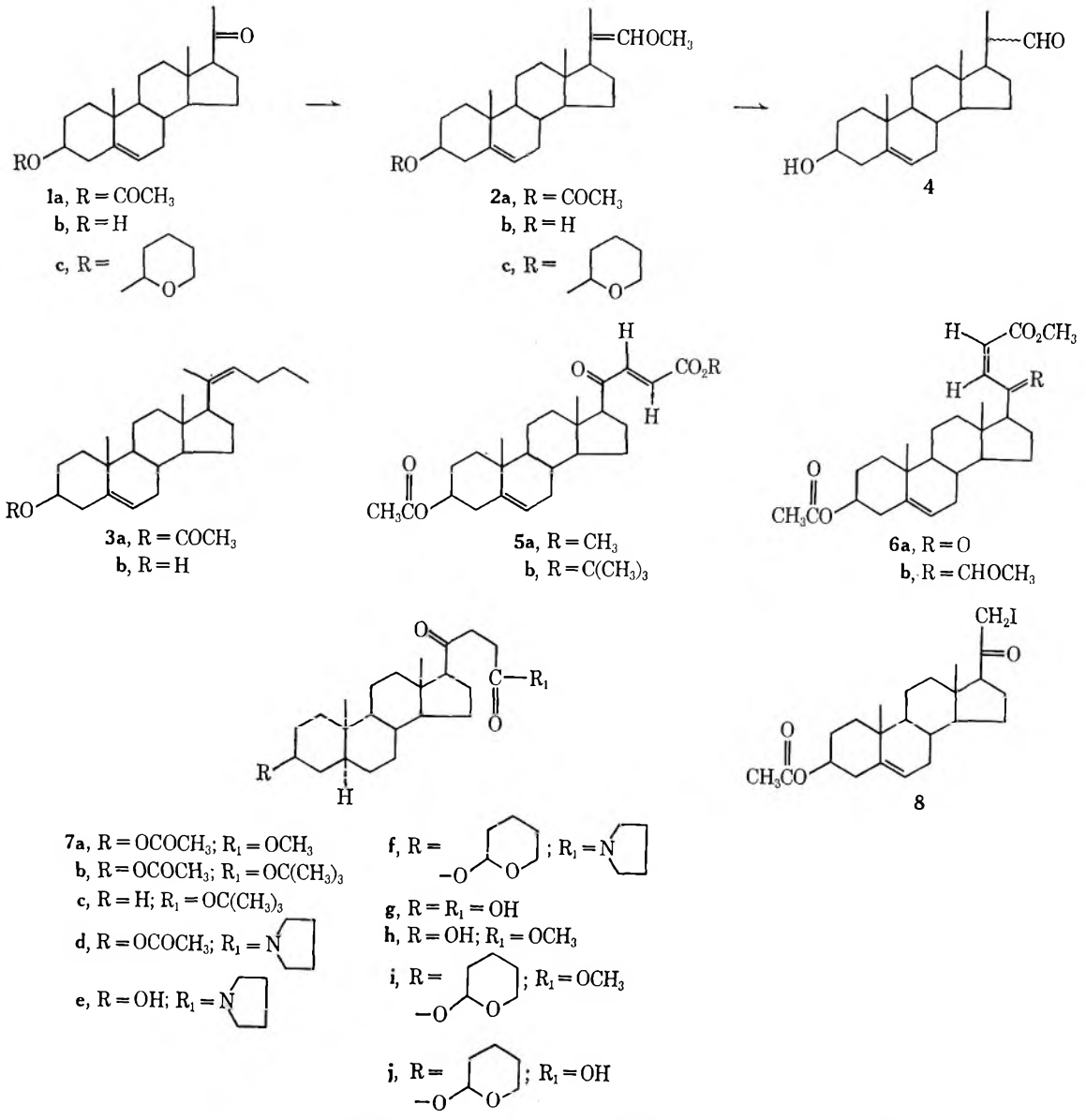
(9) Since then organometallic derivatives of chloromethyl methyl ether have been described: H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959); U. Schöllkopf and H. Küppers, *Tetrahedron Lett.*, 1503 (1964).

(10) *Cf.* D. E. Bissing, *J. Org. Chem.*, **30**, 1296 (1965); C. Screttas and A. F. Isbell, *ibid.*, **27**, 2573 (1962).

(11) F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, **79**, 5029 (1957).

(12) An infrared spectral study suggested presence of the other geometrical isomer in the mother liquors, indicating higher yields of the vinyl ether; this isomer was not isolated.

(13) M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.*, **74**, 3627 (1952).



Efforts to cause the phosphorane to react selectively with these isomers employing various modifications of the procedure developed for synthesis of **2a**, including generation of the reagent in dimethyl sulfoxide,[14] gave only complex reaction mixtures, suggesting involvement of the olefinic[15] and/or ester groups. Similar unencouraging results were obtained using saturated keto ester **7a**, thereby implicating the methyl ester.[16] Protection of the 24-carboxylate function was then undertaken by condensing *t*-butylcarboxymethylenetriphenylphosphorane with 21-iodo ketone **8** to provide *t*-butyl ester **5b**,[4] which was converted by palladium-catalyzed hydrogenation into the saturated analog **7b** and a small amount of the 3-deoxy derivative **7c**. Interestingly, keto ester **7b** was essentially unaffected by treatment with methoxymethylenetriphenylphosphorane in dimethyl sulfoxide.

Limited reactivity at the 20-oxo position of ester **7a** had been initially attributed to increased steric shielding as compared to 20 ketone **1a**, resulting in competitive reaction at the ester carbonyl; in the case of the *t*-butyl ester it is obvious that both carbonyl groups are now too sterically hindered for successful involvement.

Reducing the protecting group size by using pyrrolidine amide **7d** did not improve the situation, and again substantial amounts of starting material were recovered. Alcohol **7e** and tetrahydropyranyl ether **7f** were also prepared during this period but offered no advantage over 3β-acetoxy amide **7d**. Finally, it was decided to protect position 24 as the carboxylate anion and position 3 with a tetrahydropyranyl ether group. Toward this end, ester **7a** was saponified and the resulting carboxylic acid **7g** was remethylated to provide ester **7h**. Following reaction with dihydropyran, **7i** was isolated and converted into acid **7j**. Attempts at condensing the dimethyl sulfoxide soluble lithium salt with methoxymethylenetriphenylphosphorane or the more nucleophilic O,O-diethylcyanomethylphosphonate[17] led to good recovery of starting material **7j** emphasizing the serious steric effect at C-20 of the cholanic acid

(14) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(15) Double bonds of α,β-unsaturated ketone systems are known to react with phosphoranes to give cyclopropane derivatives: H. L. Bestmann and F. Seng, *Angew. Chem.*, **74**, 154 (1962).

(16) Selective reaction at the ketone position of keto esters can be accomplished by adding a phosphonate carbanion to excess ester. The carbanion derived from O,O-diethylmethoxymethylphosphonate appeared attractive, but would lack the requisite stability. See A. W. Johnson "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, pp 141, 203.

(17) A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).

side chain.[18] By this time, an alternate route[19] to the bufadienolide system had proved feasible and one of the next steps of proceeding *via* a 20-oxo-24-nitrile or other small carboxylic acid precursor was not undertaken. The preceding experiments did serve to further define steric requirements for Wittig reactions involving 20-oxo steroids.

Experimental Section

Each Wittig reaction was performed in a nitrogen atmosphere. Hexane solutions of *n*-butyllithium were obtained from Foote Mineral Co., while *n*-butyllithium in diethyl ether solution was prepared[20] and standardized. The diethyl ether, tetrahydrofuran, toluene, and dihydropyran were redistilled from sodium. Benzene and dimethylsulfoxide (heated at 60° for 20 hr with the hydride) were redistilled from calcium hydride. All other solvents, including pyrrolidine (from potassium hydroxide), were also redistilled. Infrared (in potassium bromide, Baird spectrophotometer) and proton magnetic resonance (deuteriochloroform solution unless described otherwise with tetramethylsilane as internal standard, Varian A-60) spectra were recorded by Dr. R. A. Hill, University of Maine. Other general experimental techniques, reagents, and chromatographic absorbents are summarized in the experimental introduction of part 2.[4]

3β-Acetoxy-20-methoxymethylene-5-pregnene (2a). Method A.—To a stirred suspension of methoxymethyltriphenylphosphonium chloride[6b] (1.9 g, 5.54 mmol) in diethyl ether (50 ml) was gradually added a solution of *n*-butyllithium in hexane (3.5 ml, 1.6 *N*, 5.6 mmol). The salt slowly dissolved to give a deep red solution. After 15 min, 3β-acetoxy-20-oxo-5-pregnene (**1a**, 2.0 g, 5.59 mmol) in diethyl ether (80 ml) was added dropwise during 15 min. The mixture became turbid and stirring was continued 24 hr at room temperature, followed by heating at reflux for 6 hr. Another period at room temperature (24 hr) was followed by a 3-hr reflux period. The solid phase was collected and washed with diethyl ether, and the filtrate was washed well with water, dried, and treated during 20 hr with methyl iodide. The supernatant liquid was decanted from precipitated solid and evaporated *in vacuo* to yield a semicrystalline mass (2.8 g) which was triturated with hot hexane (0.06 g, insoluble), and the solution was chromatographed on basic alumina (30 g). A cream-colored, crystalline solid (0.785 g) was eluted by 1:1 hexane–benzene. Recrystallization from chloroform–methanol gave slender needles, mp 142° (0.29 g). Two further recrystallizations from the same solvent gave needles: mp 151–152°; ν_{max} 1730 (acetate), 1670, and 1130 cm^{-1} (vinyl ether); pmr[21,22] δ 0.55 and 1.0 (C-18 and -19 methyls), 1.58 (C-21 methyl), 2.01 (C-3 acetate), 3.55 (methoxy), 5.38 (complex, C-6 olefin proton), and 5.78 (complex, C-22 olefin proton).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91; O, 12.42. Found: C, 77.71; H, 9.75; O, 12.19.

Further elution of the column with 1:1 and 3:1 benzene–hexane gave 3β-acetoxy-20-oxo-5-pregnene (0.21 g).[22]

Method B.—To a stirred suspension of methoxymethyltriphenylphosphonium chloride[6b] (6.70 g, 19.5 mmol) in tetrahydrofuran (75 ml) was added dropwise an ethereal solution of butyllithium (10 ml, 1.29 *N*, 12.9 mmol). The deep red mixture was stirred at room temperature for 2 hr. Solid 3β-hydroxy-20-oxo-5-pregnene (**1b**, 1.02 g, 3.25-mmol) was added in one portion and the reaction mixture was allowed to stand for 22 hr at room temperature. Following a 24-hr period at reflux, the brown solution was cooled and filtered to remove precipitated solid (2.9 g). The filtrate was diluted with diethyl ether (100 ml) and washed with water (200 ml). The aqueous phase was washed with diethyl ether (two 150-ml portions) and the combined ethereal solution was dried and concentrated *in vacuo* to furnish a dark oil (3.5 g) which was acetylated for 22 hr at room temperature. The resulting oily product (3.7 g) was chromatographed on basic alumina (100 g). The first material eluted by 1:1 benzene–hexane was triphenylphosphine (0.09 g)[22] followed in the same solvent mixture by vinyl ether **2a** as a solid (0.60 g, 42%), mp 110–116°. Two recrystallizations from methanol afforded needles: mp 125–130°; ν_{max} 1730 (acetate), 1670, and 1130 cm^{-1} (vinyl ether).

Method C.[18]—To a suspension of triphenylmethoxymethylenephosphonium chloride (73 mmol) in diethyl ether (300 ml) was added 65 ml of 1.03 *N* potassium *t*-butoxide in *t*-butyl alcohol. The reaction was conducted in a nitrogen atmosphere with stirring and 1 hr later pregnenolone acetate (**1a**, 5.1 g, 15.3 mmol) in tetrahydrofuran (150 ml) was added to the orange-red mixture over a 15-min period. The mixture was stirred at reflux temperature for 20 hr, cooled, diluted with water, and extracted with diethyl ether. The crude product was isolated and reacetylated essentially as summarized in method B to give a solid which was chromatographed on neutral alumina (120 g), and the fractions eluted by 2:1 hexane–benzene were recrystallized from methylene chloride–methanol containing a trace of pyridine to give 2.4 g of colorless crystals melting at 142–148°. Recrystallization from the same solvent mixture afforded a pure sample melting at 152–154°.

Method D.—A solution of butyllithium (10 ml, 1.46 *N*, 14.6 mmol) in pentane–heptane was added dropwise to a stirred solution of methoxymethyltri-*n*-butylphosphonium chloride[23] (6.2 g, 21.9 mmol) in tetrahydrofuran (50 ml). After 2 hr at room temperature, solid 3β-hydroxy-20-oxo-5-pregnene (**1b**, 1.15 g, 3.65 mmol) was added to the yellow solution and stirring was continued for 20 hr at room temperature and for 24 hr at reflux temperature. Following isolation and acetylation as described in method B, the brown solid (1.3 g) was chromatographed on basic alumina (40 g). Elution with 1:1 benzene–hexane gave as the first fraction **3β-acetoxy-26,27-bisnor-5,20(22)-cholestadiene (3a**, 0.55 g),[22] mp 110–112°. Four recrystallizations from aqueous methanol gave an analytical specimen of **3a**: mp 113–113.5°; $[\alpha]_D$ 0°; ν_{max} 1730 cm^{-1} (acetate); pmr[21] δ 0.55, 0.95, 1.08, 1.68 (C-21 methyl), 2.08 (C-3 acetate), and 5.1–5.5 (multiplet, 2 olefin protons).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.34; H, 10.63. Found: C, 81.44; H, 10.38.

A second fraction eluted by the same solvent system was **3β-acetoxy-20-methoxymethylene-5-pregnene (2a**, 0.46 g),[22] mp 130–138°. Five recrystallizations from methanol afforded an analytical specimen: mp 152–154°; $[\alpha]_D$ −69.3° (c 1.167); ν_{max} 1720 (acetate), 1670, and 1130 cm^{-1} (vinyl ether).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.66; H, 9.91. Found: C, 77.92; H, 9.78.

Alternate Synthesis of 3β-Acetoxy-26,27-bisnor-5,20(22)-cholestadiene (3a).—A solution of 3β-hydroxy-20-oxo-5-pregnene (2.0 g, 6.3 mmol) in tetrahydrofuran (30 ml) was treated dropwise for 10 min with an ethereal solution of *n*-butyllithium (15 ml, 0.95 *N*, 14.2 mmol). The temperature rose to 50° and the mixture became turbid. After 15 hr at room temperature, solvent was removed *in vacuo* and the resulting viscous residue was warmed with aqueous hydrochloric acid (17%). The aqueous suspension was extracted with chloroform and the extract was concentrated to a brown oil (2.3 g) which was heated at reflux 24 hr in acetic anhydride (40 ml)–glacial acetic acid (20 ml). Excess reagents were removed *in vacuo* and the residue was treated for 1 hr with saturated aqueous sodium bicarbonate. Extraction with chloroform, drying, and evaporation gave a yellow oil (2.2 g), which was chromatographed on acid-washed alumina (75 g). Elution with 1:1 benzene–hexane led to a colorless oil (1.76 g). Trituration with methanol gave a solid (0.7 g), mp 85–90°. Four recrystallizations from methanol gave colorless plates of olefin **3a**: mp 111.5–112°;[22] ν_{max} 1730 (acetate) and 1250 cm^{-1} (acetate).

3β-Hydroxy-26,27-bisnor-5,20(22)-cholestadiene (3b).—A solution of 3β-acetoxy-26,27-bisnor-5,20(22)-cholestadiene (**3a**, 0.42 g) in 5% methanolic potassium hydroxide solution was allowed to remain at room temperature for 14 hr. The solution was filtered to remove precipitated solid (0.13 g) and the filtrate was added to water (100 ml). Extraction with diethyl ether gave a colorless, viscous residue (0.19 g). The oil and precipitated solid were combined and crystallized from methanol to yield plates (0.30 g), mp 129–130°. Three recrystallizations from methanol gave the analytical specimen: mp 129.5–130°; $[\alpha]_D$ −65.1° (*c* 0.615); ν_{max} 3400 cm^{-1} (hydroxyl).

(18) We wish to thank Dr. J. P. Yardley for performing these experiments.

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

(20) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1957, p 932.

(21) Recorded by Dr. D. C. Fessler.

(22) Confirmed by mixture melting point and infrared spectral comparison with an authentic specimen.

(23) Prepared in impure form from tri-*n*-butylphosphine and methyl chloromethyl ether.

Anal. Calcd for $C_{25}H_{40}O$: C, 84.21; H, 11.31. Found: C, 83.66; H, 10.97.

3β-Hydroxy-20-methoxymethylene-5-pregnene (2b).—A sample of 3β-acetoxy-20-methoxymethylene-5-pregnene (**2a**, 0.38 g) was saponified and isolated by chloroform extraction as summarized for alcohol **3b**. The yellow, oily product (0.27 g) was triturated with methanol–water at −5° to give a solid (0.25 g, 73%), mp 133–136°. Four recrystallizations from aqueous ethyl alcohol gave shiny plates: mp 143–144°; $[\alpha]_D$ −70.6° (*c* 0.802); ν_{max} 3400 (hydroxyl), 1670, and 1130 cm^{-1} (vinyl ether).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.19; H, 10.53. Found: C, 79.97; H, 10.43.

3β-Tetrahydropyranyloxy-20-methoxymethylene-5-pregnene (2c).—A stirred suspension of methoxymethyltriphenylphosphonium chloride (2.16 g, 5.65 mmol) in tetrahydrofuran (20 ml, distilled from lithium aluminum hydride) and diethylene glycol dimethyl ether (20 ml, distilled from lithium aluminum hydride) was treated dropwise with an ethereal solution of butyllithium (5.8 ml, 0.95 *N*, 5.50 mmol). After 3 hr at room temperature, 3β-tetrahydropyranyloxy-20-oxo-5-pregnene (**1b**, 0.90 g, 2.25 mmol)[3a] in tetrahydrofuran (5 ml)–diethylene glycol dimethyl ether (5 ml) was added dropwise to the deep red solution. Stirring was continued for 20 hr at room temperature. The tetrahydrofuran was then removed by distillation and replaced by diethylene glycol dimethyl ether (20 ml) and the temperature was raised to cause refluxing (160°) and maintained there for 7 hr. The turbid brown mixture was concentrated to half volume *in vacuo*, cooled to room temperature, and treated with methyl bromoacetate (3 ml). After 12 hr at 5°, the solution was decanted from precipitated solid and washed with water six times. Evaporation *in vacuo* of solvent gave a dark oil (1.5 g), which was chromatographed on basic alumina (25 g). Elution with 2:1 hexane–benzene provided an oil (0.86 g, 83%), which on crystallization from acetone gave a solid (0.30 g): mp 80–90°; ν_{max} 1670, 1130 (vinyl ether), and 1030 cm^{-1} (tetrahydropyranyl ether). Evaporation of the mother liquor gave an oil (0.55 g) identical spectrally[22] with the solid form of vinyl ether **2c**.

Five recrystallizations of the solid from methanol yielded needles suitable for analysis, mp 116–117°, $[\alpha]_D$ −46.8° (*c* 1.282).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.49; H, 10.01.

3β-Hydroxy-4-pregnene-20-aldehyde (4).—A solution of 3β-tetrahydropyranyloxy-20-methoxymethylene-5-pregnene (**2c**, 0.70 g) in perchloric acid–diethyl ether (20 ml) was left at room temperature for 14 hr. Dilution with water and extraction with chloroform led to a dark, viscous residue (0.50 g). Chromatography on acid-washed alumina (15 g) and elution with 4:1 benzene–chloroform gave a pale yellow solid (0.37 g, 69%), which recrystallized from benzene–hexane as colorless microneedles: mp 151–156° (lit.[13] mp 150–152°); $[\alpha]_D$ −54.3° (*c* 0.58); $[\alpha]^{25}_D$ −59.3°; ν_{max} 3400 (hydroxyl), 2700 (w), and 1720 cm^{-1} (aldehyde).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.39; H, 10.42.

***t*-Butyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (5b).**[24]—To a solution of *t*-butylcarboxymethylenetriphenylphosphorane[25] (15 g, 0.04 mol) in refluxing toluene (200 ml) was added in one portion 3β-acetoxy-20-oxo-21-iodo-5-pregnene[26] (**8**, 10.5 g, 0.022 mol). Heating at reflux was maintained for 5 hr and, following addition of *t*-butyl bromoacetate (4.4 ml), continued for 2 hr longer. After cooling, the solution was filtered (16.0 g of salt) and toluene was removed *in vacuo*. The residue was chromatographed on neutral alumina (450 g) and elution with 2:1 benzene–hexane. Benzene provided *trans* olefin **5b** as a yellow solid (4.2 g, 38%), mp 140–146°. Two recrystallizations from isopropyl ether gave an analytical specimen as yellow prisms: mp 149–150°; $[\alpha]_D$ +27.5° (*c* 2.26); ν_{max} 1732 (*t*-butyl ester), 1715 (C-3 acetate), 1688 (C-20 ketone), 1670 and 1628 (C-22,23 olefin), 1368 (*t*-butyl), and 1255 cm^{-1} (acetate); pmr δ 1.49 (s, 9 H, *t*-butyl), 1.97 (3 H, C-3 acetate), and the C-22,23 olefin protons at 6.22 and 6.48 (d, 1 H, J = 15 cps) and 6.74 and 6.99 (d, 1 H, J = 15 cps).

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00; O, 17.00. Found: C, 74.25; H, 8.97; O, 17.25.

Hydrogenation of *t*-Butyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (5b).—A solution of olefin **5b** (0.80 g) in ethyl acetate (40 ml) was shaken for 4 hr under hydrogen with 10% palladium on charcoal (0.25 g). The solution was filtered and concentrated to a viscous oil containing four components, and a solution of the mixture in hexane was chromatographed on silica gel (30 g). A fraction (35 mg) eluted by benzene and pure by thin layer chromatography crystallized from methanol to yield ***t*-butyl 20-oxo-21-nor-5α-cholanate (7c)** as needles: mp 103–105°; $[\alpha]_D$ +90° (c 0.4); $\nu^{CHCl_3}_{max}$ 1750, 1710, 1370, and 1160 cm^{-1}.

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.64; O, 11.52. Found: C, 77.92; H, 10.43; O, 11.71.

A fraction (0.58 g) eluted by 7:3 benzene–chloroform crystallized after a long period from methanol. Recrystallization from methanol gave ***t*-butyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (7b)** as prisms: mp 81–83°; $[\alpha]_D$ + 68° (*c* 0.82); $\nu^{CCl_4}_{max}$ 1740, 1705, 1360, 1235, and 1140 cm^{-1}; pmr δ 1.38 (s, 9 H, *t*-butyl), 1.88 (s, 3 H, acetate), and 2.38 (m, 4 H, $COCH_2CH_2CO_2$).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; O, 16.85. Found: C, 73.31; H, 10.16; O, 16.54.

Pyrrolidine Amide of 3β-Acetoxy-20-oxo-21-nor-5α-cholanic Acid (7d).—A solution of methyl ester **7a** (0.26 g) in pyrrolidine (3 ml) was allowed to remain at room temperature for 7 days. The mixture was diluted with diethyl ether and the solution was washed with water, 2% hydrochloric acid, and water. Solvent was removed and the residue was shown by thin layer chromatography with 1:1 hexane–ethyl acetate mobile phase to contain no starting material. The product was chromatographed on silica gel, and benzene–chloroform fractions removed trace impurities. Elution with chloroform gave 0.25 g of amide **7d**. Three recrystallizations from hexane–diethyl ether provided an analytical sample as needles: mp 124–125°; ν_{max} 1740 (C-3 acetate), 1710 (C-20 ketone), 1650 (amide), and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{29}H_{45}NO_4$: C, 73.84; H, 9.62; N, 2.97; O, 13.57. Found: C, 73.59; H, 9.76; N, 3.10; O, 13.50.

Pyrrolidine Amide of 3β-Hydroxy-20-oxo-21-nor-5α-cholanic Acid (7e).—The aminolysis reaction described above (see **7d**) was repeated employing 1 g of methyl ester **7a** and 10 ml of pyrrolidine. In this case, reaction was allowed to progress for 10 days and the crude product was chromatographed on 30 g of silica gel. The fractions eluted by chloroform to 99:1 chloroform–methanol afforded 0.65 g of 3β-acetoxy amide **7d**. A fraction eluted by 9:1 chloroform–methanol gave 0.15 g of 3β-hydroxy amide **7e**. Three recrystallizations from methanol–methylene chloride yielded a pure sample as crystals: mp 222–224°; tlc, 19:1 chloroform–methanol; $[\alpha]_D$ +67° (*c* 0.51); ν_{max} 3350, 1705, and 1620 cm^{-1}.

Anal. Calcd for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26; O, 11.17. Found: C, 75.64; H, 9.89; N, 3.20; O, 11.30.

Pyrrolidine Amide of 3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanic Acid (7f).—A solution composed of benzene (2 ml), 3β-hydroxy amide **7e** (0.1 g), dihydropyran (0.7 ml), and *p*-toluenesulfonic acid monohydrate (10 mg) was stirred at room temperature for 30 min. The mixture was poured into ice–aqueous sodium carbonate and extracted with diethyl ether. The ethereal solution was washed well with water and concentrated. A solution of the residue in hexane containing 1% ethyl acetate was chromatographed on silica gel (3 g). The fractions eluted by 2:3 hexane–ethyl acetate to pure ethyl acetate afforded pyranyl ether **7f**. Two recrystallizations from hexane–methylene chloride afforded an analytical specimen (0.08 g): mp 117–119°; tlc, ethyl acetate; $[\alpha]_D$ +65° (c 0.62); ν_{max} 1700, 1645, and 1030 cm^{-1} (ether).

Anal. Calcd for $C_{32}H_{51}NO_4$: C, 74.81; H, 10.01; N, 2.73; O, 12.46. Found: C, 74.62; H, 9.66; N, 2.88; O, 12.93.

Methyl 3β-Hydroxy-20-oxo-21-nor-5β-cholanate (7h).—A solution composed of methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (**7a**, 1.14 g), methanol (45 ml), water (12 ml), and potassium carbonate (1.2 g) was heated at reflux for 4 hr. Evaporation *in vacuo* to small volume and acidification with hydrochloric acid (2 *N*) gave a white precipitate which was collected and washed with water. Drying furnished a solid (0.90 g) sparingly soluble in a variety of organic solvents. 3β-Hydroxy-20-oxo-21-nor-5α-cholanic acid (**7g**) was obtained: ν^{Nujol}_{max} 3600 (vs, hydroxyl), 2500–2800 (w, b carboxylic acid), and 1720 cm^{-1} (vs, carboxylic acid). It was used without further purification. The acid **7g** (0.89 g) suspended in 1:1 chloroform–methanol

(24) We thank Philip A. Whitehouse for assistance with this experiment.
(25) T. Moriwake, *J. Org. Chem.*, **31**, 983 (1966).
(26) C. Djerassi and C. Lenk, *J. Amer. Chem. Soc.*, **75**, 3493 (1953).

quickly dissolved on treatment at 0° with ethereal diazomethane, and excess reagent was immediately removed by nitrogen purging. Following washing with water and removal of solvent, the solid crystallized from methanol as tiny plates (0.68 g) melting at 137–140° to an opaque liquid which cleared at 150°. For analysis the sample was recrystallized from 95% ethyl alcohol to give plates: mp 139–140° to an opaque liquid clearing sharply at 152–153°; $[\alpha]^{23}D$ +150.4° (*c* 1.2); ν_{max} 3200 (hydroxyl), 1735 (methyl ester), and 1700 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.21; H, 9.37.

Methyl 3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanate (7i).—To a solution of methyl 3β-hydroxy-20-oxo-21-nor-5α-cholanate (**7h**, 0.87 g) in benzene (15 ml) was added dihydropyran (5 ml) and toluene-*p*-sulfonic acid monohydrate (40 mg). The mixture was stirred for 45 min at room temperature and then washed with saturated aqueous sodium bicarbonate and water (five times). Concentration gave a viscous oil (1.33 g) which crystallized from methanol as blades: (0.85 g) mp 93–95° (recrystallization from the same solvent did not change the melting point); $[\alpha]D$ +77.30° (c 0.41); $\nu_{max}^{CCl_4}$ 1739 (methyl ester), 1702 (ketone), and 1025 cm^{-1} (tetrahydropyranyl ether); pmr (CCl_4) δ 0.56 (s, 3 H, CH_3-18), 0.8 (s, 3 H, CH_3-19), 2.43 (s, with broad base, 4 H, $-COCH_2CH_2CO_2-$), 3.5 (s, 3 H, methyl ester), and 4.5 (diffuse signal, 1 H, acetal).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; O, 16.85. Found: C, 73.10; H, 9.53; O, 17.47.

3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanic Acid (7j).—Methyl 3β-tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanate (**7i**, 0.70 g) in methanol (30 ml) was diluted with potassium carbonate (0.75 g) in water (7.5 ml) and the solution was heated at reflux for 4 hr. Methanol was removed *in vacuo* and the solution was cooled to 0° and cautiously acidified with hydrochloric acid (1 *N*). The mixture was immediately extracted with diethyl ether (three times) and the ethereal solution was washed with water (three times). Removing solvent provided a crystalline product (0.70 g) melting at 118–120° to a clear liquid which resolidified by 165° and remelted at 250–252° dec. The analytical specimen recrystallized from isopropyl ether as prisms: mp 125° (resolidifies at 165°) and 253–255°; $[\alpha]D$ +90.23° (c 0.13); $\nu_{max}^{CHCl_3}$ 2400–2800 (w, b, carboxylic acid), 1700 (20 ketone and carboxyl), and 1010 cm^{-1} (tetrahydropyranyl ether).

Anal. Calcd for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63; O, 17.37. Found: C, 72.66; H, 9.76; O, 17.63.

Registry No.—Methoxymethylenetriphenylphosphorane, 23411-16-7; **2a**, 23439-92-1; **2b**, 23406-62-4; **2c**, 23406-63-5; **3a**, 23406-64-6; **3b**, 23406-65-7; **4**, 23439-93-2; **5b**, 23439-94-3; **7b**, 23439-95-4; **7c**, 23406-66-8; **7d**, 23439-96-5; **7e**, 23439-97-6; **7f**, 23439-98-7; **7g**, 23406-67-9; **7h**, 23439-99-8; **7i**, 23406-68-0; **7j**, 23440-00-8.

Bufadienolides. 5. Synthesis of Cardenolides[1,2]

GEORGE R. PETTIT, CHERRY L. HERALD, AND JOHN P. YARDLEY

Department of Chemistry, Arizona State University, Tempe, Arizona 85281, and Department of Chemistry, University of Maine, Orono, Maine 04473

Received February 11, 1969

Boron trifluoride catalyzed lead tetraacetate oxidation of 3β-acetoxy-20-oxo-5α-pregnane and of pregnenolone acetate was employed to obtain the corresponding 21-acetoxy derivatives. Reaction of 3β,21-diacetoxy-20-oxo-5α-pregnane (**1**) with the anion prepared from diethyl cyanomethylphosphonate and subsequent treatment with hydrochloric acid afforded the corresponding nitrile (**2**) and derived imino lactone hydrochloride (**3a**). Acid hydrolysis of the imino lactone gave 3β-acetoxy-5α-cardenolide (**4b**). Analogous transformation of ketone 6 provided 3β-acetoxy-Δ^5-cardenolide (**10b**). The two-step reaction sequence from readily available α-hydroxy ketones provides a potentially useful route to imino lactones and butenolides.

Among the naturally occurring cardenolides, several are well known medically for their specific effect upon heart muscle. Recently, unsaturated lactones of the cardenolide type have been found to inhibit cell growth.[2,3] Increasing availability of steroid butenolides related to the natural cardenolides for biological evaluation was considered an important objective of the overall bufadienolide investigation. Accordingly, when one series of experiments directed at the bufadienolide ring system began to seem impractical, they were diverted to provide the following new synthesis of cardenolides.[4]

Initially, 3β-acetoxy-20-oxo-5α-pregnane was oxidized using lead tetraacetate to 3β,21-diacetate **1**.[5a] Later the boron trifluoride catalyzed lead tetraacetate oxidation procedure[5b] was found superior for this purpose. Next, the carbanion derived from diethyl cyanomethylphosphonate was allowed to condense with 20 ketone **1**. Following removal of solvent the residue was treated with 2 *N* hydrochloric acid–diethyl ether. A crystalline product (24–65% yield) separated which was shown to be imino lactone hydrochloride **3a**.[6] The ether extract contained nitrile **2** in yields up to 72%. If instead the crude reaction product was treated first with water–diethyl ether, only nitrile **2** was obtained. The imino lactone formulation was supported by spectral evidence and confirmed by hydrolytic (methanol–hydrochloric acid) cleavage to cardenolide **4**. Under milder conditions, acid treatment was used to obtain

(1) (a) Part 4: G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, **35**, 1385 (1970). (b) This investigation was supported by Public Health Service Research Grants CA-04074-07, CA-10115-01, and CA-10115-02 from the National Cancer Institute.

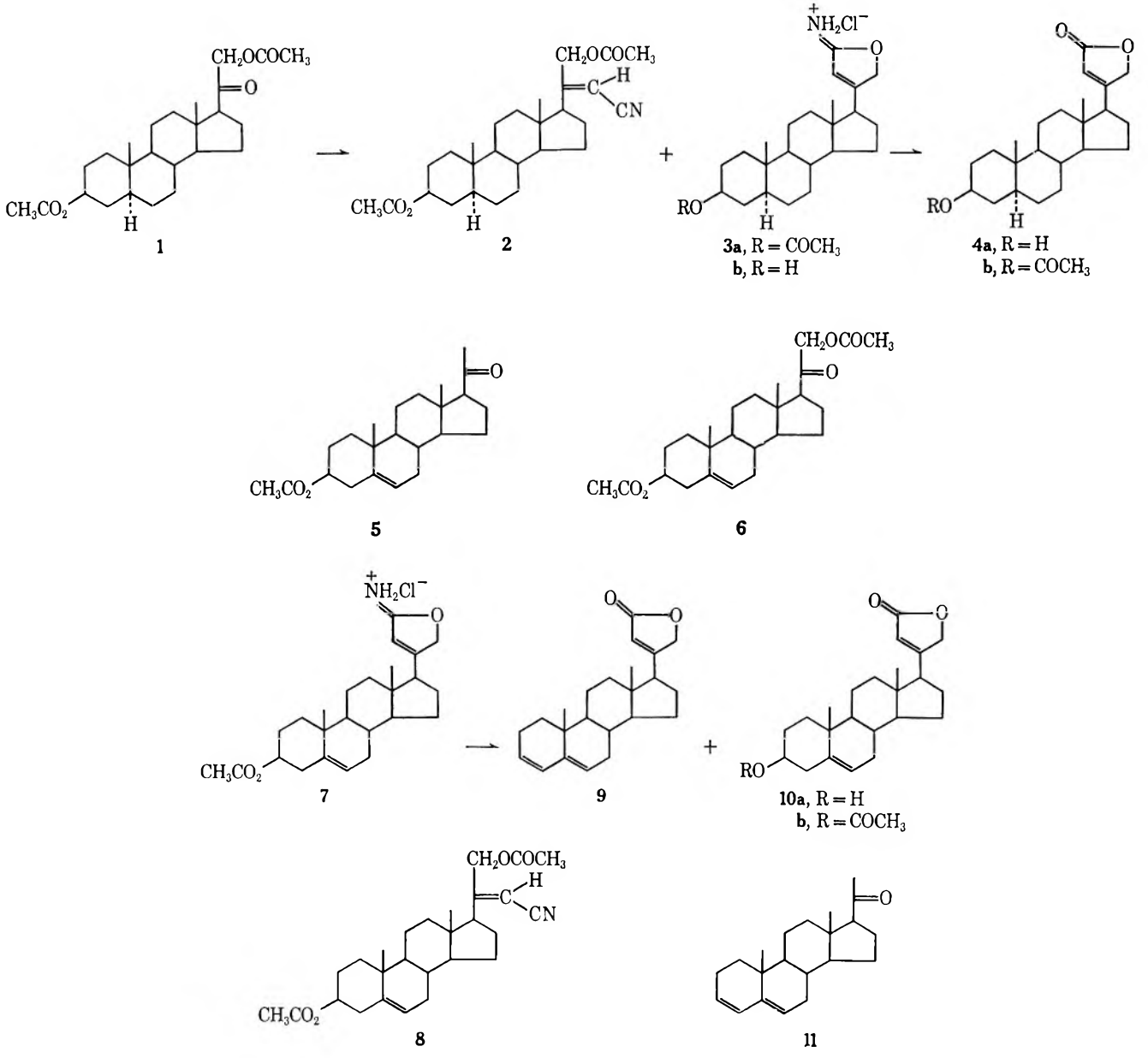
(2) The present study was based in part on the doctoral dissertation of C. L. Herald, submitted to the Graduate School, Arizona State University, Aug 1968. A preliminary account was given: G. R. Pettit and J. P. Yardley, *Chem. Ind.* (London), 553 (1966).

(3) G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970), footnotes 15 and 16.

(4) See P. E. Sonnet, *ibid.*, **33**, 3662 (1968), and for a summary of recent methods used to obtain cardenolides consult S. Sarel, Y. Yanuka, and Y. Shalon, *Israel J. Chem.* (Proceedings), **5**, 48p (1967); J. M. Ferland, Y. Lefebvre, and R. Deghenghi, *Tetrahedron Lett.*, 3617 (1966); W. Fritsch, U. Stache, and H. Ruschig, *Justus Liebigs. Ann. Chem.*, **699**, 195 (1966); N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966). Leading references prior to 1966 may be found in ref 2.

(5) (a) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939); (b) J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).

(6) Preparation of imino lactone **3a** constitutes the first example of such cardenolide derivatives. In general imino lactones are rarely encountered; for a survey see B. A. Cunningham and G. L. Schmir, *J. Org. Chem.*, **31**, 3751 (1966); B. Kamenar, C. K. Prout, and J. D. Wright, *J. Chem. Soc.*, 661 (1966); H. E. Zaugg, R. J. Michaels, A. D. Schaefer, A. M. Wenthe, and W. H. Washburn, *Tetrahedron*, **22**, 1257 (1966); H. Nohira, Y. Nishikawa, Y. Furuya, and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, **38**, 897 (1965); H. Peter, M. Brugger J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 577 (1963); D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **83**, 4076 (1961).



alcohol **3b**. Both cardenolide **4a** and the corresponding acetyl derivative **4b** had earlier been obtained by Ruzicka and colleagues,[7] and the specimens obtained here displayed corresponding physical constants and were further characterized by results of ultraviolet, infrared, and proton magnetic resonance spectral studies.

The geometry assigned olefin **2** is based on repeated attempts to convert this isomer into imino lactone **3a**. Thus the nitrile and 21-acetoxy methylene groups are assumed to manifest the *trans* relationship indicated.[8]

To make a preliminary appraisal of the new imino lactone and cardenolide syntheses scope, pregnenolone acetate (**5**) was oxidized to 21 acetate **6** and the latter was condensed with diethyl cyanomethylphosphonate as outlined above. If the reaction mixture was first diluted with water, only negligible amounts of imino lactone **7** could be detected. On the other hand, initial reaction with cold 2 *N* hydrochloric acid–diethyl ether provided 10–47% yields of imino lactone **7** accompanied by varying (18–55%) quantities of nitrile **8**. Subjecting imino lactone hydrochloride **7** to acid hydrolysis as used effectively with analogous lactone **3a** led to a mixture of products, among which was detected diene **9**. Under milder conditions using 0.6 *N* hydrochloric acid in methanol and a 7-hr reaction period, cardenolide **10a** was obtained in 90% yield accompanied by 9% diene **9**. Structures assigned cardenolides **9** and **10** were supported by results of elemental and spectral analyses. Further, pregnenolone acetate (**5**) was al-

(7) L. Ruzicka, P. A. Plattner, and J. Pataki, *Helv. Chim. Acta*, **25**, 79 (1942).

(8) The general reaction between diethyl cyanomethylphosphonate anion and 20-oxo steroids has been described: A. K. Bose and R. T. Dahil, Jr., *J. Org. Chem.*, **30**, 505 (1965). See also A. K. Bose and R. M. Ramer, *Steroids*, **11**, 27 (1968).

Reaction of ketone **1** with diethyl ethoxycarbonylmethylphosphonate in a Wittig sequence should lead directly to cardenolide **4a**, but at the time this reagent was assumed unreactive toward 20-oxo steroids (see Bose and colleagues). More recently, reaction between the anion of diethyl methoxycarbonylmethylphosphonate and 20-oxo-21-hydroxy-pregnanes has been shown, in fact, to be exothermic and to yield the corresponding cardenolide (see Fritsch and colleagues, ref 4). The 21-hydroxy group apparently has a strong orienting effect on the approaching phosphonate, and combined with thermodynamically favorable ring formation leads to a very efficient (95% yield) reaction. Presumably, the reactions described herein leading to, *e.g.*, imino lactone **3a**, might proceed in higher yield employing 20-oxo-21-hydroxypregnane precursors. The present study was already complete when this prospect came into view.

lowed to react with hydrochloric acid in methanol under conditions similar to those initially applied to imino lactone **3a**. Following chromatographic separation of the product on activated alumina and crystallization of a fraction eluted by 20:1 hexane–ethyl acetate from hexane, a 24% yield of diene **11** was obtained. Previously, diene **11** was prepared[9] by Raney nickel desulfurization of the 3-benzylthio ether of 20-oxopregna-3,5-diene.

The ready availability of various methyl ketones suggests that the α-hydroxy ketone → imino lactone → butenolide route illustrated for obtaining cardenolides **4** and **10** provides a potentially useful method for obtaining such lactones. Presently, acid sensitivity and structural effects of the ketone upon stereochemical course of the modified Wittig step would seem to be two important considerations in evaluating overall yields.

Experimental Section

Tetrahydrofuran (from sodium), all other solvents, and diethyl cyanomethylphosphonate [bp 87–89° (0.15 mm), Aldrich Chemical Co.] were redistilled. A dispersion (*ca.* 54%) of sodium hydride in mineral oil was employed as supplied by the Metal Hydrides Division, Ventron Corp. The phosphonate modification of the Wittig reaction was conducted in a nitrogen atmosphere. Acetylation was effected using 5:1 acetic anhydride–pyridine at room temperature overnight. All solvent extracts of aqueous mixtures were dried over anhydrous magnesium sulfate. Basic alumina ("Suitable for Chromatography," Merck, Rahway, N. J.) and silica gel (0.2–0.5 mm, E. Merck, Darmstadt) were used for column chromatography. Chromatography columns were prepared using a slurry of silica gel in a solvent of lesser polarity than that anticipated for initial elution. The mixture to be chromatographed was dissolved in chloroform and a slurry of silica gel in chloroform was added to the solution. Removal of solvent *in vacuo* gave a silica gel powder coated with the mixture. Addition of the powder to the silica gel column gave a uniform band of adsorbed material. Thin layer chromatograms were prepared on microscope slides using silica gel HF_{254} (E. Merck) and developed either with iodine or concentrated sulfuric acid. Preparative thin layer chromatograms were performed with 1 mm of silica gel HF_{254}.

Each analytical sample appeared as a single spot on a thin layer chromatogram and was colorless unless stated otherwise. Melting points were recorded using a Fisher-Johns melting point apparatus and were uncorrected. The ultraviolet (Cary spectrophotometer), optical rotatory dispersion (at 25°, JASCO ORD/UV-5), infrared (in potassium bromide), and nuclear magnetic resonance (deuteriochloroform solution, tetramethylsilane as internal standard Varian A-60) measurements were recorded by Miss K. Reimer. Mass spectra (Atlas CH-4B) were recorded by Dr. P. Brown. Specific rotations (chloroform solution) at the sodium D line were obtained with a Rudolph polarimeter or were provided by Dr. P. Demoen, Janssen Pharmaceutica, Beerse, Belgium. Elemental microanalyses were determined in the laboratory of Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany.

3β,21-Diacetoxy-20-oxopregn-5-ene (6).—The 3β,21 diacetates were prepared by the method of Cocker and colleagues.[5b] To a solution of pregnenolone acetate (**5**, 10 g) and lead tetraacetate (17 g) in benzene (380 ml) was added a solution of methanol (18 ml) plus boron trifluoride etherate (56 ml). The solution was stirred at room temperature for 4 hr and then poured into water. The organic layer was separated and washed four times with water. Removal of solvent gave a yellow solid which crystallized from ethyl acetate–hexane to give shiny plates (8 g, 69% yield): mp 163–166° (lit.[10] mp 165–167°); pmr δ 0.70 and 1.04 (C-18 and -19 methyls), 2.06 and 2.19 (C-3 and -21 acetates), 4.75 and 4.55 (AB quartet, J = 17 cps, C-21 methylene) and 5.40 (multiplet, 6 H).

3β,21-Diacetoxy-20-oxo-5α-pregnane (1).—The method of preparation was the same as that for **6** described in the previous experiment. Here 10 g of 3β-acetoxy-20-oxo-5α-pregnane gave 9.7 g of product. By chromatography of a benzene solution of the crude product on neutral alumina, all color was removed. Crystallization from benzene–hexane gave a pure sample of the title compound (8.4 g, 71%), mp 150–152° (lit.[5a] mp 152–153°).

Reaction of 3β,21-Diacetoxy-20-oxo-5α-pregnane (1) with Diethyl Cyanomethylphosphonate.—To a cold suspension in an ice bath of sodium hydride oil dispersion (1.9 g) in tetrahydrofuran (130 ml) was added diethyl cyanomethylphosphonate (8.5 ml) in tetrahydrofuran (30 ml) dropwise and with stirring. Next, 3β,21-diacetoxy-20-oxo-5α-pregnane (**1**, 6 g) in tetrahydrofuran (150 ml) was added rapidly to the colorless solution. The solution was stirred at room temperature for 47 hr. Removal of solvent gave an orange oil which was treated with cold 2 *N* hydrochloric acid (200 ml) and diethyl ether. A fine crystalline solid appeared which was collected, washed with water and ether, and dried in a vacuum oven at 70° (25 mm) for 2 hr to give crude 3β-acetoxy-5α-iminocard-20(22)-enolide hydrochloride **3a** (1.52 g, 24%), mp 205–224° dec. Recrystallization from methanol–ether gave an analytical sample: mp 210–225° dec; ν_{max}^{Nujol} 1740, 1670, 1600, 1240, and 1030 cm^{-1}; pmr δ 0.63 and 0.83 (C-18 and -19 methyls), 2.01 (acetate), 4.63 (3α proton), 5.44 (multiplet, C-21 methylene), and 6.75 (multiplet, H-22).

Anal. Calcd for $C_{25}H_{38}O_3NCl$: C, 68.87; H, 8.78; N, 3.21; Cl, 8.13. Found: C, 68.60; H, 8.80; N, 3.05; Cl, 8.22.

The ether layer was separated and washed successively with water, 2 *N* sodium hydroxide, and three portions of water. Aqueous and basic extracts were reextracted with diethyl ether. The combined ethereal extract was washed twice with water and evaporated to dryness, giving a light tan oil. Tlc with 2:1 hexane–ethyl acetate mobile phase showed the product to contain mostly one component plus mineral oil. Crystallization of product from ethyl acetate–hexane gave slightly yellow needles (4.6 g, 72%). Three recrystallizations from the same solvents provided a colorless, analytical sample of 3β,21-diacetoxy-20-cyanomethyl-5α-pregn-20(22)ene (**2**): mp 108–109°; λ_{max}^{EtOH} 222 mμ (ε 13,800); ν_{max} 2850–2950, 2220, 1750, 1725, 1625, 1260, 1230, and 1035 cm^{-1}; $[\alpha]^{25}D$ +34° (*c* 1.21, chloroform); pmr δ 0.60 and 0.85 (C-18 and -19 methyls), 2.02 (C-3β acetate), 2.17 (C-21 acetate), 4.75 and 4.88 (AB quartet, J = 14 cps, C-21 methylene), and 5.41 (slightly broadened singlet, H-22 vinyl).

Anal. Calcd for $C_{27}H_{39}O_4N$: C, 73.43; H, 8.90; N, 3.17. Found: C, 73.40; H, 9.05; N, 3.34.

Reaction of 3β,21-Diacetoxy-20-oxopregn-5-ene (6) with Diethyl Cyanomethylphosphonate.—With sodium hydride oil dispersion (2.65 g), diethyl cyanomethylphosphonate (11.5 ml), and tetrahydrofuran (200 ml), 3β,21-diacetoxy-20-oxo-pregn-5-ene (**6**) was converted into 3β-acetoxy-Δ⁵-iminocard-20(22)-enolide hydrochloride (**7**, 1.51 g, 47%) and 3β,21-diacetoxy-20-cyanomethylpregna-5,20(22)-diene (**8**, 0.75 g, 18%).

Removal of solvent from the reaction mixture after 48 hr left a light-colored oil which was treated with cold 2 *N* hydrochloric acid (200 ml) and diethyl ether (100 ml). A colorless, crystalline solid appeared in the aqueous phase. The solid was collected, washed with water and diethyl ether, and dried in a vacuum oven at 70° (25 mm) for 2 hr to give hydrochloride **7**, mp 224–230° dec. Recrystallization from ethanol–diethyl ether gave an analytical sample: mp 222–230° dec; λ_{max}^{EtOH} 235 mμ (ε 13,000); ν_{max} 2800–3000, 1750, 1660, 1610, 1240, and 1025 cm^{-1}; $[\alpha]^{25}D$ −48° (*c* 1.27, chloroform); pmr δ 0.68 and 1.04 (C-18 and -19 methyls), 2.05 (acetate), 4.62 (multiplet, H-3), 5.46 (broad multiplet, C-21 methylene, H-6), and 6.72 (slightly broadened singlet, H-22).

Anal. Calcd for $C_{25}H_{36}O_3NCl$: C, 69.18; H, 8.36; N, 3.23; Cl, 8.17. Found: C, 69.39; H, 8.33; N, 3.09; Cl, 8.02.

The ether layer was separated and washed successively with 2 *N* sodium hydroxide and water. Removal of solvent gave a pale yellow solid which was chromatographed on silica gel (40 g). Elution with 4:1 hexane–ethyl acetate gave colorless, crystalline 3β,21-diacetoxy-20-cyanomethyl-pregna-5,20(22)-diene (**8**, 0.75 g). Three recrystallizations from ethyl acetate–hexane gave an analytical sample: mp 182–183°; λ_{max}^{EtOH} 222 mμ (ε 14,600); ν_{max} 3000, 2250, 1750, 1740, 1625, 1230–1260, and 1040 cm^{-1}; $[\alpha]^{25}D$ −19° (*c* 2.85, chloroform); pmr δ 0.65 and 1.05 (C-18 and -19 methyls), 2.05 (C-3β acetate), 2.17 (C-21 acetate), 4.77

(9) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).

(10) L. Ruzicka, T. Reichstein, and A. Furst, *Helv. Chim. Acta*, **24**, 76 (1941).

and 4.90 (AB quartet, J = 14 cps, C-21 methylene), 5.41 (multiplet, H-6), and 5.44 (slightly broadened singlet, overlapped H-6 signal, H-22).

Anal. Calcd for $C_{27}H_{37}O_4N$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.91; H, 8.63; N, 3.08.

3β-Hydroxy-5α-card-20(22)-enolide (4a).—To a solution of imino lactone hydrochloride **3a** (6.5 g) in methanol (50 ml) was added water (150 ml) and concentrated hydrochloric acid (60 ml). The suspension was stirred at reflux for 15 hr. Next, solid from the cooled mixture was collected and dried to give 5.2 g of crude 3β-hydroxy-5α-card-20(22)-enolide (**4a**, 96%). Recrystallization from chloroform–methanol gave colorless crystals (2.71 g): mp 244–245° (lit.[7] mp 248–250°); λ_{max}^{MeOH} 217 mμ (ε 13,600); ν_{max} 3600, 3000, 1810, 1750, 1630, and 1040 cm^{-1}; pmr δ 0.63 and 0.82 (C-18 and -19 methyls), 4.73 (triplet, J = 1.5 cps, C-21 methylene), and 5.84 (multiplet, J = 1.5 cps, H-22).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.87; H, 9.64.

Acetylation of 3β-hydroxy-5α-card-20(22)-enolide (**4a**) in 5:1 acetic anhydride–pyridine gave crude acetate. Chromatography on neutral alumina provided crystalline 3β-acetoxy-5α-card-20(22)-enolide, mp 193–194° (lit.[7] mp 193–194°).

When 3β-acetoxy-5α-iminocard-20(22)-enolide hydrochloride (**3a**, 94 mg) was treated with methanol (4 ml)–concentrated hydrochloric acid (1 ml) and heated at reflux for 25 min, partial hydrolysis of the 3β acetate to 3β-hydroxy-5α-iminocard-20(22)-enolide occurred. A crystalline solid (47 mg) was obtained: mp 254–267° dec; ν_{max}^{Nujol} 1670 and 1600 cm^{-1} with absence of absorption at 1790, 1740, and 1240 cm^{-1}.

3β-Hydroxy-Δ^5-card-20(22)-enolide (10a).—To a solution of imino lactone **7** (1.1 g) in methanol (48 ml) was added water (240 ml) and concentrated hydrochloric acid (12 ml). The mixture was stirred at reflux for 7 hr, cooled, and filtered. The crude product was dried in a vacuum oven at 75° (25 mm) for 1 hr. Chromatography on silica gel (30 g) and elution with 4:1 hexane–ethyl acetate gave 0.079 g (9%) of colorless, crystalline Δ^{3,5}-diene **9**, which recrystallized from ethyl acetate–hexane as needles, mp 204–207°. Two recrystallizations from the same solvent gave an analytical sample: mp 202–207°; λ_{max}^{EtOH} 234 mμ (ε 24,100); ν_{max} 2950, 1770, 1740, 1605, and 885 cm^{-1}; $[\alpha]^{25}D$ −104° (c 1.11, chloroform); pmr δ 0.68 and 0.98 (C-18 and -19 methyls), 4.78 (triplet, J = 1.5 cps, C-21 methylene), 5.43 (multiplet, H-6), 5.71 (multiplet, H-3), 6.07 (multiplet, overlapped with H-22 signal, H-4), and 5.89 (multiplet, J = 1.5 cps, H-22).

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.46; H, 8.72.

Continued elution with 1:1 ethyl acetate–methanol gave a pale yellow solid (0.86 g, 90%): mp 240–245° (lit.[10] mp 260–262°); ν_{max} 3300–3600, 3000, 1790, 1760, 1740, and 1625 cm^{-1}; pmr δ 0.67 and 1.04 (C-18 and -19 methyls), 4.78 (broad singlet with fine splitting, C-21 methylene), 5.88 (broad singlet with fine splitting, H-22), and 5.39 (multiplet, H-6). The sterol was acetylated with 5:1 acetic anhydride–pyridine and the crude acetate was chromatographed on silica gel (30 g). Elution with 4:1 hexane–ethyl acetate gave 0.60 g of crystalline 3β-acetoxy-Δ^5-card-20(22)-enolide (**10b**). Recrystallization from acetone–hexane gave colorless crystals, mp 170–172° (lit.[10] mp 173–174°); a second recrystallization from ethyl acetate–hexane gave crystals, mp 153–154° and 173–174°. After thorough drying for 2 days at 80° (0.25 mm), an analytical sample was obtained: mp 156–158°; λ_{max}^{EtOH} 215 mμ (ε 16,300); ν_{max} 3000, 1800, 1770, 1735, 1630, 1240, and 1040 cm^{-1}; pmr δ 0.67 and 1.04 (C-18 and -19 methyls), 2.05 (acetate), 4.78 (broad singlet, C-21 methylene), 5.42 (multiplet, H-6), and 5.87 (multiplet, H-22); mass spectrum m/e 398 (parent ion, 3%), 338 (M − 60, base ion, 100%), and 323 (M − 75, 34%).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.46; H, 8.63.

Acid Hydrolysis of 3β-Acetoxy-20-oxopregn-5-ene (5).—To 3β-acetoxy-20-oxopregn-5-ene (**5**, 0.2 g) in methanol (15 ml) was added 3 N hydrochloric acid (55 ml). The suspension was stirred, heated at reflux for 20 hr, and cooled. An oil separated and was extracted with diethyl ether. The ethereal solution was washed three times with water. Removal of solvent *in vacuo* gave a light yellow oil. Tlc with 4:1 hexane–ethyl acetate mobile phase showed the oil to contain largely one component with traces of seven others, one of which corresponded to starting material. Chromatography on basic alumina (6 g, 3% water) and elution with 20:1 hexane–ethyl acetate gave a colorless oil (0.15 g). Crystallization from hexane gave 20-oxo-pregna-3,5-diene **11** (0.04 g, 24%), mp 116–121° (lit.[9] mp 139–142°). Although diene **11** appeared as a single spot by tlc with 4:1 hexane–ethyl acetate mobile phase and uv and pmr spectra gave no evidence of an impurity, the melting point was less reassuring. The uv spectrum follows: λ_{max}^{EtOH} 234 mμ (ε 20,900) and 225 (19,400) [lit.[9] λ_{max}^{EtOH} 234 mμ (ε 20,000) and 228 (18,700)]. A pmr spectrum showed signals at δ 0.69 and 0.99 (C-18 and -19 methyls), 2.15 (C-21 methyl), and 5.45–6.10 [5.45 (multiplet, H-6, three vinyl protons), 5.72 (multiplet, H-3), and 6.10 (doublet, J = 9 cps, H-4)].

Registry No.—**2**, 23330-57-6; **3a**, 23330-58-7; **4a**, 23330-59-8; **6**, 1693-63-6; **7** hydrochloride, 23367-46-6; **8**, 23367-47-7; **9**, 23330-79-2; **10a**, 19637-05-9; **10b**, 23330-61-2; **11**, 1093-87-4; 3β-hydroxy-5α-iminocard-20(22)-enolide, 23330-62-3.

Bufadienolides. 6. Synthesis of 17β-(6′α-Pyronyl)androstanes[1,2]

GEORGE R. PETTIT, JOHN C. KNIGHT, AND CHERRY L. HERALD

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received February 11, 1969

Condensation of aldehyde **2a** with the anion prepared from diethyl cyanomethylphosphonate provided the isomeric *cis,trans*- and *cis,cis*-dienes **3a** and **4**. The geometrical isomers gave Cotton-effect curves with opposite sign. Similarly, aldehyde **5** led to olefins **6a** and **7**. Ozonolysis of the isomeric dienes **6a** and **7** gave, in each case, 17β-carboxylic acid methyl ester **8**, thereby eliminating the possibility of epimerization at position 17. Aldehyde **2a**, on condensation with the anion derived from diethyl carbethoxymethylphosphonate, gave a single product, *cis,trans* olefin **3b**. The ester **3b** was converted into isobufadienolide **10** by hydrolysis with perchloric acid in ether, saponification with 5% potassium hydroxide in methanol, and enol lactonization with ethyl acetate–acetic anhydride–perchloric acid. A related but more efficient synthesis of 2-pyrone **10** was realized using *t*-butyl ester **6b**. An even more convenient new synthesis of 6-substituted 2-pyrones was achieved by condensation of the aldehyde (*e.g.*, **2a**) precursor with malonic acid. The scope of this new reaction was illustrated by preparing isobufadienolides **10**, **12**, and **16** and pyrone **14**.

Development of practical synthetic approaches to isomeric[3] bufadienolides was considered for biological reasons[2,4] an important aspect of our overall effort concerned with bufadienolide chemistry. The isobufadienolides[3] would allow an evaluation of minor structural modifications upon possible antineoplastic, cardiac, and anesthetic responses. Preparation of 6′ isobufadienolides [17β-(6′-α-pyronyl)androstanes] was selected for initial solution. As with cardenolide[1,5] and bufadienolide[6] syntheses, approaches were restricted to a few major reaction steps from readily available steroid precursors. Several useful methods are already known for obtaining 6-substituted 2-pyrones.[7] None of these seemed readily adaptable to a 20-oxopregnane precursor. Consequently, a new synthesis of 6-substituted 2-pyrones was undertaken based on the mild formylation reaction reported by Bernstein and colleagues.[8] Pregnenolone acetate (**1**) was converted with ethyl orthoformate–perchloric acid into aldehyde **2a**. Condensation of aldehyde **2a** with the anion prepared from diethyl cyanomethylphosphonate proceeded well at room temperature and provided a two-component mixture corresponding to *cis,trans*[9] and *cis,cis* olefins **3a** and **4**, which were separated by preparative thin layer chromatography. The proton magnetic resonance spectra of each isomer was consistent with the assigned structure. The optical rotatory dispersion Cotton-effect curves were of opposite sign, suggesting either the beginning of helical asymmetry in the diene system or opposite configurations at position 17. To confirm or eliminate the latter possibility, aldehyde **5** was analogously treated with the anion from diethyl cyanomethylphosphonate. Again, two isomeric nitriles (**6a** and **7**) were obtained and displayed Cotton-effect curves of opposite sign. Each was oxidized with ozone at −60° and intermediary ozonides were reduced. The methyl 17β-carboxylate **8** was the exclusive product from each isomer, thus obviating the possibility of epimerization having occurred at position 17.

Application of an acid-catalyzed cyclization (to imino lactones) reaction to the isomeric nitriles, as already successfully applied to obtaining cardenolides,[1] could now be explored. However, olefins **3a** and **4**, upon treatment with hydrochloric acid in methanol, hydrobromic acid–acetic acid, or boron trifluoride ethereate–acetic acid, led to a variety of products, among which neither the anticipated imino lactone nor the 2-pyrone could be detected. Accordingly, to reduce the possibility of side reactions, the anion derived from diethyl carbethoxymethylphosphonate was condensed with aldehyde **2a** to provide *cis,trans*-butadiene **3b**. Increased steric requirements for the ethoxycarbonyl substituent seemed to have a marked directive influence (*cf.* Bose and colleagues in ref 1) on the Wittig reaction, as presence of the isomeric *cis,cis* olefin was not detected. Similarly, condensation of aldehyde **5** with the anion prepared from diethyl *t*-butoxycarbonylmethylphosphonate afforded *cis,trans*-butadiene **6b** as exclusive product. Assuming[3] a *trans* alkoxy–aldehyde group relationship in olefins **2** and **5**, the geometrical configurations of dienes **3**, **4**, and **6** were further assigned by examining the olefin–proton coupling constants. The proton magnetic resonance spectrum of ester **3b** is illustrative. The doublet signal at δ 5.53 with J_{ab} = 12 cps was assigned to the H_a (C-21) proton of ester **3b**. The adjacent downfield doublet at δ 5.68 with J_{bc} = 15 cps was attributed to the H_c proton and the less shielded quartet at δ 7.66 with J_{ab} = 12 and J_{bc} = 15 cps to H_b. Possible further support for the *trans* relationship of protons H_b and H_c in ester **3b** was obtained by irradiating (infrared lamp) the olefin in benzene. A new isomer was isolated and tentatively formulated as *trans,cis* olefin **9** (or alternatively the *cis,cis* isomer). Vinyl protons H_a, H_b, and H_c of the butadiene resulted in coupling

(1) This investigation was supported by Public Health Service Research Grants CA-04074-07, CA-10115-01, and CA-10115-02 from the National Cancer Institute. Part 5 and Steroids and Related Natural Products. LIII: G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970).

(2) Refer to J. C. Knight, G. R. Pettit, and C. L. Herald, *Chem. Commun.*, 445 (1967), for a preliminary report.

(3) For steroids bearing, at the 17β position 3′-, 4′-, or 6′-substituted 2-pyrone rings, the term isobufadienolides is proposed. The first example of a 6′ isobufadienolide was reported in preliminary form,[2] while an example of the 3′ system was described: D. Rosenthal, J. Fried, P. Grabowich, and E. F. Sabo, *J. Amer. Chem. Soc.*, **84**, 877 (1962). No member of the 4′ isobufadienolides appears to be known.

(4) See G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970), for a summary.

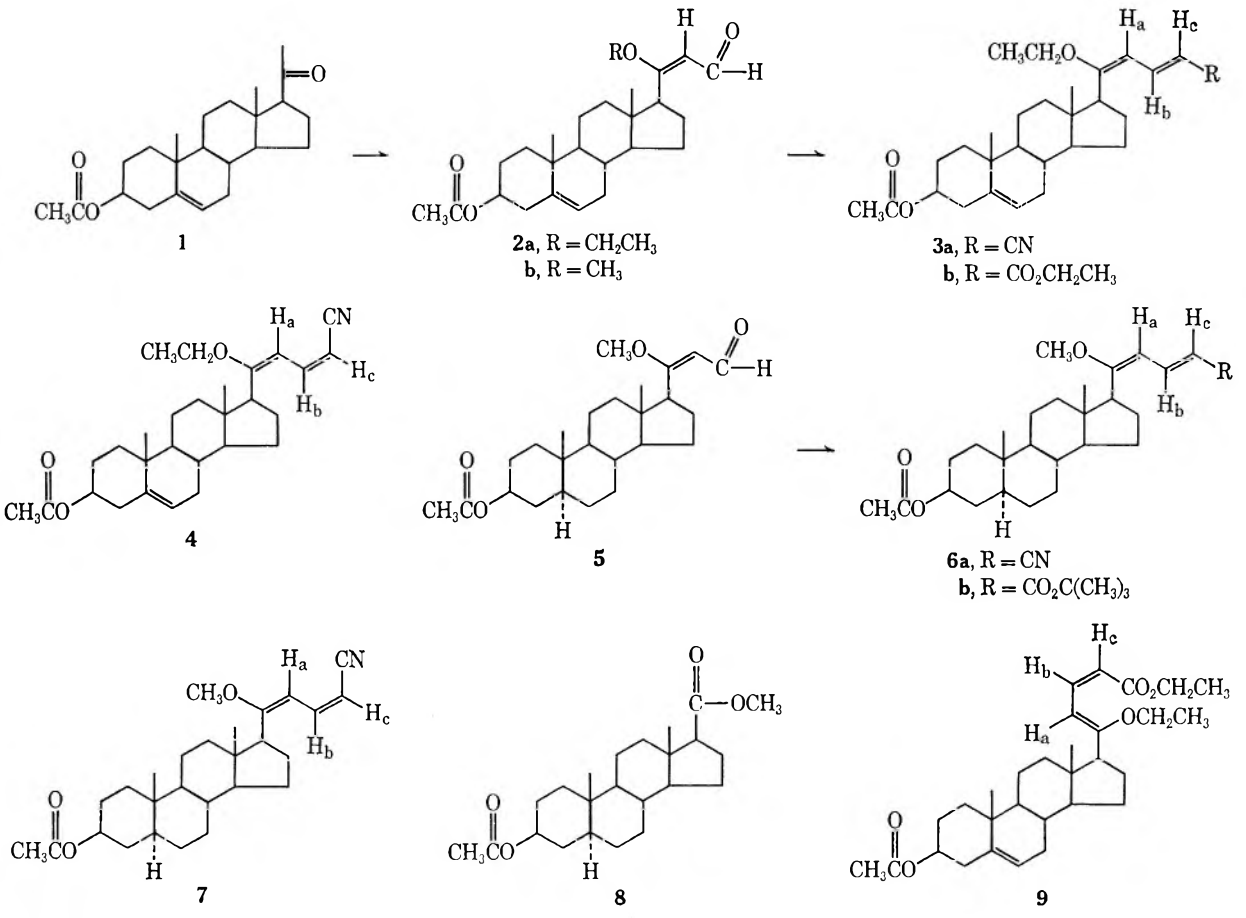
(5) G. R. Pettit and J. P. Yardley, *Chem. Ind.* (London), 553 (1966).

(6) G. R. Pettit, D. Fessler, K. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1389 (1970).

(7) (a) V. Lamberti, W. T. Weller, and J. C. M. Schogt, *Rec. Trav. Chim. Pays-Bas*, **86**, 504 (1967); (b) N. P Shusherina, N. D. Dmitrieva, E. A. Lukyanets, and R. Y. Levina, *Russ. Chem. Rev.*, **36**, 175 (1967).

(8) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 3908 (1964). In this preliminary communication the *trans* orientation of alkoxy and formyl groups in aldehydes **2a** and **2b** was favored.

(9) In this paper, the designations *cis* and *trans* are determined by disposition of carbon substituents along the butadiene system.



constants of J = 4 or 6 cps attributed to *cis* relationships.

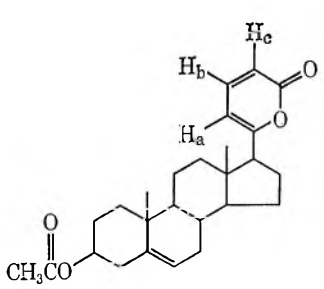
Ester **3b** was transformed into 2-pyrone **10** as follows. Enol ether hydrolysis to ketone **11** was followed by ultraviolet absorption spectra. After 4.5 hr at room temperature, reaction was complete and the ester was saponified with methanolic potassium hydroxide. A 2-min contact at ice-bath temperature with the acetic anhydride–perchloric acid enol lactonization reagent[10] provided 6′-isobufadienolide **10** in 7.4% yield. The low yield was attributed to competitive side reactions such as reverse aldol condensation during the saponification step. However, the yield was considerably improved by eliminating the saponification step and using *t*-butyl ester **6b** and *p*-toluenesulfonic acid in benzene for the cyclization sequence. Concurrently, the following pleasant discovery was made. When aldehyde **2a** was allowed to condense with malonic acid, pyrone **10** was obtained in one step. The extraordinary convenience of this Knoevenagel-[11]type reaction nicely satisfied requirements for a practical 6′-isobufadienolide synthesis, and the alternative butadiene (*cf.* **3b** or **6b**) route was discontinued.

Optimal reaction conditions for the Knoevenagel step were developed using aldehydes **2b** and **5**. A 1:2:2 mole ratio of aldehyde, malonic acid, and piperidine (or morpholine) in excess pyridine at steam-bath temperature for 1 hr proved quite effective. Dilution with water, washing with dilute hydrochloric acid, and finally purification of the pyrone by column chromatography on silica gel provided pyrones **10** and **12** in 54% yields. Substitution of N-methylmorpholine or triethylamine for the secondary amine led only to recovery of starting aldehyde. Elimination of the secondary amine or marked reduction of its concentration also inhibited pyrone formation. The scope of the two-step pyrone synthesis was further ascertained using aldehydes **13a** and **15**. Each aldehyde was obtained from the corresponding 3 or 20 ketone by treatment with trimethyl orthoformate–perchloric acid, and with only preliminary purification was used in the Knoevenagel reaction. By this means, reasonably pure specimens of pyrone **14** and isobufadienolides **16a** and **16b** were obtained in *ca.* 20% conversion. Interestingly, one of the side products accompanying (in 25% yield) pyrone **14** was a nitrogen-containing steroid assigned enamine structure **13b**. Support for the enamine formulation resided with results of element microanalyses, maximum ultraviolet absorption at 344 mμ (ε 15,080), infrared absorption bands at 1740, 1650, and 1605 cm^{-1}, a proton magnetic resonance signal at δ 9.66 attributable to an aldehyde proton, and lack of a signal for methoxyl and broad signals at δ 3.37 and 1.64 (piperidine protons).

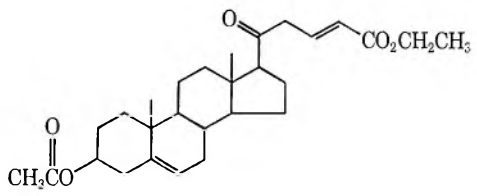
The pmr spectrum of pyrone **14** proved valuable for interpreting the isobufadienolide pyrone ring proton signals. The H_c proton of pyrone **14** appeared as a doublet at δ 6.16 with J_{cb} = 9 cps and H_b as a doublet at δ 7.10 with J_{bc} = 9 cps. The doublet at δ 6.04 with J = 7 cps exhibited, for example, by bufadienolide **16a** would then correspond to the H_a proton with the H_c doublet at δ 6.18 (J_{cb} = 10 cps) and the H_b quartet at δ 7.32 (J_{ba} = 7, J_{bc} = 10 cps) completing the inter-

(10) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

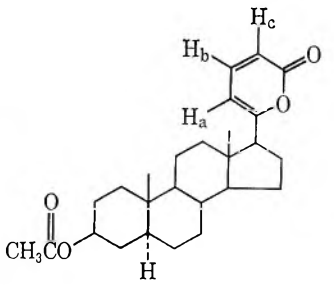
(11) A comprehensive review of the Knoevenagel reaction has been prepared: G. Jones, *Org. React.*, **15**, 204 (1967).



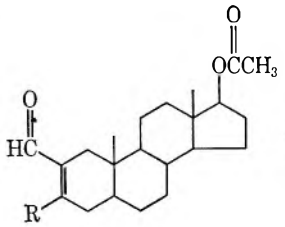
10



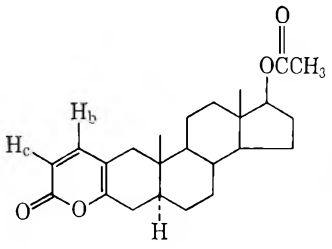
11



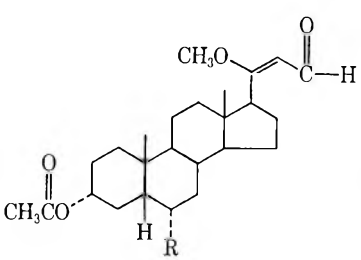
12



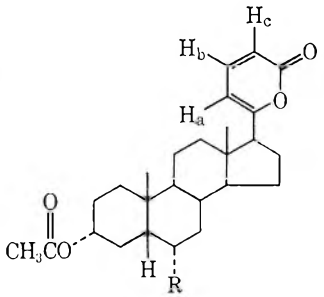
13a, R = OCH_3
b, R = N



14



15a, R = H
b, R = $OCOCH_3$



16a, R = H
b, R = $OCOCH_3$

pretation.[12] Isobufadienolides **10**, **12**, and **16** displayed analogous pyrone-ring pmr signals and characteristic[13] maximal ultraviolet absorption near 300 mμ. Results of these physical measurements combined with infrared[7b,14] spectra and elemental analyses adequately confirmed the structure of each 2-pyrone.

The preceding facile two-step conversion of ketones into 6-substituted 2-pyrones offers promise of being generally applicable to obtaining such oxygen heterocyclic compounds. A comprehensive study of the mechanism and side products arising from the malonic acid step may implicate an iminium salt intermediate.[11,15]

Experimental Section

Preparative thin layer chromatograms were performed using 20 × 20 mm glass plates coated with 1 or 2 mm of silica gel HF_{254} (E. Merck). Melting points were recorded using a Kofler or Fisher-Johns melting point apparatus. Other general experimental methods used here are summarized in the experimental section of part 5.[1]

3β-Acetoxy-20-ethoxy-21-formylpregna-5,20-diene (2a).—With the procedure outlined by Bernstein and colleagues,[8] perchloric acid (1.8 ml) was added to a suspension of pregnenolone acetate (1, 3.3 g) in triethyl orthoformate (50 ml). The solution was swirled for 3 min and pyridine (5 ml) was added followed by water (150 ml). The yellow mixture was extracted with diethyl ether and the ethereal extract was washed well with water. Removal of solvent *in vacuo* gave a solid residue which recrystallized from methanol as large, pale yellow blades (2.5 g): mp 176–178° (another recrystallization from methanol raised the melting point to 182–186°); pmr δ 0.68 and 1.03 (C-18 and -19 methyls), a triplet centered at 1.36 (methyl of ethyl group, J = 3 cps), 2.02 (acetate), 2.9–3.3 (H-17α), a quartet centered at 3.84 (methylene of ethyl group, J = 3 cps), 5.32 (H-6 vinyl), 5.40 (doublet, J = 8 cps, H-21 vinyl), and 9.89 (doublet, J = 8 cps, aldehyde proton).

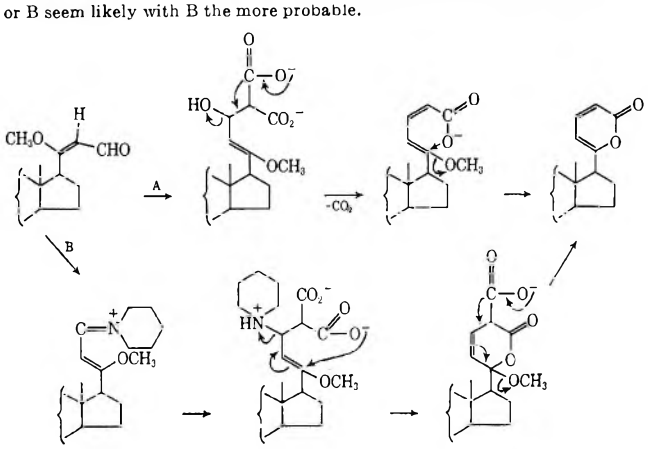
3β-Acetoxy-20-ethoxy-24-cyano-21-norchola-5,20(22),23-triene (3a and 4).—To a cool (ice bath) suspension of sodium hydride oil dispersion (3.4 g) in tetrahydrofuran (60 ml) was added diethyl cyanomethylphosphonate (15 g) in tetrahydrofuran (60 ml), dropwise with stirring. With an elapsed time of *ca.* 10 min, reaction had subsided and aldehyde **2a** (6.2 g) in tetrahydrofuran (150 ml) was added in one portion. Stirring at room temperature was continued for 3 days; optimum reaction time was not determined. Solvent was removed *in vacuo* from the clear orange solution and the residual orange oil was dissolved in diethyl ether. The ethereal solution was washed successively with 2 *N* hydrochloric acid, 2.5 *N* sodium hydroxide, and water. Distillation of the ether gave a yellow solid. Two recrystallizations from methanol provided small rosettes (5.7 g), mp 154–156°. A thin layer chromatogram revealed the product to be a two-component mixture (the *cis,cis* and *cis,trans* isomers). Preparative thin layer chromatography with 1:9 ligroin–ethyl acetate mobile phase, run three times, led to the less polar *cis,cis* isomer **4** and the more polar *cis,trans* isomer **3a**. The *cis,trans* isomer **3a** recrystallized from methanol–chloroform as short, shining needles: mp 195–196°; λ_{max} 295 mμ (ε 30,530); $[\alpha]_D$ −283° (*c* 1.09); RD (*c* 0.05, ethanol) $[\alpha]_{300}$ −4500°, $[\alpha]_{350}$ −2500°, $[\alpha]_{400}$ −1100°, $[\alpha]_{450}$ −700°, $[\alpha]_{500}$ −500°, $[\alpha]_{550}$ −400°, and $[\alpha]_{589}$ −300°; pmr δ 0.68 and 1.06 (C-18 and -19 methyls), a triplet centered at 1.36 (methyl of ethyl group, J = 7 cps), 2.06 (acetate), 2.98 (H-17α), a quartet centered at 3.86 (methylene of ethyl group J = 7 cps), 5.07 (doublet, J = 16 cps, H_c), 5.52 (doublet, J = 12 cps, H_a), 5.47 (H-6), and 7.32 (quartet, J_{ab} = 12 cps, J_{bc} = 16 cps, H_b).

(12) We wish to thank Dr. M. Dines and Dr. W. H. Perkel, Department of Chemistry, University of Illinois, Urbana, Ill., for kindly informing us that they have "consistently found that the splitting constant for the vinyl protons on carbons 3 and 4 of the pyrone ring vary from 9–10 Hz while those for protons on carbons 4 and 5 are in the range 5.5–6.8 Hz."

(13) K. Meyer, *Helv. Chim. Acta*, **46**, 178 (1963).

(14) R. H. Wiley and S. C. Slaymaker, *J. Amer. Chem. Soc.*, **78**, 2393 (1956); R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959); R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.*, **81**, 5242 (1959).

(15) Without benefit of additional study, mechanistic pathways such as A or B seem likely with B the more probable.



Anal. Calcd for $C_{28}H_{39}NO_3$: C, 76.85; H, 8.98; N, 3.20. Found: C, 76.99; H, 8.73; N, 3.33.

The *cis,cis* isomer **4** recrystallized from methanol–chloroform as light, fluffy needles: mp 194–195°; λ_{max} 295 mμ (ε 28,270); $[\alpha]_D$ +15° (*c* 0.60); RD (*c* 0.058, ethanol) $[\alpha]_{330}$ +1414°, $[\alpha]_{350}$ +655°, $[\alpha]_{400}$ +207°, $[\alpha]_{450}$ +138°, $[\alpha]_{500}$ +86°, and $[\alpha]_{589}$ 0°; pmr δ 0.66 and 1.04 (C-18 and -19 methyls), 1.36 (triplet, methyl of ethyl group, J = 7 cps), 2.04 (acetate), 2.6–2.9 (H-17α), 3.92 (quartet, methylene of ethyl group, J = 7 cps), 4.78 (H_c, doublet, J_{bc} = 11 cps), 5.40 (H-6), 5.85 (doublet, J_{ab} = 13 cps, H_a), and 7.08 (quartet, J_{ab} = 13 cps, J_{bc} = 11 cps, H_b).

Anal. Found: C, 77.16; H, 9.33; N, 3.52, 3.93.

3β-Acetoxy-20-methoxy-24-cyano-21-nor-5α-chola-20(22),23-diene (6a and 7).—The general procedure used for obtaining dienes **3a** and **4a** was repeated using diethyl cyanomethylphosphonate in tetrahydrofuran (50 ml), 3.4 g of sodium hydride oil dispersion in tetrahydrofuran (50 ml), and 3β-acetoxy-20-methoxy-21-formyl-5α-pregna-20-ene (4.7 g)[8] in tetrahydrofuran (100 ml). In this case, a thin layer chromatogram of the crude product indicated partial acetate hydrolysis and the mixture was acetylated. The *cis,cis*- and *cis,trans*-butadienes were separated by preparative thin layer chromatography with 5:1 hexane–ethyl acetate mobile phase. A 0.67-g aliquot from 3.4 g of crude material gave 0.16 g of *cis,trans* isomer **6a** and 0.14 g of *cis,cis* isomer **7**. Each isomer was subjected to another preparative thin layer chromatogram to yield 0.083 g of *cis,trans*- and 0.13 g of *cis,cis*-diene. The *cis,trans*-diene **6a** recrystallized from methanol–chloroform as plates: mp 185–186°; $\lambda_{max}^{CH_3OH}$ 292 mμ (ε 35,900); ν_{max} 2950, 2210, 1740, 1610, 1280, 1250, 1040, 960, and 860 cm^{-1}; $[\alpha]^{20}D$ −133° (*c* 0.42); RD (*c* 0.05, methanol) $[\alpha]_{240}$ +1680°, $[\alpha]_{254}$ −3080°, $[\alpha]_{328}$ −3080°, $[\alpha]_{400}$ −840°, and $[\alpha]_{589}$ −240°; pmr δ 0.58 and 0.82 (C-18 and -19 methyls), 2.01 (acetate), 3.62 (methoxyl), 5.04 (doublet, J_{bc} = 15 cps, H_c), 5.46 (doublet, J_{ab} = 11 cps, H_a), and 7.23 (quartet, J_{ab} = 11 cps, J_{bc} = 15 cps, H_b).

Anal. Calcd for $C_{27}H_{39}NO_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.06; H, 9.26; N, 3.37.

The *cis,cis* isomer **7** recrystallized from methanol–chloroform as needles: mp 188–189°; $\lambda_{max}^{CH_3OH}$ 292 mμ (ε 25,600); ν_{max} 3000, 2240, 1750, 1240, 1040, 845, and 730 cm^{-1}; $[\alpha]^{20}D$ +130° (*c* 0.62); RD (*c* 0.05, methanol) $[\alpha]_{238}$ −4560°, $[\alpha]_{256}$ +1360°, $[\alpha]_{322}$ +2360°, $[\alpha]_{400}$ +280°, $[\alpha]_{589}$ +40°; pmr δ 0.59 and 0.83 (C-18 and -19 methyls), 2.01 (acetate), 3.68 (methoxyl), 4.77 (doublet, J_{bc} = 9 cps, H_c), 5.84 (doublet, J_{ab} = 11 cps, H_a), and 7.67 (quartet, J_{bc} = 9 cps, J_{ba} = 11 cps, H_b).

Anal. Found: C, 76.33; H, 9.19; N, 3.41.

Ozonolysis of 3β-Acetoxy-20-methoxy-24-cyano-21-nor-5α-chola-20(22),23-diene (6a and 7).—Ozone (Welsbach Ozonator, 60 V, oxygen at 6 psi, flowmeter 0.04) was passed for 15 min through a gas dispersion tube into a solution of *cis,cis*-diene **7** (66 mg) in dry ethyl acetate (20 ml) at −60°. The solution was next flushed with oxygen for 10 min and concentrated to a crystalline residue. Zinc dust (0.2 g) was added to a solution of the solid in glacial acetic acid (5 ml). After 30 min at room temperature, the solution was filtered and diluted with water. The crystals which separated were collected, washed with water, and dried to yield 47 mg (81%) of pure (by thin layer chromatography) methyl 3β-acetoxy-5α-androstane 17β-carboxylate (**8**), mp 149–151°.

Employing the same procedure with *cis,trans* isomer **6a** (51.5 mg) in ethyl acetate (25 ml) gave 44 mg (98%) of pure (by thin layer chromatography) ester **8**, mp 146–148°. Both specimens of ester **8** were identical with an authentic specimen as evidenced by thin layer chromatographic and infrared (ν_{max} 3000, 1750, 1265, and 1045 cm^{-1}) comparison. The pmr spectra were also identical and displayed signals at δ 0.64 and 0.82 (6 methyl protons), 2.01 (acetate), 3.67 (methoxyl), and 4.66 (multiplet, H-3α).

3β-Acetoxy-20-ethoxy-24-ethoxycarbonyl-21-norchola-5-*cis*-20(22)-*trans*-23-triene (3b).—The ylide prepared from diethyl carbethoxymethylphosphonate (6.7 g) in tetrahydrofuran (20 ml) and sodium hydride oil dispersion (1.1 g) in tetrahydrofuran (20 ml) was allowed to react with aldehyde **2** (2.1 g) in tetrahydrofuran (50 ml) as described above for obtaining isomeric olefins **3a** and **4**. In this experiment, the reaction was allowed to proceed for *ca.* 22 hr. The crude product recrystallized from methanol as needles (1.85 g), mp 141–145°. Further purification by preparative thin layer chromatography with 17:3 ligroin–ethyl acetate mobile phase gave an analytical specimen: mp 153–155°; $\lambda_{max}^{CHCl_3}$ 305 mμ (ε 27,500); $[\alpha]_D$ −249° (*c* 4.08); ν_{max} 1730 (acetate), 1700 (ethyl ester), and 1240 cm^{-1}; pmr δ 0.66 and 1.02 (C-18 and -19 methyls), 1.32 and 1.26 (triplets, J = 7 cps, methyls of ethoxys), 2.04 (acetate), 2.90 (H-17α), 3.93 and 4.20 (quartets, J = 7 cps, methylenes of ethoxys), 4.60 (multiplet, H-3α), 5.42 (multiplet, H-6 vinyl), 5.53 (doublet, J_{ab} = 12 cps, H_a), 5.68 (doublet, J_{cb} = 15 cps, H_c), and 7.66 (quartet, J_{ab} = 12 cps, J_{cb} = 15 cps, H_b).

Anal. Calcd for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.41; H, 9.03.

Irradiation of 3β-Acetoxy-20-ethoxy-24-ethoxycarbonyl-21-norchola-5-*trans*-20(22)-*trans*-23-triene (3b).—A specimen of *cis,trans* isomer **3b** (1.0 g) in benzene (100 ml) was irradiated with a Sylvania industrial infrared lamp (250 W) for 73 hr. The reaction mixture was chromatographed on silica gel (200 g) and a fraction eluted by 19:1 ligroin–ethyl acetate afforded an isomer tentatively assigned *trans,cis* structure **9**. Recrystallization from methanol gave 0.05 g of diamond-shaped plates: mp 147–149°; λ_{max} 305 mμ (ε 25,800); ν_{max} 1730, 1700, and 1240 cm^{-1}; $[\alpha]_D$ −6° (*c* 1.26); pmr δ 0.66 and 1.02 (C-18 and -19 methyls), 1.28 (triplet, J = 7 cps, methyl of ethoxy), 1.32 (triplet, J = 7 cps, methyl of ethyl ester), 2.04 (acetate), 3.92 (quartet, J = 7 cps, methylene of ethoxy ether), 4.14 (quartet, J = 7 cps, methylene of ethyl ester), 4.6 (multiplet, H-3α), 5.38 (multiplet, H-6 vinyl), 5.33 (quartet, J_{bc} = 4 cps, J_{ba} = 6 cps, H_b), 6.88 (doublet, J_{ab} = 6 cps, H_a), and 6.96 (doublet, J_{cb} = 4 cps, H_c).

Anal. Calcd for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.31; H, 9.19.

The nmr spectrum of the remaining material showed it to be substantially unchanged olefin **3b**.

3β-Acetoxy-20-methoxy-24-*t*-butoxycarbonyl-21-nor-5α-chola-*cis*-20(22)-*trans*-23-diene (6b).—Synthesis of *t*-butyl ester **6b** (1.4 g) was accomplished using diethyl *t*-butoxycarbonylmethylphosphonate[16] (7.8 g), sodium hydride oil dispersion (1.0 g), aldehyde **5** (2.0 g), and tetrahydrofuran (200 ml total) essentially (16-hr reaction period) as summarized for obtaining ethyl ester **3b**. The product in hexane was chromatographed on silica gel (50 g). Elution with 9:1 hexane–ethyl acetate provided 1.4 g of *cis,trans* olefin **6b**. Recrystallization from hexane afforded an analytical sample: mp 154–156°; $\lambda_{max}^{CHCl_3}$ 301 mμ (ε 10,400); ν_{max} 2950, 1735, 1715, 1625, 1375, 1300, 1260, 1150, 985, and 870 cm^{-1}; $[\alpha]^{25}D$ −150° (*c* 2.33); pmr δ 0.60 and 0.83 (C-18 and -19 methyls), 1.49 (*t*-butyl), 2.02 (acetate), 3.62 (methoxyl), 5.50 (doublet, J_{ab} = 11 cps, H_a), 5.64 (doublet, J_{bc} = 14 cps, H_c), and 7.55 (quartet, J_{ab} = 11 cps, J_{bc} = 14 cps, H_b).

Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.65. Found: C, 74.20; H, 9.84.

3β-Acetoxy-17β-(6′α-pyronyl)androst-5-ene (10). Method A.—To a diethyl ether (100 ml) solution of *cis,trans* olefin **3b** (1g) was added 72% perchloric acid (1 ml)–water (0.5 ml). Hydrolysis of the enol ether was followed by viewing disappearance of the ultraviolet absorption maxima at 305 mμ and was complete after 4.5 hr at room temperature. The solution was washed well with water and solvent was removed *in vacuo*. A solution of the residue (keto ester **11**) in 5% potassium hydroxide–methanol (100 ml) was heated at reflux for 20 min. Following concentration of solvent, neutral material was removed by extraction with chloroform and the acidic fraction was added to a cold (ice bath) ethyl acetate solution (200 ml) containing 1 *M* acetic anhydride and 10^{-3} *M* perchloric acid.[10] Two minutes later the yellow solution was diluted with diethyl ether and washed with dilute aqueous sodium bicarbonate. Removal of solvent led to a yellow oil which was triturated with boiling ligroin. Removal of solvent from the ligroin extract gave a pale yellow oil (0.75 g) that partially crystallized on standing. The semisolid in 9:1 ligroin–ethyl acetate was chromatographed on silica gel (80 g). Elution with 4:1 ligroin–ethyl acetate provided a fraction which crystallized from diethyl ether as fine needles (0.17 g): mp 213–216°; λ_{max} 305 mμ (ε 6,270); ν_{max} 1730, 1630, and 1550 cm^{-1}; $[\alpha]_D$ −67° (*c* 0.82); pmr[17] δ 0.66 (C-18 methyl), 1.04 (C-19 methyl), 2.04 (C-3 acetate), 4.6 (multiplet, H-3α), 5.4 (multiplet, H-6), 6.01 (quartet, J_{bc} = 6.5 cps, J_{ac} = 0.75 cps, H_a), 6.13 (quartet, J_{ab} = 9 cps, J_{ac} = 0.75 cps, H_c), and 7.27 (quartet, J_{ab} = 9 cps, J_{cb} = 6.5 cps, H_b).

Anal. Calcd for $C_{26}H_{34}O_4$ (mol wt, 410): C, 76.06; H, 8.35. Found: C, 76.30; H, 8.22; mol wt, M^+ − 60 at *m/e* 350 (mass spectrum).[18]

(16) B. J. Magerlein and F. Kagan, *J. Amer. Chem. Soc.*, **82**, 593 (1960).

(17) We are indebted to Dr. J. Kutney for providing the 100-MHz spectra.

Method B.—To a benzene solution (30 ml) containing *t*-butyl ester (6b, 0.10 g) was added a few small crystals of *p*-toluenesulfonic acid and 3 drops of water. The solution was heated at reflux and benzene was allowed to slowly distil. After 18 hr, the solution was allowed to cool to room temperature. The benzene solution was washed well with water and dried. Chromatography of crude material on silica gel (6 g) gave two compounds. The less polar compound **17** was eluted with 9:1 hexane–ethyl acetate. Crystallization of the colorless oil (28 mg) from ethanol–water gave colorless crystals: mp 105–107°; ν_{max} 3000, 1740, 1700, 1660, 1630, 1240, 1030, and 970 cm^{-1}; pmr δ 0.60 and 0.84 (C-18 and -19 methyls), 2.03 (acetate), 1.88 (doublet of doublet J = 6.5, 1.5 cps, methyl on double bond), 6.17 (doublet J = 15 cps, with fine splitting, J = 1.5 cps), and 6.83 (complex multiplet, H_b).[19]

Pyrone **12** was eluted with 6:1 hexane–ethyl acetate. Recrystallization of colorless, crystalline solid (37 mg) gave needles, mp 232–234°, identical spectrally with pyrone prepared by method C.

Method C.—The following procedure proved very convenient and was routinely used for obtaining pyrone **10**. To aldehyde **2b** (2.0 g, 4.8 mmol), prepared from ketone **1** and trimethyl orthoformate as summarized for obtaining aldehyde **2a**,[8] in pyridine (40 ml) was added malonic acid (1.0 g, 9.6 mmol) and piperidine (1 ml, 10 mmol). The solution was heated on a steam bath for 1 hr and evolution of carbon dioxide was noted. Upon cooling to room temperature the mixture was poured into cold (ice bath) 2 *N* hydrochloric acid. The yellow solid which separated was extracted with chloroform and the combined extract was washed with 2 *N* hydrochloric acid and water. Following removal of solvent, the residue was chromatographed on silica gel (100 g). Elution with 4:1 hexane–ethyl acetate provided 1.1 g (55%) of pyrone **10**. Recrystallization from chloroform–hexane gave 0.89 g of pale yellow crystals, mp 213–217°. Alternatively, recrystallization from ethyl acetate gave almost colorless crystals with the same melting point. Comparison of pyrone **10** specimens from methods A and B by mixture melting point determination and infrared spectra confirmed their mutual identity.

3β-Acetoxy-17β-(6′α-pyronyl)-5α-androstane (**12**).—The method B procedure for obtaining pyrone **10** was employed for converting 2.0 g of aldehyde **5** into α-pyrone **12**. Crude product was chromatographed on silica gel (150 g). Elution with 5:1 hexane–ethyl acetate gave 1.1 g (54%) of oily pyrone. Crystallization from chloroform–hexane gave 0.79 g of yellow crystals, mp 234–238°. Two recrystallizations from the same solvent provided a colorless, crystalline, analytical specimen: mp 235–237°; $\lambda_{max}^{CHCl_3}$ 307 mμ (ε 7,930); ν_{max} 2950, 1735, 1630, 1555, 1250, and 820 cm^{-1}; $[\alpha]^{25}D$ +9.8° (*c* 6.86); RD (*c* 0.57, chloroform) $[\alpha]_{348}$ +326°, $[\alpha]_{400}$ +67°, and $[\alpha]_{589}$ +7°; pmr δ 0.64 and 0.85 (C-18 and -19 methyls), 2.02 (acetate), 6.00 (doublet, J_{bc} = 6.5 cps, H_a), 6.14 (doublet, J_{ab} = 9 cps, H_c), and 7.29 (partially masked quartet, J_{bc} = 6.5 cps, J_{ab} = 9 cps, H_b).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.59; H, 8.62.

2-Formyl-3-methoxy-17β-acetoxy-5α-androst-2-ene (**13a**).—To 3-oxo-17β-acetoxy-5α-androstane (5.5 g) in trimethyl orthoformate (85 ml) was added dropwise 2.7 ml of 70% perchloric acid with stirring. After 5 min at room temperature, a yellow solid began to separate and the mixture was warmed to 40° for 7 min. Addition of pyridine (10 ml) followed by water precipitated a yellow solid which was extracted with diethyl ether. The ethereal extract was washed with water and concentrated to dryness. The crude aldehyde was chromatographed on silica gel (250 g). A fraction (3.2 g, 51%) eluted by 4:1 hexane–ethyl acetate corresponded to aldehyde **13a**. Crystallization from acetone–hexane provided 2.0 g of needles: mp 191–197° (lit.[20] mp 210–214°); $\lambda_{max}^{CH_3OH}$ 280 mμ (ε 13,500) [lit.[20] $\lambda_{max}^{CH_3CH_2OH}$ 278.5 mμ (ε 13,560)]; ν_{max} 2950, 1750, 1650, 1580, 1240, and 1040 cm^{-1}; pmr δ 0.72 and 0.83 (C-18 and -19 methyls), 2.05 (acetate), 3.75 (methoxyl), 4.58 (multiplet, H-17α), and 10.10 (aldehyde proton).

17β-Acetoxy-5α-androstano[2,3-*e*]-2-pyrone (**14**).—With aldehyde **13a** (3 g), malonic acid (1.5 g), pyridine (100 ml), and piperidine (1.5 ml), conversion into pyrone **14** was accomplished as summarized above for obtaining pyrone **10** and the crude product was chromatographed on silica gel (120 g). A fraction (1 g) eluted by 4:1 hexane–ethyl acetate was rechromatographed on 40 g of silica gel to provide 0.6 g (20%) of 17β-acetoxy-5α-androstano-[2,3-*e*]-2-pyrone (**14**). Crystallization from acetone–hexane gave a pure specimen of crystals (0.5 g): mp 207–210°; $\lambda_{max}^{CHCl_3}$ 312 mμ (ε 7450); ν_{max} 2950, 1735, 1640, 1550, 1240, 1030, and 820 cm^{-1}; $[\alpha]^{25}D$ +68° (*c* 4.71); RD (*c* 1.95, chloroform) $[\alpha]_{360}$ +471°, $[\alpha]_{400}$ +226°, and $[\alpha]_{589}$ +60°; pmr δ 0.82 (C-18 and -19 methyls), 2.07 (acetate), 4.66 (multiplet, H-17α), 6.16 (doublet, J_{cb} = 9 cps, H_c), and 7.10 (doublet, J_{bc} = 9 cps, H_b); mass spectrum *m/e* 384 (parent ion, 100%), 370 (M − 14, 9%), 356 (M − 28, 49%), 342 (M − 42, 34%), 324 (M − 60, 53%), and 309 (M − 75, 39%).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.21; H, 8.37.

A fraction (0.86 g) eluted by acetone from the silica gel column chromatogram crystallized from chloroform–hexane as pale yellow crystals, mp 203–205° dec, formulated as **2-formyl-3-(N-piperidino)-17β-acetoxy-5α-androst-2-ene** (**13b**). An analytical specimen was obtained: $\lambda_{max}^{CH_3OH}$ 244 mμ (ε 15,080); ν_{max} 3000, 1740, 1650, 1600, 1240, 1200, 1130, and 1040 cm^{-1}; $[\alpha]^{25}D$ +141° (*c* 2.28); pmr δ 0.70 and 0.80 (C-18 and -19 methyls), 1.64 (multiplet, methylene), 2.02 (acetate), 3.37 (multiplet, 4 H, $-CH_2N-$), and 9.66 (aldehyde proton).

Anal. Calcd for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.72; H, 9.57; N, 3.31.

3α-Acetoxy-17β-(6′α-pyronyl)-5β-androstane (**16a**).—A sample of 3α-acetoxy-20-oxo-5β-androstane (5g) was converted into 3α-acetoxy-20-methoxy-21-formyl-5β-pregna-20-ene (**15a**, 2.7 g) using the general procedure summarized for obtaining aldehyde **2b**. A specimen of aldehyde **15a** gave the following data: mp 105–108°; ν_{max} 2950, 1735, 1650, 1600, 1240, and 1020 cm^{-1}; pmr δ 0.64 and 0.96 (6 methyl protons), 2.04 (acetate), 3.15 (multiplet, H-17α), 3.68 (methoxyl), 4.77 (multiplet, H-3β), 5.56 (doublet, J = 8 cps, H-21 vinyl), and 9.90 (doublet, J = 8 cps, aldehyde proton). Aldehyde **15a** (5.5 g) was condensed in pyridine (80 ml)–morpholine (2.5 ml) with malonic acid (2.5 g) as summarized for the synthesis of pyrone **10** (method B). The crude product was chromatographed on silica gel (150 g) and a fraction eluted by 4:1 hexane–ethyl acetate gave 1.6 g of viscous, yellow oil. Crystallization of the oil from benzene–hexane provided 1.2 g (21%) of pyrone **16a**, mp 147–148°. Two recrystallizations from acetone–hexane gave an analytical sample with the same melting point: $\lambda_{max}^{CHCl_3}$ 307 mμ (ε 8,870); ν_{max} 2950, 1750, 1640, 1560, 1260, 1090, 1040, and 795 cm^{-1}; $[\alpha]^{25}D$ +75° (*c* 0.91); RD (*c* 0.096, chloroform) $[\alpha]_{344}$ +1000°, $[\alpha]_{400}$ +167°, and $[\alpha]_{589}$ +42°; pmr δ 0.62 and 0.97 (C-18 and -19 methyls), 2.06 (acetate), 4.70 (multiplet, H-3β), 6.04 (doublet, J_{bc} = 7 cps, H_a), 6.18 (doublet, J_{ab} = 10 cps, H_c), and 7.32 (quartet, J_{bc} = 7 cps, J_{ab} = 10 cps, H_b), mass spectrum *m/e* 412 (parent ion, 10%), 352 (M − 60, base ion, 100%), and 337 (M − 75, 51%).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.93; H, 8.74.

3α,6α-Diacetoxy-17β-(6-α-pyronyl)-5β-androstane (**16b**).—A sample (1.5 g) of 3α,6α-diacetoxy-20-methoxy-21-formyl-5β-pregna-20-ene was prepared from 3α,6α-diacetoxy-20-oxo-5β-pregnane (2.0 g): ν_{max} 2950, 1740, 1660, 1600, 1240, and 1020 cm^{-1}; pmr δ 0.63 and 1.00 (C-18 and -19 methyls), 2.05 (acetate), 3.70 (methoxyl), 4.75 (multiplet, H-3β), 5.19 (multiplet, H-6β), 5.53 (doublet, J = 8 cps, H-21), and 9.90 (doublet, J = 8 cps, aldehyde proton). Aldehyde **15b** (1.5 g), pyridine (30 ml), morpholine (0.8 ml), and malonic acid (0.75 g) were combined according to the general procedure summarized for obtaining pyrone **10** (method B). Chromatography with 2:1 hexane–ethyl acetate as eluent of the crude product on silica gel (50 g) gave 0.88 g (57%) of pyrone **16b** containing small amounts of side products. Rechromatography on basic alumina (24 g) and elution with 5:1 hexane–ethyl acetate provided 0.38 g (24%) of colorless oil. The oil crystallized from acetone–hexane as crystals (0.20 g), mp 151–153°. Slow recrystallization led to a pure specimen as needles: mp 152–155°; $\lambda_{max}^{CHCl_3}$ 305 mμ (ε 8,490); ν_{max} 3000, 1750, 1640, 1560, 1240, 1020, and 800 cm^{-1}; $[\alpha]^{25}D$ −9° (*c* 0.44); RD (*c* 0.75, chloroform) $[\alpha]_{352}$ −6°, $[\alpha]_{400}$ −5°, and $[\alpha]_{589}$ −3°; pmr δ 0.62 and 1.00 (C-18 and -19 methyls), 2.04 and 2.06 (6 acetate methyl protons), 4.73 (multiplet, H-3β),

(18) We wish to thank John Occolowitz for providing the mass spectral data.

(19) The pmr spectrum of the less polar compound showed an olefin splitting pattern very similar to that of crotonic acid: "Varian Spectra Catalog," Vol. 1, No. 62, N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Ed., Varian Associates, 1962.

(20) D. Burn, G. Cooley, J. W. Ducker, B. Ellis, D. N. Kirk, and V. Petrow, *Tetrahedron Lett.*, 733 (1964).

5.20 (multiplet, H-6β), 6.02 (doublet, J_{bc} = 7 cps, H_a), 6.18 (doublet, J_{ab} = 10 cps, H_c), and 7.31 (quartet, J_{ab} = 10 cps, J_{bc} = 7 cps, H_b); mass spectrum *m/e* 470 (parent ion, 56%), 410 (M − 60, 3%), 350 (M − 120, 58%), and 335 (M − 135, 100%, base ion).

Anal. Calcd for $C_{28}H_{38}O_6$ (mol wt, 470): C, 71.46; H, 8.14. Found: C, 71.37; H, 7.94.

Registry No.—**2a**, 23330-29-2; **3a**, 23330-30-5; **3b**, 15019-24-6; **4**, 23330-32-7; **6a**, 23367-40-0; **6b**, 23330-33-8; **7**, 23330-34-9; **8**, 3330-50-5; **9**, 23330-36-1; **10**, 15019-25-7; **12**, 23330-38-3; **13a**, 23367-41-1; **13b**, 23330-39-4; **14**, 23330-40-7; **15a**, 23330-41-8; **16a**, 23330-42-9; **16b**, 23330-43-0.

Bufadienolides. 7. Synthesis of 3β-Acetoxy-5α,14α-bufa-20,22-dienolide[1-3]

GEORGE R. PETTIT, DYRAL C. FESSLER, KENNETH D. PAULL, PETER HOFER, AND JOHN C. KNIGHT

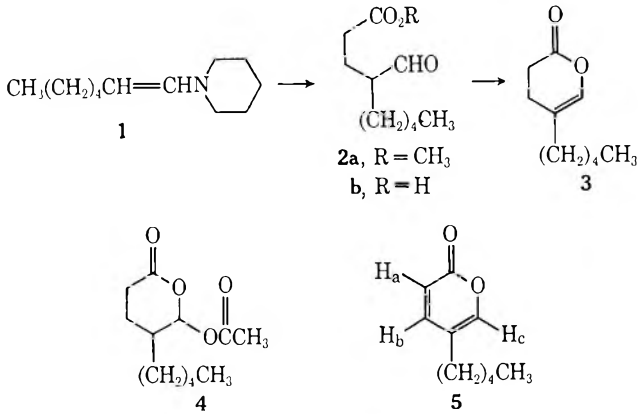
Department of Chemistry, Arizona State University, Tempe, Arizona 85281, and Department of Chemistry, University of Maine, Orono, Maine 04473

Received May 14, 1969

A new synthetic route to 5-substituted 2-pyrones is described. Alkylation of enamine **1** with methyl acrylate, cyclization of carboxylic acid **2b** employing *p*-toluenesulfonic acid in benzene, and dehydrogenation of enol lactone **3** with a palladium catalyst or by a N-bromosuccinimide sequence comprised the key steps to α-pyrone **5**. Other methods (utilizing derivatives of acetic acid) investigated for the enol lactonization reaction gave mainly lactone **4**. Application to bufadienolide chemistry was studied by transformation of dehydroepiandrosterone *via* intermediates **6**–**8** to 3β-acetoxy-14α-bufa-5,20(21)-dienolide (**9**). Similar conversion of epiandrosterone acetate (**10**) led to bufenolide **16**, which was dehydrogenated to bufadienolide **17** using sulfur. Other dehydrogenation methods, including those quite useful with enol lactone **3**, were unsatisfactory.

Two 5-substituted 2-pyrones were synthesized in 1941.[4] Twenty years elapsed before further syntheses of such 2-pyrones were described.[5] A total of *ca.* six such examples have been reported. For reasons already elaborated[6] we wished to find an effective synthesis of 5-substituted 2-pyrones which could be conveniently adapted to synthesis of bufadienolides. After a number of superficially promising syntheses had been eliminated, the following approach proved satisfactory and was studied in detail. The new method is based on an aliphatic aldehyde precursor, and heptaldehyde was selected for model experiments.

Condensation of heptaldehyde with piperidine provided enamine[7] **1**. Since attempts to condense enamine **1** with ethyl propiolate in dioxane or dimethylformamide solution were unpromising,[8] the use of methyl acrylate was investigated. Alkylation[9] of enamine **1** with methyl acrylate in refluxing acetonitrile gave aldehyde **2a** in 75% yield following hydrolysis. Mild saponification of methyl ester **2a** provided carboxylic acid **2b**. Benzene containing *p*-toluenesulfonic acid proved most effective (64%) for conversion of acid **2b** into enol lactone **3**.[10] When preparation of enol lactone **3** was attempted employing the acetic anhydride–perchloric acid reagent in ethyl acetate[11a] or isopropenyl acetate–perchloric acid,[11b] the exclusive product was tetrahydropyran **4**. With acetic anhydride–sodium acetate[11c] a mixture of both lactones **3** and **4** was obtained. Structure assignments for the oily lactones **3** and **4**, are based on the method of synthesis and supporting spectral data. For example, lactone **3** exhibited carbonyl absorption at 1770 cm^{-1} and olefin stretching at 1680 cm^{-1} characteristic of a δ-enol lactone. In the pmr spectrum the vinyl proton signal appeared as a quintet (J = 1 Hz) at δ 6.4. Lactol acetate **4** exhibited an acetate methyl singlet at δ 2.18, and the proton at position 6 appeared as two doublets centered at δ 6.28 (J = 5 Hz) and 6.58 (J = 2 Hz), indicating a mixture of configurational isomers.



(1) Part 6 and Steroids and Related Natural Products. LIV: G. R. Pettit, J. C. Knight, and C. L. Herald, *J. Org. Chem.*, **35**, 1393 (1970). The present investigation was supported by Public Health Service Research Grants CA-04074-05, CA-10115-01, CA-10115-02, and CA-10115-03 from the National Cancer Institute. The mass spectrometers were obtained using National Science Foundation Grants GB-4939 and GP-6979.

(2) Based in part on dissertations submitted by D. C. Fessler and K. D. Paull to the Graduate School, Arizona State University, Oct 1968 and Sept 1969, respectively.

(3) A preliminary report of the present study has been published: G. R. Pettit, D. C. Fessler, K. D. Paull, P. Hofer, and J. C. Knight, *Can. J. Chem.*, **47**, 2511 (1969).

(4) J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

(5) For these references see G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *ibid.*, **35**, 1385 (1970). D. Bertin, L. Nedelec, and J. Mathieu, French Patent 1,369,962 (1962); *Chem. Abstr.*, **62**, 616 (1965). F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969).

(6) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(7) For a review refer to J. Szmuszkovicz in "Advanced Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 1–113.

(8) Condensation of propiolates with enamines of ketones can lead to a variety of products: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

(9) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); H. Fritz and O. Fischer, *Tetrahedron*, **20**, 1737 (1964).

(10) An investigation of the preparation and properties of such enol lactones has recently been summarized: P. Haverkamp Begeman, V. Lambert, and W. T. Weller, *Rec. Trav. Chim. Pays-Bas*, **87**, 1335 (1968). The enol lactones were found sensitive to both oxygen and water and darkened rapidly on exposure to air. See also ref 13b for synthesis of δ-lactones.

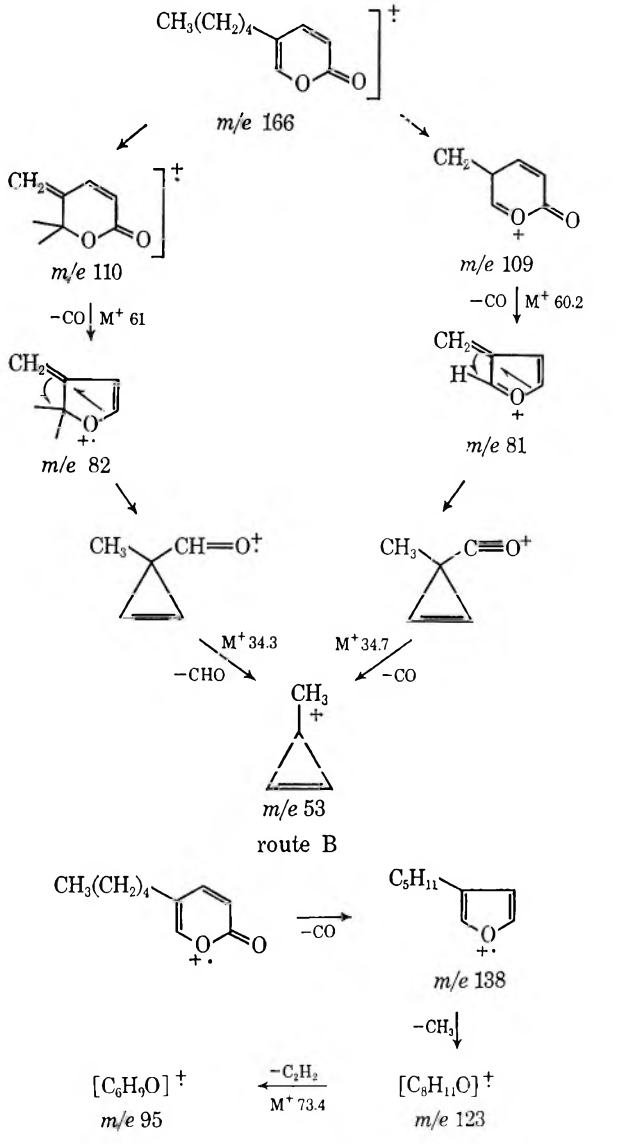
(11) (a) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966). (b) N. P. Shusherina, E. A. Luk'yanets, T. L. Tsilevich, and R. Ya Levina, *J. Org. Chem. USSR*, **2**, 1194 (1966). (c) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952); T. M. Harris and C. S. Combs, Jr., *J. Org. Chem.*, **33**, 2399 (1968).

Dehydrogenation of enol lactone **3** to pyrone **5** was achieved by means of a palladium catalyst in refluxing *p*-cymene,[12] which provided a 50% yield of pyrone **5**. Pyrone **5** was also obtained in 42% yield somewhat less conveniently by bromination of enol lactone **3** with N-bromosuccinimide followed by dehydrobromination with lithium bromide in dimethylformamide.[13]

The structure of pyrone **5** was amply supported by mass and spectral data. Based on recent studies of the mass spectral fragmentation of 2-pyrones,[14] routes A and B have been suggested for the observed fragmentation of pyrone **5** (Scheme I). A number of the postulated transformations received support from metastable ions (M^+). Cleavage at the benzyl bond appeared to be the primary mode (route A) of molecular ion (*m/e* 166) fragmentation. Formation of the benzylic-type ion (*m/e* 109) is a transformation characteristic of alkylbenzenes,[15] and as with alkylbenzenes containing side chains longer than propyl, the β cleavage was accompanied by rearrangement of one hydrogen atom, giving rise to the ion at *m/e* 110. Loss of carbon monoxide from both the *m/e* 110 and 109 ions could then lead to furan-type ions at *m/e* 81 and 82. The *m/e* 53 ion might then arise from the *m/e* 82 ion by migration of a hydrogen atom and loss of CHO, or from the *m/e* 81 ion by migration of a hydrogen atom and loss of carbon monoxide. Pertinent aspects of the remaining mass spectrum can be interpreted by initial loss of carbon monoxide from the molecular ion as suggested by route B.

SCHEME I

POSSIBLE FRAGMENTATION OF 5-PENTYLPYRAN-2-ONE (5)



Other spectral characteristics of pyrone **5** were in complete accord with an α-pyrone structure. The ultraviolet absorption maximum at 298 mμ (ϵ 5150)[16] and infrared[17a] absorption at 1755, 1730, 1650, and 1550 cm^{-1} were as anticipated. The pmr spectrum[17b] exhibited a doublet at δ 6.15 (J = 11 Hz) for H_a, a pair of doublets at δ 7.2 (J = 3 and 11 Hz) for H_b, and a doublet centered at δ 7.23 (J = 3 Hz) for H_c. With the structure of pyrone **5** thereby firmly established, the new route to 5-substituted 2-pyrones was next extended to two typical steroidal aldehydes, namely, **7e** and **12e**.

Nitrile **6a** was prepared by allowing dehydroepiandrosterone acetate to react with the carbanion derived from diethyl cyanomethylphosphonate[18] in tetrahydrofuran. Saponification of the 3-acetate followed by reaction with dihydropyran provided tetrahydropyranyl ether **6b**. The plan here was to reduce nitrile **6b** using lithium triethoxyaluminohydride[19] to the corresponding aldehyde. However, attempts to reduce nitriles **6a** or **6b** or the partially reduced derivatives **7a** or **7b** proved unsatisfactory. To circumvent this problem, the 17(20) olefin was selectively hydrogenated over 5% palladium on calcium carbonate to yield nitrile **7a**. Similarly, olefin **6b** was easily reduced to **7b**. Saponification of nitrile **7a** led to carboxylic acid **7c**, which was acetylated using acetic anhydride–acetic acid to provide acid **7d**. The acid chloride derived from carboxylic acid **7d** was reduced[20] over a palladium catalyst to give aldehyde **7e**[21] in 83% yield. Condensation of aldehyde **7e** with piperidine gave enamine **7f**. Alkylation of enamine **7f** with methyl acrylate in acetonitrile followed by hydrolysis gave a two-component mixture. Preparative layer chromatography on silica gel led to recovery of aldehyde **7e** and methyl ester **8a** (50% yield). Attempts to improve conversion of aldehyde **7e** into methyl ester **8a** by changing reaction conditions and solvent did not result in any improvement, and

(12) D. Rosenthal, P. Grabowich, E. Sabo, and J. Fried, *J. Amer. Chem. Soc.*, **85**, 3971 (1963).

(13) See, *e.g.*, (a) B. Berkoz, L. Cuellar, R. Grezemkovsky, N. V. Avila, and A. D. Cross, *Proc. Chem. Soc.*, 215 (1964); (b) V. Lambert, W. T. Weller, and J. C. M. Schogt, *Rec. Trav. Chim. Pays-Bas*, **86**, 504 (1967).

(14) Some controversy over the furan-like ion structure has been raised: W. H. Pirkle and M. Dines, *J. Amer. Chem. Soc.*, **90**, 2318 (1968). We wish to thank Professor P. Brown for a very helpful discussion of the mass spectrum of pyrone **5**.

(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," 2nd ed, Holden-Day, Inc., San Francisco, Calif., 1967, p 81.

(16) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 140.

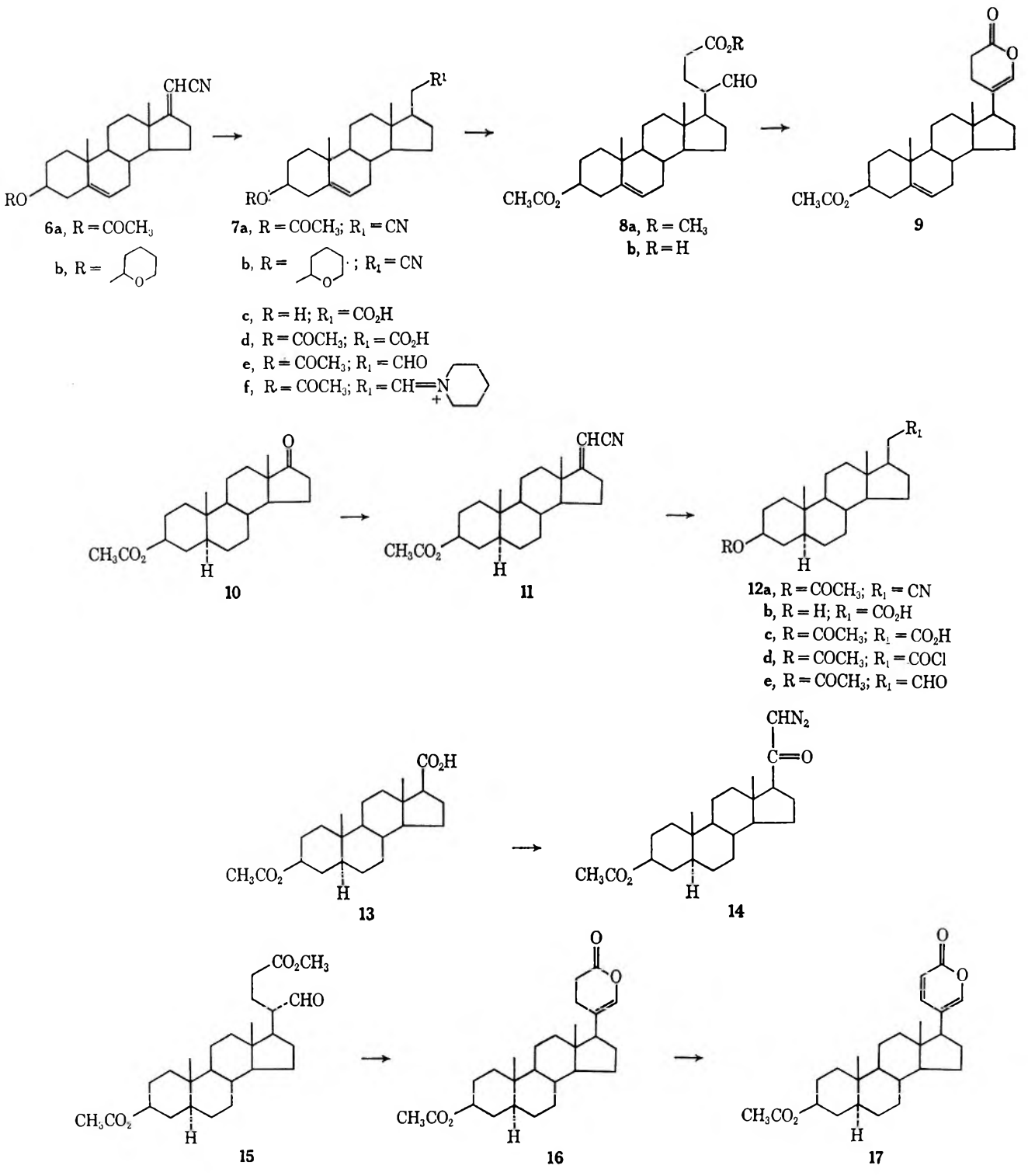
(17) (a) R. H. Wiley and S. C Slaymaker, *J. Amer. Chem. Soc.*, **78**, 2393 (1956); R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959). (b) W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, **6**, 1 (1969).

(18) A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).

(19) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **86**, 1085 (1964).

(20) See, *e.g.*, Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 589 (1963); a review by E. Mosettig and R. Mozingo, *Org. React.*, **4**, 362 (1948); I. G. Csizmadia, J. Font, and O. P. Strausz, *J. Amer. Chem. Soc.*, **90**, 7360 (1968).

(21) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968).



the best yield was realized by recycling recovered aldehyde **7e**. Conversion of methyl ester **8a** into enol lactone **9** (30–40% yield) was conducted as noted above for the conversion of methyl ester **2a** into enol lactone **3**. By an analogous series of reactions, 3β-acetoxy-17-oxo-5α-androstane (**10**) was converted, *via* nitrile **11**, carboxylic acid **12c**, aldehyde **12e**, and methyl ester **15**, into enol lactone **16**. In this case, carboxylic acid **12c** was also prepared by hydrogenation of acid **7d** and by Wolff rearrangement of diazo ketone **14**[5a] prepared from 17-carboxylic acid **13**. Enol lactones **9** and **16** represent the first examples of buf-20(21)-enolides.

Interestingly, a considerable number of experiments directed at dehydrogenating enol lactone **9** or **16** in *p*-cymene using palladium on carbon proved quite ineffectual. More vigorous reaction conditions than those employed for formation of pyrone **5** led to extensive production of side products. Model experiments, primarily with enol lactone **3**, attempting to utilize 2,3-dichloro-5,6-dicyanoquinone in refluxing dioxane (with or without acid catalyst)[22] or trityl perchlorate[23] in refluxing acetic acid, led only to isolation of starting material. Treatment with selenium dioxide[24] in re-

(22) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(23) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York., N. Y., 1967, p 1256.

(24) C. R. Engel and S. Rakhit, *Can. J. Chem.*, **40**, 2153 (1962); E. J. Agnello and G. D. Laubach, *J. Amer. Chem. Soc.*, **79**, 1257 (1957).

fluxing *t*-butyl alcohol gave a mixture of products among which, *e.g.*, pyrone **5** was not detected by thin layer chromatography. With the rigid steric requirements of lactones **9** and **16** possibly obviating the palladium on carbon technique, the potentially less versatile N-bromosuccinimide method was evaluated.[25] Application of the N-bromosuccinimide reaction used to obtain pyrone **5** from enol lactone **3** also proved unsatisfactory.[25] Eventually a practical and reliable method for dehydrogenation of buf-20(21)-enolide **16** to bufa-20,22-dienolide **17** was achieved by heating with sulfur[25] for 30 min at 221–227°. Yields of bufadienolide, **17** amounted to 60–70%. Use of the new method with olefins such as **9** required milder conditions and led to an extensive study of steroid–sulfur reactions which will be reported in a further contribution. Once synthesis of bufadienolide **17** was satisfactorily realized, objectives of the present investigation were complete.

The new synthesis of 5-substituted 2 pyrones illustrated by transformation of heptaldehyde to pyrone **5** presents a convenient route to such substances. Also, the reaction sequence offers a particularly useful approach to buf-20(21)-enolides. Synthesis of such steroidal lactones and subsequent sulfur dehydrogenation to the corresponding bufadienolides should more readily allow assessment of structure–activity relationships in this area of steroid chemistry.

Experimental Section

Catalytic hydrogenations were performed at room temperature using a slight positive pressure of hydrogen. Ether refers to diethyl ether and ligroin to fractions boiling at 60–110°. Acetonitrile (from phosphorus pentoxide), tetrahydrofuran (from potassium hydride), heptaldehyde, and diethyl cyanomethylphosphonate (at 1.5 mm) were redistilled prior to use. Dimethylformamide was distilled from calcium oxide and stored over molecular sieve type 4-A. All solvent extracts of aqueous solutions were dried with magnesium sulfate or sodium sulfate.

Neutral alumina (E. Merck, A. G. Darmstadt) and silica gel (E. Merck, 0.05–0.2 mm) were used for column chromatography. Silica gel HF_{254} (E. Merck) spread on microscope slides was employed for thin layer chromatography. The thin layer chromatographic solvents were, unless differently indicated, 4:1 or 7:3 hexane–ethyl acetate, and with acidic compounds 9:1:0.1 hexane–ethyl acetate–acetic acid. Visualization involved iodine vapor or heating with 2% ceric sulfate in 2 *N* sulfuric acid. ChromAR 1000 (Mallinckrodt) or silica gel HF_{254} (1.5 mm layer) were employed for preparative layer separations. Identity of specimens was established by infrared spectral and thin layer chromatographic comparison.

Elemental microanalytical data were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Liquid analytical samples were prepared by distillation employing a 1-in. simple column. All samples submitted for analysis were colorless and exhibited a single spot on a thin layer chromatogram. Melting points were determined with a Kofler melting point apparatus. Spectra were recorded by D. C. F. and Miss K. Reimer as follows (unless otherwise noted): infrared, Beckman IR-12 in potassium bromide (solids) or neat (liquids); optical rotatory dispersion, JASCO ORD/UV-5 (dioxane solution); pmr, Varian A-60 (deuteriochloroform solution and tetramethylsilane as internal standard). Low-resolution mass spectra were determined by Mr. E. Bebee by using an Atlas CH-4B, and high-resolution mass spectra by Dr. P. Brown employing an Atlas SM-1B. Both mass spectrometers were equipped with a molecular beam type inlet system.

Methyl 4-Formylnonanoate (2).—A solution of 1-piperidinohept-1-ene (1, 36.3 g),[26] methyl acrylate (27.7 g, 25% excess), and acetonitrile (300 ml) was heated at reflux for 40 hr. Acetic acid (10 ml) and water (60 ml) were added and refluxing was continued for 1 hr. The solution was saturated with sodium chloride and the organic layer was washed with saturated sodium chloride solution (100 ml). Evaporation and distillation of the residue at reduced pressure gave a colorless liquid (30.0 g). A pure sample was prepared by redistillation: bp 114° (4 mm); $n^{24}D$ 1.4412; ν_{max} 1745 (broad), 1440, 1255, and 1170 cm^{-1}; pmr δ 3.7 (3 H, methyl ester) and 9.54 (1 H, J = 4 cps, aldehyde).

The 2,4-dinitrophenylhydrazone crystallized from methanol as yellow needles, mp 70.5–72°.

Anal. Calcd for $C_{17}H_{24}N_4O_6$: C, 53.67; H, 6.36; N, 14.73. Found: C, 53.69; H, 6.52; N, 14.74.

5-Pentyl-3,4-dihydropyran-2-one (3).—Enough methanol and tetrahydrofuran were added to a mixture of methyl 4-formylnonanoate (5 g) and aqueous (40 ml) sodium carbonate (2.5 g) to give a homogeneous solution. After 3 hr at room temperature, the solvent was evaporated at reduced pressure until a clear solution resulted. The solution was washed with ether (two 50-ml portions) and acidified with 10% hydrochloric acid. The precipitated oily layer was extracted with ether (two 50-ml portions) and the combined ethereal extract was washed with water (50 ml) and evaporated at reduced pressure to yield crude acid **2b**. The acid (3.7 g) was heated for 24 hr at reflux in benzene (100 ml) containing *p*-toluenesulfonic acid (0.1 g), with continuous separation of water. The benzene solution was washed with saturated sodium bicarbonate solution (two 25-ml portions) and water (25 ml) and concentrated at reduced pressure, and the residue was distilled *in vacuo* to yield enol lactone **3** (2.7 g). An analytical sample was prepared by redistillation: bp 102–103° (1.5 mm); $n^{24}D$ 1.4648; ν_{max} 1770 (carbonyl), 1680 (olefin), 1350, 1150, 1090, and 940 cm^{-1}; pmr δ 6.4 (quintet, 1 proton, J = 1 cps, vinyl proton).

Anal. Calcd for $C_{10}H_6O_{12}$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.53.

2-Oxo-5-*n*-pentyl-6-acetoxytetrahydropyran (4). Method A.—A solution of acid **2b** (4.2 g) in ethyl acetate (150 ml) was treated for 10 min with the 2 M acetic anhydride and 2 × 10^{-3} M perchloric acid reagent described by Edwards and Rao.[11a] The solution was washed with saturated sodium bicarbonate (150 ml) and concentrated at reduced pressure, and the residue was distilled *in vacuo* to yield lactol acetate **4** (3.4 g) as a colorless liquid. A pure sample was obtained by redistillation: bp 160–161° (4.0 mm); $n^{24}D$ 1.4569; ν_{max} 2920, 1770 (broad), 1225, and 1120 cm^{-1}; pmr δ 2.18 (s, 3 H, acetate methyl), 6.28 (d, J = 4 cps) integrating as one proton, and 6.58 (d, J = 2 cps); mass spectrum m/e (rel intensity) 168 (M − 60, 35), 156 (21), 140 (16), 112 (100), 96 (70), and 84 (72).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.78; H, 8.68.

Method B.—A mixture of acid **2b** (1.6 g), isopropenyl acetate (3 ml), and 72% perchloric acid (2 drops)[11b] was held for 15 min at reduced pressure on a rotary evaporator to remove acetone. The reaction mixture was diluted with ethyl acetate (30 ml), washed with saturated sodium bicarbonate solution, and concentrated under reduced pressure, and the oily residue was distilled *in vacuo* to provide 1.0 g of lactone **4**.

Method C.—A solution of acid **2b** (1.6 g) and acetic anhydride (10 ml)[11c] was heated at reflux under nitrogen for 2 hr. Sodium acetate (0.03 g) was added and heating at reflux was continued for 2 hr. The acetic anhydride was removed azeotropically using toluene and the resulting oil was distilled *in vacuo* to yield lactone **4** (0.6 g) and a mixture (0.8 g) of lactones **3** and **4**.

5-Pentylpyran-2-one (5). Procedure A. Palladium on Carbon.—A mixture of commercial-grade (Eastman) *p*-cymene (50 ml) and 10% palladium on carbon (1 g) was dried by azeotropic removal of solvent (10 ml). To the mixture was added 5-pentyl-3,4-dihydropyran-2-one (**3**, 3.0 g), and heating at reflux was continued for 6.5 hr. Nitrogen was bubbled through the mixture. Following concentration by distillation to *ca.* 25 ml the solution was chromatographed on silica gel (90 g). Elution with 4:1 hexane–ethyl acetate gave 1.7 g of crude product. A pure specimen of pyrone **5** was obtained by redistillation: bp 101–102°

(25) With lower boiling δ enol lactones, halogenation followed by dehydrohalogenation has been extensively used for obtaining 2-pyrones: N. P. Shusherina, R. Y. Levina, E. A. Luk'yanets, and I. S. Trubnikov, *J. Gen. Chem. USSR*, **32**, 3534 (1962); N. P. Shusherina, R. Y. Levina, Z. S. Sidenko, and M. Y. Lur'e, *Zhur. Obshch. Khim.*, **29**, 403 (1959); N. P. Shusherina, E. A. Luk'yanets, and R. Y. Levina, *J. Gen. Chem. USSR*, **34**, 18 (1964); N. P. Shusherina, E. A. Luk'yanets, and R. Y. Levina, *J. Org. Chem. USSR*, **1**, 2266 (1965). However, application of these methods to buf-20(21)-enolide **16** proved unworkable.

(26) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).

(0.8 mm); λ_{max} 298 mμ (ε 5150); mass spectrum *m/e* (rel intensity) 166 (M^+, 57), 138 (7), 110 (52), 109 (100), 99 (26), 95 (14), 82 (28), 81 (33), and 53 (45); ν_{max} 1755 and 1730 (pyrone carbonyl doublet), 1650 and 1550 (vinyl), and 1120 and 830 cm^{-1}; pmr δ 2.5 (triplet, 2 H, *J* = 7 cps, benzylic protons), 6.15 d, *J* = 11 cps, H_a), 7.2 (two doublets, *J* = 11 and 3 cps, H_b), and 7.23 (d, *J* = 3 cps, H_c).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; mol wt, 166.099373 [mass spectrum *m/e* 166 (M^+)]. Found: C, 72.50; H, 8.68; mol wt, 166.105060. Calcd for $C_6H_6O_2$: mol wt, 109.028952. Found: mol wt, 109.031643 (mass spectrum *m/e* 109).

Procedure B. N-Bromosuccinimide.—A mixture of 5-pentyl-3,4-dihydropyran-2-one (**3**, 0.3 g), N-bromosuccinimide (0.36 g), benzoyl peroxide (0.05 g), and carbon tetrachloride (10 ml) was heated at reflux for 1 hr. The mixture was cooled and washed with water (two 10-ml portions), and solvent was removed under reduced pressure. The oily residue was heated under a nitrogen atmosphere in dimethylformamide (5 ml) containing lithium bromide (0.52 g) at 100° for 2 hr. The solution was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water (four 20-ml portions) and evaporated at reduced pressure to yield a brown oil (0.35 g), which was chromatographed on silica gel (3 g). Elution with 4:1 hexane–ethyl acetate gave 0.14 g of pyrone **5**.

Upon standing for *ca.* 2 weeks at room temperature in a sealed vial protected from light, pyrone **5** became yellow and a more polar contaminant was detected by thin layer chromatography.

3β-Acetoxy-20-cyano-21-norpregna-5,17(20)-diene (6).—A solution of diethyl cyanomethylphosphonate (71.0 g) in tetrahydrofuran (250 ml) was added dropwise under nitrogen to a stirred suspension of sodium hydride (8.5 g of 51% in oil) in tetrahydrofuran (400 ml) at ice-bath temperature. The clear yellow solution was stirred for 0.5 hr. A solution of 3β-acetoxy-17-oxoandrost-5-ene (20.0 g) in tetrahydrofuran (200 ml) was added and the resulting solution was allowed to stand at room temperature for 16 hr. The mixture was concentrated under reduced pressure to *ca.* 200 ml, poured into water (600 ml), and extracted with ethyl acetate. The ethyl acetate layer was washed with water and evaporated under reduced pressure to a pasty solid contaminated with mineral oil, which crystallized from ethyl acetate–hexane as needles (8.6 g). The filtrate was concentrated under reduced pressure and the residue was extracted with several portions of boiling hexane (500 ml total). Concentration of the hexane, followed by cooling, yielded a colorless solid which crystallized from methanol as needles (7.4 g) and was identical with the product from the first crop. Two recrystallizations from methanol afforded a pure sample as needles: mp 228–231°; $[\alpha]_D$ −84°; ν_{max} 2218 (C≡N), 1735, and 1250 cm^{-1} (acetate); pmr δ 0.85 (3 H, C-18 methyl), 1.08 (3 protons, C-19 methyl), 2.05 (3 protons, acetate), 5.0 (triplet, 1 H, *J* = 3 cps, H-20), and 5.3 (multiplet, 1 H, H-6).

Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.07; H, 8.67; N, 4.16.

3β-Acetoxy-20-cyano-21-norpregna-5-ene (7a).—A mixture of diene **6** (16.2 g) and 5% palladium on calcium carbonate (2 g) in tetrahydrofuran (400 ml) was hydrogenated for 24 hr. The solution was filtered through Celite and evaporated under reduced pressure to a white solid (16.0 g), mp 188–189.5°. The crystallizations from methanol afforded a pure sample as fluffy needles: mp 195–196°; ν_{max} 2250 (C≡N), 1735, and 1240 cm^{-1} (acetate); RD (24°, *c* 0.505) $[\alpha]_{650}$ −39.6°, $[\alpha]_{589}$ −51.5°, $[\alpha]_{450}$ −106.9°, $[\alpha]_{350}$ −277.7°, $[\alpha]_{300}$ −376.2°, and $[\alpha]_{250}$ −782.2°; pmr δ 0.67 (3 H, C-18 methyl), 1.08 (3 H, C-19 methyl), and 2.05 (3 H, acetate).

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.53; H, 9.52; N, 3.90.

3β-(Tetrahydropyran-2′-yloxy)-20-cyano-21-norpregna-5,17(20)-diene (6b).—A solution prepared from dihydropyran (1.85 g), *p*-toluenesulfonic acid (0.1 g), benzene (250 ml), tetrahydrofuran (50 ml), and 3β-hydroxy-20-cyano-21-norpregna-5,17(20)-diene (6.0 g, obtained from saponification of acetate **6a**) was stirred at room temperature for 24 hr. The solution was concentrated under reduced pressure to *ca.* 150 ml, washed with 10% sodium carbonate solution (400 ml) and water (50 ml), and evaporated at reduced pressure to a colorless solid which crystallized from methanol (yield 6.3 g). Two recrystallizations from 100% ethanol gave an analytical sample: mp 181–188°; ν_{max} 2960, 2220 (C≡N), 1645 (C=C), and 1040 cm^{-1}; pmr δ 0.84 (singlets for C-18 methyl of *cis* and *trans* isomers), 0.95, 1.0 (3 H, C-19 methyls), 4.7 (broad, 1 H), 5.1 (triplet, 1 H, *J* = 2 cps, H-20), and 5.3 (broad, 1 H, H-6).

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.92; H, 9.44; N, 3.54. Found: C, 79.1; H, 9.24; N, 3.28.

3β-(Tetrahydropyran-2′-yloxy)-20-cyano-21-norpregna-5-ene (7b).—Nitrile **6b** (1.0 g) was hydrogenated over 5% palladium on calcium carbonate (0.4 g) as described for **6a** to yield **7b** (0.7 g). Crystallization from 100% ethanol followed by two recrystallizations from methanol afforded an analytical sample: mp 158–160°; ν_{max} 2940, 2245 (C≡N), 1450 (doublet), and 1040 cm^{-1}; pmr δ 0.62 (3 H, C-18 methyl), 1.0 (3 H, C-19 methyl), 4.7 (broad, 1 H), and 5.3 (broad, 1 H, H-6).

Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.37; H, 9.70; N, 3.36.

3β-Acetoxypregna-5-en-21-oic Acid (7d).—A solution of nitrile **7a** (15 g) and potassium hydroxide (10 g) in ethylene glycol (400 ml) was heated at reflux under a nitrogen atmosphere until evolution of ammonia ceased. The warm reaction mixture was poured over ice (1 l.), acidified with 5 *N* sulfuric acid, and filtered. The resulting acid **7c** was dissolved in 2:1 acetic anhydride–acetic acid and allowed to stand for 8 hr. The acetylation mixture was poured into water (300 ml). After 12 hr the crude product (11.0 g) was collected by filtration. Three recrystallizations from acetone–hexane led to a pure sample as needles: mp 187–187.5°; ν_{max} 1735 (acetate), 1710 (acid), 1240, and 1040 cm^{-1}; RD (24°, c 0.504) $[\alpha]_{650}$ −39.7°, $[\alpha]_{589}$ −51.6°, $[\alpha]_{450}$ −96.2°, $[\alpha]_{350}$ −176.5°, $[\alpha]_{300}$ −327.4°, and $[\alpha]_{250}$ −719.2°; pmr δ 0.67 (3 H, C-18 methyl) and 1.08 (3 H, C-19 methyl).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.74; H, 9.10.

3β-Acetoxypregna-5-en-21-al (7e).—A solution of oxalyl chloride (5 ml) in benzene (15 ml) was added to an ice-cold solution of carboxylic acid **7d** (3.0 g) in benzene (50 ml). The pale yellow solution was allowed to stand for 1.5 hr and solvent was evaporated under reduced pressure to a yellow solid. Traces of oxalyl chloride were removed by addition and evaporation of dry benzene (three 50-ml portions).

The acid chloride was dissolved in dry toluene (50 ml) and heated in an oil bath to 110° with palladium on barium sulfate (0.5 g of 5%). Hydrogen was then bubbled through the mixture for 2 hr. Upon cooling, the solution was filtered through basic alumina. Continued elution with benzene and removal of solvents at reduced pressure led to a colorless solid (2.4 g), mp 141–145°. Two crystallizations from hexane afforded a pure sample: mp 141–142.5° (lit. mp 141–144°); ν_{max} 2880, 1735, 1245, and 1140 cm^{-1}; RD (24°, *c* 0.504) $[\alpha]_{650}$ −44.6°, $[\alpha]_{589}$ −50.6°, $[\alpha]_{306}$ −398.8°, $[\alpha]_{274}$ −259.9°, and $[\alpha]_{250}$ −436.5°; pmr δ 0.60 (3 H, C-18 methyl), 1.08 (3 H, C-19 methyl), and 9.8 (triplet, 1 H, *J* = 2 cps, aldehyde).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.09; H, 9.65.

Methyl 3β-Acetoxy-21-oxochol-5-en-24-oate (8a).—A mixture of aldehyde **7e** (1 g), anhydrous potassium carbonate (2 g), piperidine (1 g), and dry toluene (50 ml) was stirred at room temperature for 3 hr. The solution was filtered and evaporated under reduced pressure to dryness. Traces of piperidine were removed by addition and evaporation of dry toluene (two 50-ml portions). To enamine **7f** in acetonitrile (75 ml) was added methyl acrylate (0.5 g) and the solution was heated at reflux for 60 hr. Acetic acid (0.2 ml) and water (4 ml) were added and heating at reflux was continued for 1 hr. The reaction mixture was cooled, washed with saturated sodium chloride solution, and concentrated under reduced pressure to an oil (1 g). The two-component oil (tlc) was separated by preparative layer chromatography with 7:3 hexane–ethyl acetate development. The two zones were scraped from the plate and eluted with ethyl acetate. The top zone led to a solid identical with starting aldehyde (0.3 g) and the lower zone yielded methyl ester **8a** (0.5 g) which crystallized as needles from hexane: mp 109–111°; ν_{max} 1740 (broad), 1255, 1225, and 1050 cm^{-1}; pmr δ 0.70, 0.75, (C-18 methyls of the C-20 epimers), 1.05 (C-19 methyl), 2.05 (3 H, acetate), 3.7 (3 H, methyl ester), 4.6 (broad, 1 H, H-6), and 9.54 (d, 1 H, *J* = 4.5 cps, aldehyde).

Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.10. Found: C, 73.04; H, 9.09.

3β-Acetoxy-14α-bufa-5,20(21)-dienolide (9).—A solution composed of methyl ester **8a** (0.1 g), 5% aqueous sodium carbonate (1.5 ml), methanol (1 ml), and tetrahydrofuran (2 ml) was stirred at room temperature for 1.5 hr. The organic solvents were removed at reduced pressure and the resulting aqueous mixture was

acidified with 5 *N* sulfuric acid. The mixture was extracted with ethyl acetate, and after removal of solvent a thin layer chromatographic analysis indicated that some hydrolysis of the 3-acetate group had occurred.[27] Thus the crude acid **8b** was reacetylated by treatment with 1:5 acetic anhydride–pyridine for 1 hr followed by addition of 50% acetic acid and evaporation to dryness. Acid **8b** in benzene (25 ml) containing *p*-toluenesulfonic acid (0.04 g) was heated at reflux for 12 hr with continuous separation of water. The benzene solution was washed with water. After evaporation at reduced pressure the resulting yellow solid was purified by preparative layer chromatography with 7:3 hexane–ethyl acetate development. Elution of the major zone with ethyl acetate gave lactone **9** (0.04 g), which crystallized from ethyl acetate–hexane as needles: mp 184–186°; ν_{max} 1780 (enol lactone), 1735 (acetate), 1675 (olefin), 1260, and 1020 cm^{-1}; RD (25°, *c* 0.485) $[\alpha]_{650}$ −41.2°, $[\alpha]_{589}$ −53.2°, $[\alpha]_{450}$ −84.7°, $[\alpha]_{350}$ −123.5°, and $[\alpha]_{300}$ −185.5°; pmr δ 0.60 (C-18 methyl), 1.05 (C-19 methyl), 4.6 (broad, 1 H, H-3), and 6.4 (broad singlet, 1 H, H-21).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.82; H, 8.62.

3β-Acetoxy-20-cyano-21-nor-5α-pregna-17(20)-ene (11).—The experimental procedure employed for obtaining nitrile **6** was repeated employing sodium hydride (12.9 g, 0.29 mmol of 54% in mineral oil), diethyl cyanomethylphosphonate (61 g, 0.35 mmol), 3β-acetoxy-17-oxo-5α-androstane (48 g, 0.15 mmol), and tetrahydrofuran (750 ml). The ketone was added during a 1-hr period and the resulting yellow solution was stirred at room temperature for 19 hr. At that point no starting material was detected by tlc and the solution was concentrated at reduced pressure to *ca.* 200 ml, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate extract (400 ml) was washed successively with 5% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. Following removal of solvent the residue was recrystallized from ethyl acetate–ligroin to yield 36 g of needles, mp 127–188°. Two impurities in trace amounts were present, as evidenced by a thin layer chromatogram. Further purification was accomplished as now summarized for the mother liquor material. The ethyl acetate–ligroin filtrate was concentrated and the viscous, oily residue was chromatographed in pentane on a column of silica gel (200 g). Elution with pentane eliminated the mineral oil and the fraction obtained with benzene was recrystallized from benzene–pentane to yield 9.6 g of nitrile **11**, which exhibited one spot on a tlc plate with 4:1 pentane–ethyl acetate mobile phase. The total yield of comparable product amounted to 89%. Two recrystallizations from ethyl acetate–pentane and another two from methanol afforded an analytical specimen as needles: mp 199–200°; ν_{max} 2210 (C≡N), 1730, 1640, and 1245 cm^{-1}.

Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.52; H, 9.45; N, 4.05.

3β-Acetoxy-20-cyano-21-nor-5α-pregnane (12a).—A mixture of olefin **11** (20 g), 5% palladium on calcium carbonate (5 g), and tetrahydrofuran (500 ml) was hydrogenated for 48 hr as reported above for preparation of nitrile **7a**. Three recrystallizations from methanol afforded an analytical sample as needles: mp 200–202°; ν_{max} 2240 (C≡N), 1725, and 1250 cm^{-1}.

Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.52; H, 9.52; N, 4.05.

3β-Acetoxy-5α-pregnan-21-oic Acid (12b). Method A. From 3β-Acetoxy-20-cyano-21-nor-5α-pregnane (12a).—Base hydrolysis of nitrile **12a** (19.5 g) was conducted for 27 hr in refluxing ethylene glycol (400 ml) containing potassium hydroxide (11 g) as described above using nitrile **7a**. The crude product was acetylated with 1:3 acetic anhydride–pyridine at room temperature. The acetylation mixture was diluted with water and extracted with ethyl acetate. Following removal of ethyl acetate the residue was dissolved in hot acetic acid and water was added to the opalescence point. Upon cooling the solid which separated was collected, washed with water, and recrystallized from methanol to yield 17.1 g, mp 190–195° (lit.[28] mp 191–193°), of carboxylic acid **12b**. The acid displayed one spot on a thin layer chromatogram with 4:1:0.5 pentane–ethyl acetate–acetic acid and was used without further purification.

Method B. From 3β-Acetoxy-5α-androstane-17β-carboxylic Acid (13).—A solution of 3β-acetoxy-5α-androstane-17β-carboxylic acid (**13**, 18 g)[29] in thionyl chloride was prepared. After 3 hr at room temperature the thionyl chloride was removed by slow distillation followed by addition and evaporation under reduced pressure of dry benzene. The crude residue was crystallized from ligroin to give the pure acid chloride, and the mother liquor was treated with 1:1 water–acetic acid. By the latter means 2.7 g of acid **13** was recovered. A solution of the recrystallized acid chloride in ether (400 ml) was added dropwise to an ethereal solution of diazomethane and stirred for 14 hr, after which the solvent was distilled. The yellow, oily residue crystallized from ligroin to give three crops of the crude diazo ketone, which were combined and chromatographed in 19:1 pentane–ethyl acetate on a column of silica gel (200 g). Elution with 17:3 pentane–ethyl acetate and recrystallization from pentane afforded 3β-acetoxy-20-oxo-21-diazo-5α-pregnane[5a] (5.6 g), mp 133–137°. Additional diazo ketone was obtained from the ligroin mother liquor to provide a total yield of 8.1 g (49%): ν_{max}^{Nujol} 2100, 1735, and 1610 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87. Found: C, 71.67; H, 8.76.

A solution of the diazo ketone (5.6 g) in dioxane (30 ml) was added dropwise over 20 min to a stirred suspension of freshly prepared silver oxide from 4 g of silver nitrate in dioxane (50 ml) containing 10% aqueous sodium thiosulfate (40 ml). After 45 min at 60°, *ca.* 90% of the calculated volume of nitrogen had been evolved. The mixture was cooled, diluted with 10% potassium carbonate solution (25 ml), and extracted with 1:1 pentane–ether (200 ml). The dark ethereal layer was extracted with 10% potassium carbonate (four 50-ml portions). The combined basic extract was cooled and carefully acidified with 6 *N* nitric acid. The aqueous mixture was extracted with chloroform (three 150-ml portions) and the organic layer was filtered through a layer of Celite. The chloroform solution was extracted with 10% potassium carbonate (four 30-ml portions) and the aqueous extract was cooled and acidified with 6 *N* hydrochloric acid. Again the precipitated acid was extracted with chloroform. Removal of solvent gave a glassy residue which solidified upon trituration with pentane. Reacetylation with 1:1 acetic anhydride–pyridine (at room temperature for 24 hr, followed by hydrolysis with water–acetic acid) and crystallization from water–acetic acid gave acid **12b** (3.0 g, 54%), mp 187–193°.

Method C. From 3β-Acetoxypregna-5-en-21-oic Acid (7d).—A specimen of carboxylic acid **7d** (5.0 g) in tetrahydrofuran (150 ml) was hydrogenated employing 10% palladium on carbon (0.75 g) as catalyst. After 24 hr, catalyst (0.5 g) was added and hydrogenation was resumed until complete as evidenced by pmr. Recrystallization from acetone–hexane gave 2.9 g (with another 2.0 g recovered from the mother liquor) of carboxylic acid **12b**, shown to be homogeneous by tlc. Two recrystallizations from acetone–hexane gave a product melting at 190–191°.

The specimens of carboxylic acid **12b** prepared by methods A, B, and C were shown to be identical, thereby confirming the 17β side-chain orientation.

3β-Acetoxy-21-formyl-5α-pregnane (12e).—The treatment of acid **12b** (2.7 g)[28] with oxalyl chloride followed by hydrogenation over 10% palladium on barium sulfate as described for aldehyde **7e** gave aldehyde **12e** (1.9 g, 72%). Crystallization from hexane afforded an analytical sample: mp 125–128°; ν_{max} 2940, 1740 (broad), 1255, and 1040 cm^{-1}; RD (25°, *c* 0.450) $[\alpha]_{400}$ −16.0°, $[\alpha]_{305}$ −66.7°, and $[\alpha]_{260}$ +11.1°; pmr δ 0.62 (3 H, C-18 methyl), 0.86 (3 H, C-19 methyl), 2.18 (3 H, acetate), and 9.8 (triplet, 1 H, J = 2 cps, aldehyde).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.81; H, 9.96.

Later the above Rosenmund reduction was somewhat improved by carefully regulating with a water aspirator the hydrogen flow while maintaining a slightly reduced internal pressure. The reaction mixture temperature was maintained (oil bath) at 90–93° for 2 hr. Yields of aldehyde **12e** ranged from 86 to 96%, but in two experiments on a 10-g (acid **12b**) scale the yield dropped to *ca.* 60%.

Methyl 3β-Acetoxy-20-formyl-21-nor-5α-cholanate (15).—The piperidino enamine of aldehyde **12e** (2.7 g) was prepared and alkylated with methyl acrylate as summarized in the experiment leading to ester **8a**. The resulting oil (2.5 g) was dissolved in 19:1 hexane–ethyl acetate and adsorbed on a column of silica gel

(27) Higher concentrations of tetrahydrofuran in the saponification-step suppressed hydrolysis of the 3 acetate and eliminated need for reacetylation.

(28) R. E. Marker, H. Crooks, E. Jones, and A. Shabica, *J. Amer. Chem. Soc.*, **64**, 1276 (1942).

(29) P. Kurath and M. Capezzuto, *ibid.*, **78**, 3527 (1956).

(150 g). Continued elution with the same solvent resulted in some (0.45 g) recovery of aldehyde **12e**. Elution with 9:1 hexane–ethyl acetate afforded methyl ester **15** (1.5 g). An analytical sample was obtained by preparative chromatography on ChromAR 1000 with 17:3 hexane–ethyl acetate development (band eluted with ether) followed by crystallization from ethyl acetate–hexane: mp 123–126°; ν_{max} 2960, 1740 (broad), 1390, and 1260 cm^{-1}; pmr δ 0.62 (singlets, 3 H, C-18 methyl of C_{20} epimers), 0.7, 0.8 (3 H, C-19 methyl), 2.05 (3 H, acetate), 3.65 (3 H, methyl ester), and 9.5 (d, J = 4 cps, aldehyde).

Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.91; H, 9.26.

In somewhat larger scale experiments, molecular sieve type 4A (3.5 g/3 g of aldehyde **7e**) was employed in place of anhydrous potassium carbonate with comparable results. The crude product in 2:1 pentane–benzene was chromatographed on a column of silica gel (250 g/3 g of starting aldehyde). Fractions eluted by 9:1 pentane–ethyl acetate contained aldehyde **12e** and those elated with 17:3 pentane–ethyl acetate contained methyl ester **15**. Yields of methyl ester **15** ranged from 45 to 49%.

3β-Acetoxy-5α-14α-buf-20(21)-enolide (16).—To a solution of methyl ester **15** (0.55 g) in tetrahydrofuran (15 ml)–methanol (6 ml) was added 10 ml of 5% aqueous sodium carbonate. The mixture was stirred at room temperature for 3 hr, neutralized with 6 *N* hydrochloric acid and concentrated to *ca.* 10 ml using a rotating evaporator. The aqueous phase was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate. The combined ethyl acetate extract was extracted with 10% aqueous potassium carbonate. Next, the combined aqueous solution was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with water and evaporated to yield 0.38 g (72%) of colorless, crystalline carboxylic acid exhibiting one spot on a thin layer chromatogram with 4:1:0.2 pentane–ethyl acetate–acetic acid mobile phase. A specimen (0.53 g) prepared in the same manner was dissolved in dry benzene (50 ml) containing *p*-toluenesulfonic acid (0.06 g). The solution was heated at reflux for 25 hr employing a Dean–Starke trap containing molecular sieve type 4-A. The solution was cooled and added to a column of silica gel (7 g). Elution with benzene (400 ml) gave 0.37 g (73%) of colorless crystals, mp 181–184°. The product **16** appeared as a single spot on a thin layer chromatogram with 4:1 pentane–ethyl acetate mobile phase. Recrystallization from ethyl acetate–hexane afforded an analytical sample as needles: ν_{max} 2940, 1760 (enol lactone carbonyl), 1740 (acetate carbonyl), 1670 (olefin), 1260, and 1140 cm^{-1} (doublet); RD (25°, c 0.515) $[\alpha]_{420}$ 0° (slightly negative 420–650°), $[\alpha]_{350}$ +27.2°, $[\alpha]_{320}$ +58.3°, and $[\alpha]_{290}$ +166.9°; pmr δ 0.60 (3 H, C-18 methyl), 0.83 (3 H, C-19 methyl), 2.05 (3 H, acetate), and 6.36 (broad, 1 H, H-21).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.27; H, 8.99.

3β-Acetoxy-5α-14α-bufa-20,22-dienolide (17).—An intimate mixture of enol lactone **16** (0.10 g) and sulfur (0.20 g) was heated at 221–227° under a nitrogen atmosphere for 0.5 hr. After 1 min in the required temperature range, evolution of hydrogen sulfide was detected using moist lead acetate paper and by odor. After cooling, the mixture was dissolved in carbon disulfide. A thin layer chromatogram with 4:1 pentane–ethyl acetate mobile phase indicated a major component accompanied by a lesser quantity of starting material **16** and a more polar side product. The carbon disulfide solution was chromatographed on a column of silica gel (20 g). The oily fraction (**17**) eluted by 2:1 benzene–ether weighed 0.06 g (60%) and was essentially pure by tlc. The analytical sample was further purified by preparative tlc on ChromAR 1000 with 10:1 pentane–ethyl acetate mobile phase and recrystallized twice from methanol to afford needles: mp 194–195°; λ_{max} 300 mμ (ϵ 5500); ν_{max} 1740, 1640, 1540, 1250, 835, and 800 cm^{-1}; pmr δ 0.53 and 0.83 (C-18 and -19 methyls), 4.7 (diffuse, H-3α), 6.25 (d, J = 10.5 cps, H-23), and 7.20–7.41 (complex, 2-pyrone ring protons).[30]

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80; mol wt, 412. Found: C, 75.75; H, 9.03; mol wt, 412 (mass spectrum).

Registry No.—**2a**, 23079-69-8; 2,4-dinitrophenylhydrazone of **2a**, 23330-09-8; **3**, 23079-70-1; **4**, 23330-10-1; **5**, 23079-71-2; **6a**, 2312-10-9; **6b**, 23330-13-4; **7a**, 23330-14-5; **7b**, 23330-15-6; **7d**, 23330-16-7; **7e**, 16934-54-6; **8a**, 23367-52-4; **9**, 23017-35-8; **11**, 23330-19-0; **12a**, 23017-30-3; **12e**, 23017-32-5; **15**, 23017-33-6; **16**, 23017-34-7; **17**, 23017-36-9; 3β-acetoxy-20-oxo-21-diazo-5α-pregnane, 23330-24-7.

(30) Decoupling experiments showed the doublet at δ 6.18 coupled to the δ 7.20–7.41 signals and further supported the structural assignment.

Bufadienolides. 8. 12(13→14)*abeo* Skeletal Rearrangements[1]

GEORGE R. PETTIT, T. R. KASTURI,[2] JOHN C. KNIGHT, AND JOHN OCCOLOWITZ

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received February 11, 1969

Several methods were developed for converting isodigitoxigenin (**2a**) into methyl acetals **4b** and **4c**. Of these, methanolysis (followed by acetylation) of isodigitoxigenin in the presence of *p*-toluenesulfonic acid proved most useful. Each isomer reached an equilibrium corresponding to *ca.* 3:1 acetal **4c** to **4b** within 15 min in benzene containing *p*-toluenesulfonic acid. Addition of dihydropyran to the equilibrium mixture resulted in excellent conversion into vinyl ether **5a**. Heating either acetal **4b** or **4c** in benzene containing *p*-toluenesulfonic acid led to a skeletal rearrangement culminating in formation of C-norcardenolide **6**. In addition to results of physical measurements, the structure of spiran **6** was confirmed by degradation to methyl ketone **8**. Similar rearrangement of isodigitoxigenin gave spiran **9** accompanied by C-norcardenolide **6**. Treating lactone **9** with *p*-toluenesulfonic acid in methanol–water provided acetals **10a** and **10b**, which on further contact with *p*-toluenesulfonic acid in refluxing benzene gave lactone **9** and cardenolide **6**. Evidence underlying the stereochemical assignments noted for structures **4**, **9**, and **10** was also discussed.

Selection of digitoxigenin (**1a**) as a starting point for total synthesis of isobufalin and bufalin required a number of accessory experiments. Protection of the 14-oxygen substituent during reconstruction of the digitoxigenin lactone ring seemed best performed by utilizing isodigitoxigenin (**2a**), which could be converted to hemiacetal **4a**. Model experiments could then be undertaken to determine the direction of cleavage reactions which might be anticipated with acetals such as **2b** and **4c**. Accordingly, digitoxin (**1b**)[3a] was con-

(1) (a) Part 7: G. R. Pettit, D. C. Fessler, K. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1398 (1970). This investigation was supported by Public Health Service Research Grants CA-04074-07, CA-10115-01, and CA-10115-02 from the National Cancer Institute. Summaries, in part, of the present investigation have been presented: (b) T. R. Kasturi, G. R. Pettit, and J. Occolowitz, *Chem. Commun.*, 334 (1967); (c) G. R. Pettit, J. C. Knight, and T. R. Kasturi, *ibid.*, 688 (1967).

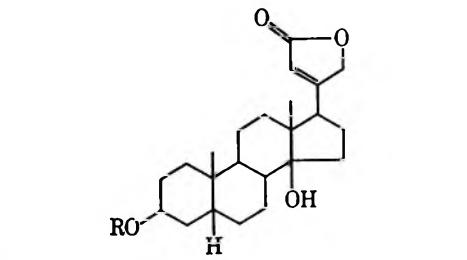
(2) On sabbatical leave from the Indian Institute of Science, Bangalore, India.

(3) (a) M. Kuhn, H. Lichti, and A. von Wartburg, *Helv. Chim. Acta*, **45**, 881 (1962); (b) S. Rangaswami and T. Reichstein, *ibid.*, **32**, 939 (1949); (c) N. Danieli, V. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966).

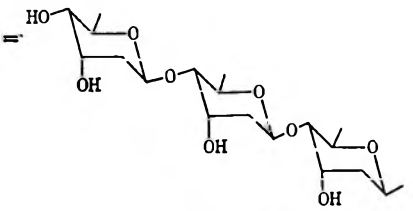
verted[3b] *via* digitoxigenin (**1a**)[3c] into isodigitoxigenin (**2a**).[4a]

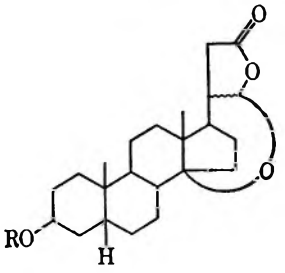
Next, isodigitoxigenin was saponified and methylated with diazomethane to yield the methyl ester of isodigitoxigeninic acid (**4a**) as described by Reichstein.[4b] When hemiacetal **4a** was allowed to react with methanol containing 48% hydrobromic acid, acetals **4b** and **4c** were obtained following acetylation and chromatographic separation. By another route, hemiacetal **4a** was acetylated[4b] to yield acetate **4d** and the latter, upon contact[5] with methanol, gave acetal **4b** with inversion at C-21. Treatment of lactone **2a** with refluxing aqueous methanol[6] containing a catalytic amount of *p*-toluenesulfonic acid and acetylation of the product furnished the most convenient route to acetals **4b** and **4c**. Following separation by column chromatography, acetals **4c**, mp 147–149°, and **4b**, mp 194–199°, were obtained. The acid-catalyzed methanol technique was comparably effective for converting isodigitoxigeninic acid (**4e**), easily isolated from the mother liquors[4a] remaining from preparation of isodigitoxigenin, into the isomeric acetals. Each of the foregoing procedures gave identical specimens of the acetals (**4b** and **4c**), and elemental analyses and pmr and infrared spectra were completely consistent with the assigned structures.

The not unequivocal stereochemical assignments for acetals **4b** and **4c** were based on the following evidence. The H-20–H-21 coupling constant for the 21 proton of acetal **4c** was 8 Hz, while in acetal **4b** a value of $J = 5.5$ Hz was observed. With at least a quasichair conformation for the pyran ring, the larger coupling constant would be assigned to the *trans* vicinal protons of acetal **4c** and the smaller value to *cis* protons of **4b**.[7] Support[8] for the epimeric nature of acetals **4b** and **4c** was obtained by treating each in benzene with *p*-toluenesulfonic acid. Within 15 min both isomers gave an equilibrium mixture containing *ca.* 3:1 isomer **4c** to **4b**. One hour after adding dihydropyran to either mixture, essentially complete conversion into vinyl ether **5a** occurred. Similarly, when equatorial acetal **4c** was saponified and remethylated and the product was dissolved in benzene and treated with *p*-toluenesulfonic acid and dihydropyran, pyranyl ether **5b** was obtained, accompanied under these conditions by acetal **4f**. For large-scale preparation of pyranyl ether **4f** it was found most convenient to treat the crude epimer mixture obtained by methanolysis of isodigitoxigenin, directly with dihydropyran and *p*-toluenesulfonic acid in benzene. Chromatographic separation on silica gel gave **4f**, accompanied by smaller amounts of axial epimer **4g**. The most significant feature in the pmr spectrum of dihydropyran **5a** was a sharp singlet at δ 5.97 attributable to the 21-vinyl proton.



1a, R = H

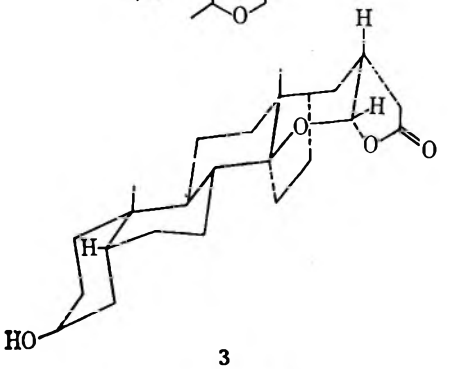
b, R = 



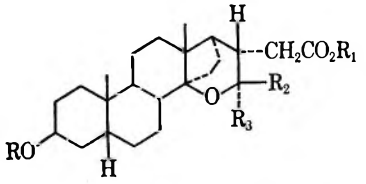
2a, R = H

b, R = $COCH_3$

c, R = 



3



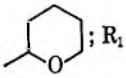
4a, R = H; $R_1 = CH_3$; R_2 or R_3 = OH or H

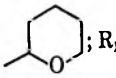
b, R = $COCH_3$; $R_1 = CH_3$; R_2 = H; $R_3 = OCH_3$

c, R = $COCH_3$; $R_1 = CH_3$; $R_2 = OCH_3$; R_3 = H

d, R = $COCH_3$; $R_1 = CH_3$; $R_2 = OCOCH_3$; R_3 = H

e, R = R_1 = H; R_2 or R_3 = OH or H

f, R =  ; $R_1 = CH_3$; $R_2 = OCH_3$; R_3 = H

g, R =  ; $R_1 = CH_3$; R_2 = H; $R_3 = OCH_3$

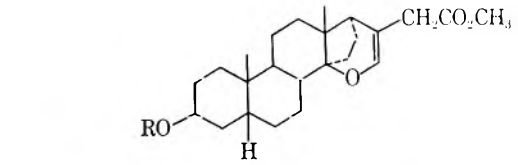
(4) (a) W. A. Jacobs and E. L. Gustus, *J. Biol. Chem.*, **78**, 573 (1928); C. Lindig and K. Repke, *Monatsber. Deut. Akad. Wiss. Berlin*, **4**, 522 (1962); *Chem. Abstr.*, **62**, 4089 (1965). By applying conformational analysis, structure **3** (20*S*,21*S*) was tentatively assigned to isodigitoxigenin by (b) O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **39**, 1876 (1956). On the same conformational basis, possible mechanism of formation, and interpretation of the isodigitoxigenin proton magnetic resonance spectrum, we also support Professor Reichstein's proposal. The protons at positions 20 and 21 in conformer **3** correspond to a dihedral angle of *ca.* 45° and the coupling constant of $J = 4$ Hz found is consistent with such a relationship.

(5) *Cf.* H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.*, **73**, 5252 (1951).

(6) W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *ibid.*, **82**, 3409 (1960).

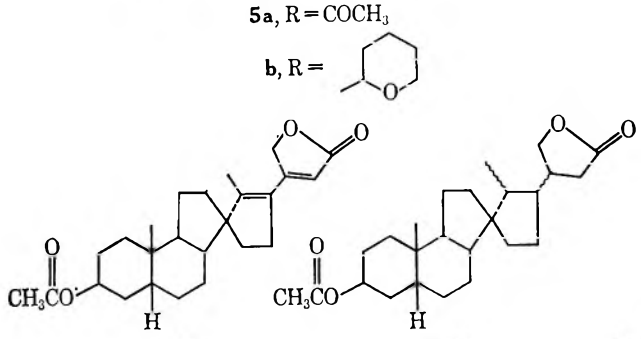
(7) P. Roffey and M. V. Sargent, *Chem. Commun.*, 913 (1966); K. J. van der Merwe, L. Fourie, and de B. Scott, *Chem. Ind.* (London), 829 (1967); J. A. Knight, J. C. Roberts, P. Roffey, and A. H. Sheppard, *Chem. Commun.*, 706 (1966); G. Buchi, D. M. Foulkes, M. Kurono, and G. F. Mitchell, *J. Amer. Chem. Soc.*, **88**, 4534 (1966).

(8) Further evidence for the isomeric relationship of acetals **4b** and **4c** was obtained by oxidizing both to the same lactone: G. R. Pettit, T. R. Kasturi, J. C. Knight, and K. A. Jaegg, *J. Org. Chem.*, **35**, 1410 (1970).

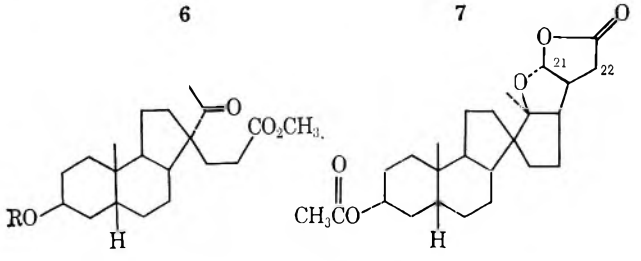


5a, R = $COCH_3$

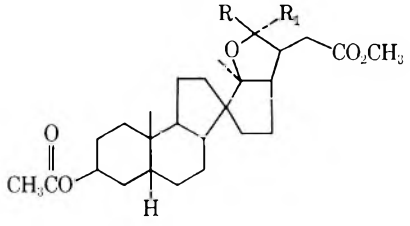
b, R =



6 7



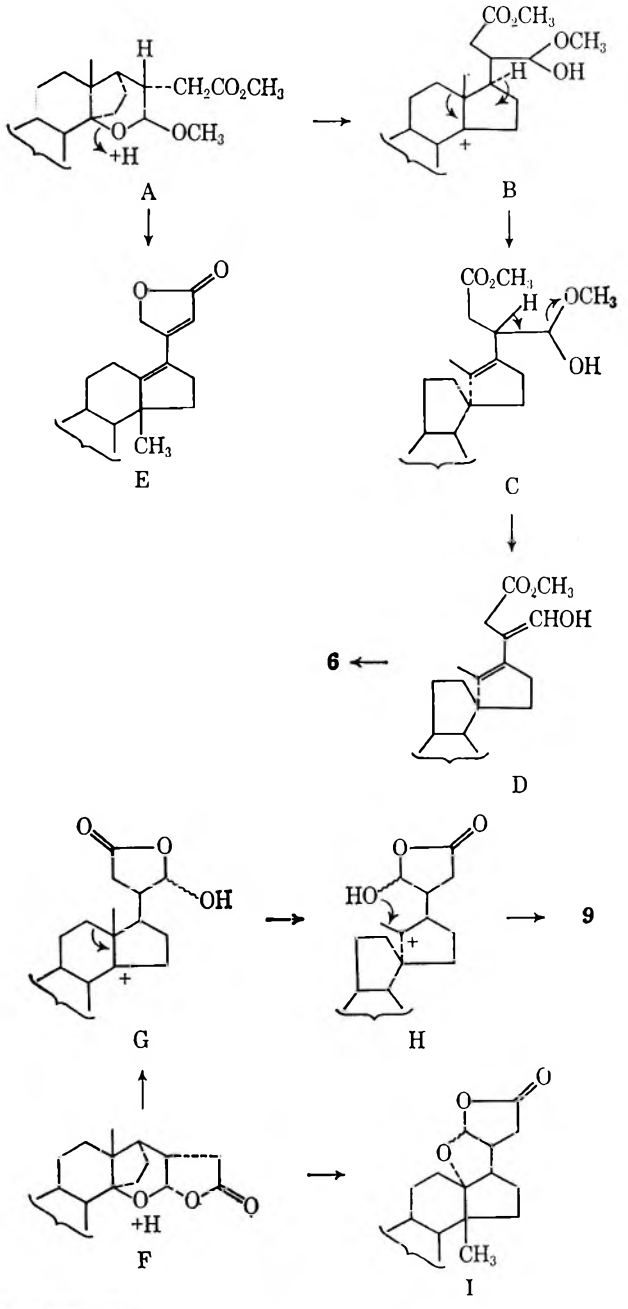
8 9



10a, R = OCH_3; R_1 = H

b, R = H; R_1 = OCH_3

When either acetal **4b** or **4c** was heated in refluxing benzene with *p*-toluenesulfonic acid, the elimination reaction[9] began to follow a more complex course, and resulted in a new substance, mp 165–166°, which displayed maximal ultraviolet absorption at 288 mμ (ε 22,760) indicative of extended conjugation and split carbonyl absorption in the infrared spectrum at 5.54 and 5.73 μ characteristic of an unsaturated lactone.[10] The molecular ion appeared at 398 and confirmed loss of not 1 but 2 mol of methanol. Signals at δ 1.02 and 1.05 for the tertiary methyl group protons of, for example, acetal **4c** had shifted to δ 0.98 and 1.82 and suggested the presence of a vinyl methyl group. The acetate methyl protons appeared at δ 2.07 as in starting material, but the 21-methoxyl and methyl ester signals were absent. Instead, two methylene protons were apparent at δ 5.1 and one vinyl proton at δ 5.82. These data implicated a Westphalen-type rearrangement[1b,11] involving the C–D ring juncture. Although A–B ring juncture Westphalen rearrangements have invariably been reported to entail methyl migration, the possibility of a methylene shift in the present case could not be readily excluded, and indeed seemed likely.[12] The presence of *p*-toluenesulfonic acid would be expected to give a protonated form of acetal **4c** such as A. The ensuing carbonium ion (B) could undergo Wagner–Meerwein rearrangement with the 12-methylene group to spiran C. Elimination of a second mole of methanol from intermediate C would yield enol D. Lactonization



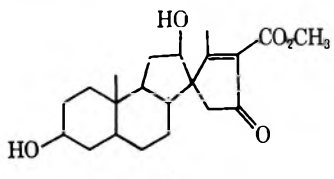
A B C D E F G H I 6 9

(9) U. Schmidt and P. Grafen, *Justus Liebigs Ann. Chem.*, **686**, 97 (1962).

(10) See, *e.g.*, R. N. Jones, C. L. Angel, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959); R. N. Jones and C. Sandorfy, "Chemical Applications of Spectroscopy," Interscience Publishers, New York, N. Y., 1956.

(11) M. M. Janot, P. Devissaquet, M. Pais, Q. K. Huu, F. X. Jarreau, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 4318 (1967).

(12) Later we found that A. Lardon and T. Reichstein [*Helv. Chim. Acta*, **45**, 943 (1962)] had suggested a similar methylene migration to account for rearrangement of a 14β-hydroxy-15-oxo steroid. More recently, structure i



i

has been proposed for an analogous reaction product: C. W. Shoppee, N. W. Hughes, R. E. Lack, and B. C. Newman, *Tetrahedron Lett.*, 3171 (1967); C. W. Shoppee, N. W. Hughes, and R. E. Lack, *J. Chem. Soc., C*, 786 (1968). As indicated in ref 2b, steroids bearing a spiran nuclear ring system are rarely encountered.

and shift of the olefinic double bond into conjugation with the carbonyl group would provide the first example of a C-norcardenolide (**6**). Alternatively, methyl migration by an analogous route would yield 14β-methyl cardenolide E.

To make a definitive choice between alternatives **6** and E, chemical evidence was necessary. Hydrogenation of the rearrangement product **6** resulted in the adsorption of 2 mol of hydrogen and the resulting tetrahydro derivative showed a molecular ion at 402 and no ultraviolet absorption owing to conjugation. The infrared spectrum displayed absorption at 5.65 (γ lactone) and 5.8 μ (acetate) and the pmr spectrum displayed a doublet (J = 7 Hz) at δ 0.78 assigned to a secondary methyl group at position 13. Other aspects of the pmr spectrum were also consistent with spiran structure **7**. Structure E was eliminated conclusively by ozonolysis of olefin **6** at −70°, oxidation of the crude ozonide, methylation with diazomethane, and acetylation. This sequence afforded methyl ketone **8** as major product,[13] and confirmed structure **6**. The pmr spectrum of this ketone exhibited signals at δ 0.94 (19-methyl group), 2.05 (3-acetate), 2.14 (methyl ketone), 3.67 (methyl ester), and 5.08 (3α proton).

Under reaction conditions which led to the rearrangement **4c** → **6**, digitoxigenin gave only 14-dehydrodigitoxigenin,[14] and in a separate experiment the 14-dehydro cardenolide was unaffected.[15] Meanwhile, experiments concerned with cleaving the 14β,21-epoxy bond of isodigitoxigenin were also under way. Treatment with p-toluenesulfonic acid in refluxing benzene gave the only useful results and led to a new substance (**9**) accompanied by C-norcardenolide **6** and starting material. The three-component mixture was separated by preparative layer chromatography. Evidence for assigning C-norcardanolide structure **9** was obtained by considering the empirical formula which was $C_{25}H_{36}O_5$, physical measurements, and possible modes of formation. To accommodate a molecular weight identical with that of starting material **2b** and pmr signals at δ 0.98 (C-19 methyl) and 1.35 (C-18 methyl), skeletal rearrangement of isodigitoxigenin acetate must have occurred. If it is assumed that protonation (F) of isodigitoxigenin results in carbonium ion G, then Wagner–Meerwein rearrangement to H and thence to tetrahydrofuran **9** would seem plausible. The C-norcardanolide (**9**) structure was entirely consistent with the physical data. For example, downfield shift of the C-18 methyl signal to δ 1.35 is quite characteristic of that shown by a methyl group bonded to carbon bearing an electronegative oxygen.[16] Appearance of the 21-proton signal in lactone **9** as a doublet at δ 5.87 with an H-21–H-20 coupling constant of 4 Hz suggested a small dihedral angle. Such information, combined with conformational limitations (as assessed with Dreiding models), suggests structure **9** as a reasonable stereochemical assignment.

To eliminate further the possibility of the isodigitoxigenin rearrangement product arising by a methyl migration (*cf.* I), additional information was collected. Acetals **10a** and **10b** were obtained by methanolysis of C-norcardanolide **9**. The result was comparable with the reaction leading to acetals **4b** and **4c**, and stereochemical assignments were made in analogous fashion. Heating either acetal **10a** (21R) or **10b** (21S) in benzene containing p-toluenesulfonic acid provided a mixture composed of spirans **6** and **9**, thereby eliminating a 14β-methyl possibility.[17]

The 12(13 → 14)*abeo*[18] skeletal rearrangements discovered during the present investigation may actually be fairly general in scope, and steroids containing the spiro C–D ring juncture may be uncovered in natural products. Since such rearrangement reactions could now be recognized and/or avoided in projected synthetic approaches to bufalin, the objectives of the present study were reached. Future X-ray crystallographic determinations in this area are planned to settle unequivocally the stereochemical assignments for isodigitoxigenin (**2**), tetrahydropyran **4**, and spirans **6**, **9**, and **10**.

Experimental Section

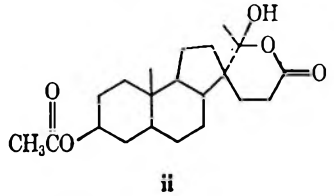
Solvent extracts of aqueous solutions were dried over sodium sulfate and concentrated under reduced pressure using a rotatory evaporator. Acetylation refers to 1:3 acetic anhydride–pyridine at room temperature for 20 hr. Chromatographic solvents were redistilled and ligroin refers to a fraction boiling at 60–80°. Basic alumina (Merck, Rahway, "suitable for chromatography") and silica gel (0.05–0.20 mm, E. Merck, Darmstadt) were used for column chromatography. Thin layer and preparative layer chromatographic plates were prepared using, respectively, silica gel HF_{254} and silica gel G supplied by E. Merck. The introduction to the experimental section of part 7[1] provides other general information necessary here.

Digitoxigenin (**1a**).[19]—In a typical experiment, digitoxin (**1b**, 10 g) in a solution prepared from methanol (500 ml) and 0.1 N sulfuric acid (500 ml) was heated at reflux for 30 min. The hydrolysis and isolation procedure was based on one reported by Rangaswami and Reichstein.[3b] Recrystallization of the crude product from methanol–diethyl ether gave 4.82 g of digitoxigenin, mp 245° (lit.[4a] mp 252°).

Isodigitoxigenin (**2a**).—By essentially the procedure of Jacobs and Gustus,[4a] digitoxigenin (**1a**, 21.0 g) was ground to a fine powder and stirred with methanol (200 ml) containing potassium hydroxide (5.0 g) at 15° for 1 hr. The solid isodigitoxigenin was collected and washed with methanol to yield 13.5 g. One recrystallization from ethanol and one from acetone gave needles, mp 270–273° (at *ca.* 175° the needles become rectangular plates, lit.[4a] mp 271°). Recrystallization from acetone–chloroform was equally effective.

Dilution of the methanol filtrate with water gave a precipitate of digitoxigenin. Acidification of the filtrate and extraction

(13) In one experiment a neutral product was also obtained which might correspond to structure ii but was not further characterized.



ii

(14) E. Hauser, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **49**, 1212 (1966).

(15) Results of these experiments indicted that transformation A → **6** may be a concerted process, such as steroid "backbone"-type rearrangements; see, *e.g.*, J. Bascoul and A. Crastes de Paulet, *Chem. Commun.*, 256 (1908); J. C. Jacquesy, J. Levisalles, and J. Wagnon, *ibid.*, 25 (1967); J. W. Blunt, J. M. Coxon, M. R. Hartshorn, and D. N. Kirk, *Tetrahedron*, **23**, 1811 (1967). Also, the exclusive formation of spiran **6** in preference to a 14β-methyl derivative again points to a concerted reaction.

(16) See, *e.g.*, T. R. Kasturi, E. Raghavan, S. Dev, and D. K. Banerjee, *Tetrahedron*, **22**, 745 (1966).

(17) The results of this study led us to reinvestigate the classical Westphalen rearrangement involving, *e.g.*, 3β-chloro-5α-hydroxy-6β-acetoxycholestane reported by A. Fischer, M. J. Hardman, M. P. Hartshorn, D. N. Kirk, and A. R. Thawley, *ibid.*, **23**, 159 (1967). Evidence so far accumulated completely substantiates methyl migration in the A–B system.

(18) IUPAC–IUB Revised Tentative Rules, *J. Org. Chem.*, **34**, 1517 (1969).

(19) We wish to thank Dr. K. A. Jaeggi for performing several of these experiments.

with chloroform led to isodigitoxigeninic acid (**4e**, 5.7 g).[4a] Acid **4e** was not further purified but used as summarized below in method C for obtaining acetals **4b** and **4c**.

Acetylation of isodigitoxigenin and recrystallization from acetone–chloroform afforded fine needles: mp 258–262° (lit.[4b] mp 250°); pmr δ 1.00 (C-18 and -19 methyls), 2.00 (C-3 acetate), 2.39–2.90 (complex, $COCH_2$–), 4.96 (H-3α), and 5.70 (J = 4 Hz, OCHO).

Methyl 3β-Acetoxy-14β,21-epoxy-21ζ-methoxy-5β-(20*S*)-norcholanate (4b and 4c). Method A.—Isodigitoxigenin (**2a**, 0.5 g) was saponified and the resulting isodigitoxigeninic acid was methylated with diazomethane essentially as reported by Jacobs and Gustus.[4a] The crude methyl ester,[4a] mp 126–127° (lit.[4a] mp 128°), in methanol (25 ml) containing 48% hydrobromic acid (2 drops) was allowed to remain at room temperature for 20 hr. The solution was concentrated to a small volume and then diluted with water. A diethyl ether extract of the aqueous solution was washed with dilute sodium bicarbonate and water. Following removal of solvent, the residue was acetylated and the resulting acetate ester was chromatographed on basic alumina (12 g). Elution with hexane gave a semisolid (0.16 g) which crystallized from hexane or methanol to yield short, thick needles of acetal **4b**, mp 194–199°.

Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.25; H, 9.12; O, 20.54.

Continued elution with 1:1 hexane–benzene gave a viscous oil (0.18 g) which crystallized from methanol to yield large prisms of acetal **4c**, mp 147–149°.

Anal. Found: C, 69.98; H, 9.02; O, 20.85.

Method B.—The methyl ester of isodigitoxigeninic acid (**4a**, see method A or preparation of isodigitoxigenin) was acetylated as described by Schindler and Reichstein.[4b] A specimen of diacetate **4d** was thus obtained: mp 174–176° (lit.[4b] mp 173–175°); pmr δ 1.02 and 1.18 (C-18 and -19 methyls), 2.07 (C-3 acetate), 2.12 (C-21 acetate), 3.7 (methyl ester) and 5.7 (J = 8 Hz, H-21α).

A solution of acetate **4d** (0.15 g) in methanol (15 ml) containing a trace of 48% hydrobromic acid was heated at reflux for 2 hr. Upon cooling, the solid which separated was collected and recrystallized from methanol. A pure sample of acetal **4b** was obtained as long, thin plates, mp 195–196°.

Method C.—The following procedure for obtaining acetals **4b** and **4c** proved routinely effective and was considerably more efficient than proceeding by way of methods A and B. Further, isodigitoxigeninic acid could be substituted for isodigitoxigenin with comparable results. For small-scale conversion, isodigitoxigenin (0.5 g) in methanol (50 ml) containing *p*-toluenesulfonic acid (0.05 g) and water (2.5 ml) was heated at reflux for 20 hr. After removal of methanol and dilution with water, the mixture was extracted with diethyl ether. The ethereal extract was washed with dilute sodium bicarbonate and water. Solvent was evaporated and the residue (0.4 g) was acetylated. The resulting acetate was chromatographed on basic alumina (9 g). Elution with hexane provided a solid (0.22 g), mp 187–189°, which recrystallized from hexane as long, thin plates. Recrystallization from methanol led to an analytical sample of acetal **4b**: mp 194–196°; $[\alpha]_D$ −75° (*c* 1.0); RD (*c* 1.0) $[\alpha]_{300}$ −370°, $[\alpha]_{350}$ −242°, $[\alpha]_{400}$ −178°, $[\alpha]_{450}$ −140°, $[\alpha]_{500}$ −105°, $[\alpha]_{589}$ −74°, and $[\alpha]_{600}$ −70°; ν_{max}^{KBr} 1728, 1745, and 1235 cm^{-1}; pmr δ 1.02 and 1.05 (C-18 and -19 methyls), 2.07 (C-3 acetate), 3.32 (C-21 acetate), 3.68 (methyl ester), and 4.73 (J = 5.5 Hz, H-21β).

Further elution with 1:1 hexane–benzene provided 0.15 g of solid acetal **4c**, mp 136–139°. Recrystallization from methanol gave a pure specimen as thick plates: mp 142–144°; $[\alpha]_D$ +9.0° (*c* 1.33); RD (c 0.97) $[\alpha]_{300}$ +72°, $[\alpha]_{350}$ +51.5°, $[\alpha]_{400}$ +41°, $[\alpha]_{450}$ +33°, $[\alpha]_{500}$ +29°, $[\alpha]_{589}$ +21°, and $[\alpha]_{600}$ +20°; ν_{max}^{KBr} 1735, 1240, and 1256 cm^{-1}; pmr δ 1.08 and 1.12 (C-18 and -19 methyls), 2.07 (C-3-acetate), 3.45 (C-21 methoxy), 3.68 (methyl ester), and 4.23 (doublet, J = 8 Hz, H-21α).

A quite useful larger scale method was based on the digitoxigenin–isodigitoxigeninic acid mixture obtained from digitoxigenin. For example, a mixture composed of isodigitoxigenin (8.0 g) and isodigitoxigeninic acid (3.5 g) in methanol (850 ml)–water (40 ml) containing *p*-toluenesulfonic acid (0.85 g) was heated at reflux for 24 hr (reaction was complete as evidenced by thin layer chromatography). Isomers **4b** and **4c** were isolated, acetylated, and separated as noted directly above. Comparable yields of acetal **4b**, mp 194–199°, and acetal **4c**, mp 147–149°, were obtained. Later, experiments showed that the isomers could be readily separated by column chromatography on silica gel and elution with 19:1 ligroin–ethyl acetate.

Samples of isomeric acetals **4b** and **4c** obtained by methods A–C were compared and found identical.[20]

Equilibration of Methyl 3β-Acetoxy-14β,21-epoxy-21-methoxy-5β-(20*S*)-norcholanate (4b and 4c).—To a solution of acetal **4b** (0.30 g) in benzene (10 ml) was added *p*-toluenesulfonic acid (0.05 g). Aliquots were removed at intervals of 15 min and evaluated by thin layer chromatography with 19:1 chloroform–ethyl acetate mobile phase. Under these conditions, acetal **4b** reached equilibrium with epimer **4c** within 15 min and remained constant for the 3-hr period studied. The equilibrium mixture contained a ratio of *ca.* 3:1 acetal **4c** to acetal **4b**. Repeating the experiment with acetal **4c** gave identical results.

Methyl 3β-Acetoxy-14β,21-epoxy-5β-norchol-20(21)-enate (5a).—To each of the equilibrium mixtures of acetals **4b** and **4c** described in the preceding experiment was added dihydropyran (0.5 ml). In each case, within 15 min nearly all the acetal was transformed into vinyl ether **5a**, and with a lapse of 1 hr, olefin **5a** was the only substance present as evidenced by thin layer chromatography with 19:1 ligroin–ethyl acetate mobile phase. The pale yellow reaction mixture was diluted with diethyl ether and washed with dilute sodium bicarbonate and water. Removal of solvent gave a residue which was chromatographed on silica gel. Elution with 19:1 ligroin–ethyl acetate led to olefin **5a**. Recrystallization from methanol gave an analytical specimen (0.38 g combined yield): mp 103–105°; $[\alpha]_D$ −25° (*c* 0.59); ν_{max}^{KBr} 1742, 1670, and 1255 cm^{-1}; pmr δ 1.10 and 1.06 (C-18 and -19 methyls), 2.04 (C-3 acetate), 2.90 (singlet, C-22 methylene), 3.68 (methyl ester), 5.14 (H-3α), and 6.0 (H-21 vinyl).

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.82; H, 9.02.

Methyl 3β-Pyranyloxy-14β,21-epoxy-5β-norchol-20(21)-enate (5b).—A solution of acetal **4c** [(21*S*)-methoxy, 4.64 g) in methanol (200 ml) containing water (20 ml) and potassium hydroxide (10 g) was heated at reflux for 3 hr. A major portion of the methanol was removed under reduced pressure and the concentrated solution was diluted with water and acidified with 2*N* hydrochloric acid. The mixture was extracted with diethyl ether and the ethereal extract was washed with water. Following removal of solvent, the viscous residue was methylated with diazomethane. The resulting oily ester slowly solidified on standing to yield 4.1 g. To a solution of the ester in dry benzene (30 ml) was added dihydropyran (3.75 ml) and *p*-toluenesulfonic acid (0.10 g). The mixture was stirred at room temperature overnight for 19.5 hr and then diluted with diethyl ether and washed with dilute sodium bicarbonate and water. Solvent was removed *in vacuo* and the resulting yellow oil was chromatographed on silica gel (200 g). Elution with 19:1 ligroin–ethyl acetate and recrystallization of that fraction from methanol provided olefin **5b** as long needles (2.72 g), mp 122–123°. Another specimen purified by chromatography on basic alumina, elution with 1:1 hexane–benzene, and recrystallization from pentane melted at 124–125°. Another recrystallization from pentane gave an analytical sample as needles: mp 125–126°; $[\alpha]_D$ −29° (*c* 0.80); RD (c 0.75) $[\alpha]_{300}$ −260°, $[\alpha]_{350}$ −137°, $[\alpha]_{400}$ −87°, $[\alpha]_{450}$ −53°, $[\alpha]_{500}$ −37°, $[\alpha]_{589}$ −23°, and $[\alpha]_{600}$ −23°; ν_{max}^{KBr} 1736 and 1662 cm^{-1}; pmr δ 0.97 and 1.05 (C-18 and -19 methyls), 2.88 (C-22 methylene), 3.65 (methyl ester), and 5.97 (H-21 vinyl).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38; O, 16.92. Found: C, 73.64; H, 9.34; O, 17.08.

A more detailed study of olefin **5b** homogeneity by thin layer chromatography using the solvent system 1:99 ethyl acetate–chloroform saturated with water gave resolution into two components. The two closely related substances were presumed to represent epimers resulting from the newly introduced 3β-tetrahydropyran ring asymmetric center and were not further characterized.

Methyl 3β-Pyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norcholanate (4f). Method A.—A sample of 3β acetate **4c** (2.8 g) was saponified and remethylated as described in the preceding experiment (see **5b**). A solution of the crude methyl ester in dry benzene (20 ml) containing dihydropyran (2.5 ml) and *p*-toluenesulfonic acid (0.07 g) was stirred at room temperature for 1 hr. The solution was washed with water, dilute sodium bicarbonate, and water. Following removal of solvent, the residue was chro-

(20) The identical composition was established by thin layer chromatographic, proton magnetic resonance, and infrared spectral (in potassium bromide) comparisons.

matographed on basic alumina (100 g). Elution with 1:1 hexane–benzene gave an oily fraction (2.3 g). Crystallization and recrystallization from pentane gave a pure sample as needles: mp 128–130°; $[\alpha]_D$ +31° (*c* 0.59); RD (*c* 1.18) $[\alpha]_{300}$ +101°, $[\alpha]_{350}$ +87°, $[\alpha]_{400}$ +64°, $[\alpha]_{450}$ +49°; $[\alpha]_{500}$ +40°, $[\alpha]_{589}$ +22°, and $[\alpha]_{600}$ +21°; ν_{max}^{KBr} 1735 cm^{-1}; pmr δ 0.96 and 1.08 (C-18 and -19 methyls), 3.44 (acetal methoxy), 3.66 (methyl ester), 3.96 (pyranyl ether acetal proton), 4.25 (J = 8 Hz, H-21), and 4.64 (H-3α).

Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.50; H, 9.54; O, 19.16.

Method B.—For routine and larger scale preparation of acetal **4f** and vinyl ether **5b**, the following procedure was preferred. The crude methanolysis product (21.6 g, mixture of acetals **4b** and **4c**) from isodigitoxigenin and isodigitoxigeninic acid was dissolved in dry benzene (110 ml). Dihydropyran (22.5 ml) and *p*-toluenesulfonic acid (0.55 g) were then added. After stirring for 10 min at room temperature, the solution was washed with dilute sodium bicarbonate and water. Solvent was removed and the crude product was chromatographed in 19:1 ligroin–ethyl acetate on silica gel (400 g). Before 9:1 petroleum ether–ethyl acetate was used, a number of impure fractions (12.5 g total) were collected. Elution with 9:1 ligroin–ethyl acetate gave methyl 3β-pyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norcholanate (**4f**, 10.1 g) as needles, mp 132–134°. Further elution with ethyl acetate gave 3β-pyranyloxy isodigitoxigenin (**2c**, 0.43 g), characterized by the infrared spectrum and by cleavage of the pyranyloxy group with *p*-toluenesulfonic acid in aqueous methanol to give isodigitoxigenin.

Careful rechromatography of the initially eluted fractions provided the epimeric methyl 3β-pyranyloxy-14β,21-epoxy-(21*R*)-methoxy-5β-(20*S*)-norcholanate (**4g**), crystallized from methanol as plates: mp 159–161°; $[\alpha]_D$ −62.4° (*c* 0.75); pmr δ 0.98 (C-18 methyl), 1.04 (C-19 methyl), 3.28 (acetal methoxyl), 3.68 (ester methoxyl), 3.96 (pyranyl acetal proton), 4.68 (H-3), 4.74 (doublet, J = 5.5 Hz, acetal OCHO–).

Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59; mol wt, 504. Found: C, 71.07; H, 9.30; mol wt 504 (mass spectrum).

Since isomer **4g** was not desired for further work, the initial fractions were usually treated with dihydropyran and *p*-toluenesulfonic acid as described below to convert the axial epimer into the more useful vinyl ether **5b**.

The mixture (12.5 g) eluted prior to acetal **4f** was dissolved in benzene (100 ml), and both tetrahydropyran (20 ml) and *p*-toluenesulfonic acid (0.50 g) were added. The solution was stirred at room temperature for 7.5 hr and the product was isolated and purified as described directly above. The fraction eluted by 19:1 ligroin–ethyl acetate was a colorless, mobile oil which crystallized from methanol as needles corresponding to methyl 3β-pyranyloxy-14β,21-epoxynor-5β-chol-20(21)-enate (**5b**), mp 122–123°. Continued elution gave a mixture of acetal-containing fractions (2.10 g). The crude material was again pooled and combined with the mother liquors from recrystallization of vinyl ether **5b**. Retreatment with dihydropyran and *p*-toluenesulfonic acid in benzene led to an additional quantity (2.32 g) of vinyl ether **5b**.

3β-Acetoxy-12(13→14)*abeo*-$\Delta^{13(17)}$-5β-cardenolide (6).—A solution composed of equatorial acetal isomer **4c** (0.20 g), dry benzene (30 ml), and *p*-toluenesulfonic acid (0.04 g) was heated at reflux for 10 hr. Water was removed during this period by a Dean–Stark trap. After cooling, the clear solution was washed with water, dilute sodium bicarbonate, and water. Following removal of benzene, the residue was chromatographed on basic alumina (6 g). Elution with 1:1 hexane–benzene gave a viscous oil (0.14 g). Trituration with hexane caused crystallization, mp 155–160°. Recrystallization from acetone–hexane provided pale yellow plates: mp 165–166°; λ_{max}^{EtOH} 288 mμ (ϵ 22,760); $[\alpha]_D$ +36° (*c* 0.5); RD (*c* 1.10) $[\alpha]_{350}$ +145°, $[\alpha]_{400}$ +97°, $[\alpha]_{450}$ +68°, $[\alpha]_{500}$ +55°, $[\alpha]_{589}$ +36°, and $[\alpha]_{600}$ +36°; λ_{max}^{KBr} 5.54, 5.73, 6.13, 6.30, 7.92, and 8.0 μ; $\lambda_{max}^{CHCl_3}$ 5.58, 5.73, and 6.16 μ; pmr δ 0.98 and 1.82 (C-18 and -19 methyls), 2.07 (C-3 acetate), 5.1 (C-21 methylene), and 5.82 (H-22 vinyl).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60; O, 16.06; mol wt, 398. Found: C, 75.18; H, 8.44; O, 16.80; mol wt, 398 (mass spectrum).

When the preceding experiment was continued over a longer period or when toluene or *p*-cymene was substituted for benzene, the reaction began to follow (as evidenced by thin layer chromatography) a more complex path. Monitoring by thin layer chromatography indicated that the 10-hr reaction period in benzene was most desirable for obtaining C-norcardenolide **6**.

Dehydration of Digitoxigenin (1a).—A solution prepared from benzene (25 ml), digitoxigenin (**1a**, 0.25 g), and *p*-toluenesulfonic acid (0.04 g) was heated at reflux for 20 hr. After cooling, the product was isolated as summarized in the preceding experiment (see **6**) and the residue (0.22 g) was chromatographed on basic alumina (7 g). Elution with 1:1 hexane–benzene gave a solid (0.2 g). Recrystallization from acetone gave 14-dehydrodigitoxigenin,[14] mp 198-200°.[21]

Hydrogenation of 3β-Acetoxy-12(13→14)*abeo*-$\Delta^{13(17)}$-5β-cardenolide (7).—A mixture composed of cardenolide **6** (0.1 g), 5% palladium on barium sulfate (0.1 g), and glacial acetic acid (15 ml) was stirred in a slightly positive pressure of hydrogen for 10 hr. At this point, hydrogenation appeared complete and the catalyst was removed by filtration and washed with diethyl ether. The filtrate was concentrated to a solid residue. A solution of the crude product in diethyl ether (50 ml) was washed with water, dilute sodium bicarbonate, and water. Ether was removed and the residue was chromatographed on neutral alumina (3 g). Elution with 1:1 hexane–benzene led to a solid (0.06 g) which recrystallized from acetone as crystals, mp 201–216°. The isomeric mixture corresponding to structure **7** was not further separated. At this stage, the isomeric mixture exhibited the following data: $[\alpha]_D$ +19° (c 1.0); $\lambda_{max}^{CHCl_3}$ 5.65 and 5.80 μ; pmr δ 0.78 (doublet, J = 7 Hz, C-18 methyl), 0.95 (C-19 methyl), 2.07 (C-3 acetate), and 5.08 (H-3α).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.62; H, 9.45; O, 15.91; mol wt, 402. Found: C, 74.66; H, 9.37; O, 15.90; mol wt, $M^+ - 60$ peak at 342 (mass spectrum).

Ozonolysis of 3β-Acetoxy-12(13→14)*abeo*-5β-$\Delta^{13(17)}$-cardenolide (6).—Ozone (Welsbach ozonator) was passed for 15 min through a solution of diene **6** (0.15 g) in dry ethyl acetate (30 ml) at −70°. The bluish solution was evaporated in a current of dry nitrogen. A solution of the oily residue in glacial acetic acid (30 ml)–water (1 ml) was treated with concentrated hydrochloric acid (1 drop) and 30% hydrogen peroxide (2 ml) at room temperature; *ca.* 2 days later, the solution was diluted with water and extracted with diethyl ether. The ethereal extract was washed with 5% sodium bicarbonate solution and water. Removal of solvent gave 0.05 g of neutral oil, while acidification of the sodium bicarbonate extract followed by extraction with diethyl ether led to 0.1 g of oily carboxylic acid. Methylation of the acid with ethereal diazomethane and acetylation gave oily ketone **8**. Purification by preparative thin layer chromatography gave an oily, analytical sample: bp 120–125° (bath temperature of evaporative distillation at 0.1 mm); $[\alpha]_D$ +34° (*c* 0.52); RD (*c* 1.09) $[\alpha]_{350}$ +225°, $[\alpha]_{400}$ +119°, $[\alpha]_{450}$ +81°, $[\alpha]_{500}$ +60°, $[\alpha]_{589}$ +38°, and $[\alpha]_{600}$ +37°; λ_{max}^{neat} 5.75 and 5.80 μ; pmr δ 0.94 (C-19 methyl), 2.05 (C-3 acetate), 2.14 (methyl ketone), 3.67 (methyl ester), and 5.08 (H-3α); mass spectrum *m/e* 378 (M^+), 360 (M − 18), 347 (M − 31), 335 (M − 43), 318 (M − 60), 291 (M − 87), 243, 201 and 157.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.13. Found: C, 69.12; H, 8.66; O, 22.40.

Rearrangement of Isodigitoxigenin Acetate (2b).—By distillation, solvent (30 ml) was removed from a solution of isodigitoxigenin acetate (**2b**, 1.87 g) in benzene (250 ml). *p*-Toluenesulfonic acid (0.24 g) was added and the mixture was heated at reflux for 3 days. After cooling and washing with dilute sodium bicarbonate solution and water, solvent was removed. The solid residue was chromatographed on silica gel (200 g) in 4:1 benzene–ethyl acetate, which removed most of the unchanged starting material (1.0 g) and gave a fraction enriched in the less polar rearrangement product **9** (0.75 g).

The enriched fraction was rechromatographed on silica gel in 19:1 benzene–ethyl acetate and separated into three fractions. The first weighed 60 mg and consisted of two nonpolar components arising from loss of the acetate at C-3. Continuing elution with the same solvent gave a second fraction which was further separated by preparative layer chromatography (multiple development, with chloroform as mobile phase) into recovered isodigitoxigenin acetate (200 mg) and C-norcardanolide **9** (120 mg). Recrystallization from methanol gave a pure sample as colorless rosettes: mp 195–196°; $[\alpha]_D$ −9° (*c* 0.53); RD (*c* 0.53) $[\alpha]_{300}$ −132°, $[\alpha]_{350}$ −66°, $[\alpha]_{400}$ −40°, $[\alpha]_{450}$ −23°, $[\alpha]_{500}$ −19°, $[\alpha]_{589}$ −9°, and $[\alpha]_{600}$ −9°; $\nu_{max}^{CHCl_3}$ 1776, 1733, and 1241

(21) Identical (see ref 20) with an authentic specimen prepared as described in reference 14.

cm^{-1}; pmr δ 0.98 and 1.35 (C-18 and -19 methyls), 2.00 (C-3 acetate), 2.6–2.9 (m, C-22 methylene), 4.92 (H-3α), and 5.87 (H-21); mass spectrum m/e 416 (M^+) and 356 ($M^+ - 60$).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; O, 19.20. Found: C, 72.12; H, 8.64; O, 19.42.

The last fraction eluted from the column weighed 0.2 g and was virtually pure isodigitoxigenin acetate with only traces of rearrangement product **9** present.

It was later found that the reaction was greatly concentration dependent, and that if the volume of benzene was reduced to *ca.* 35 ml/1 g of isodigitoxigenin acetate, no starting material at all remained after 24 hr at reflux. Reducing the volume still further or prolonging the reflux time lead to increasing amounts of C-norcardenolide **6**. The products were most satisfactorily purified by preparative layer chromatography on large plates (40 × 20 cm), developed up to eight times in chloroform. On silica gel HF_{254} the rearrangement product gave a pale blue fluorescence under ultraviolet light, and the extent of the band owing to unchanged starting material was revealed by spraying the plates with water.

Alcoholysis of 3β-Acetoxy-12(13→14)*abeo*-13α-methyl-13β,-21α-epoxy-5β-cardanolide (9).—A solution prepared from cardanolide **9** (0.11 g), methanol (10 ml), water (0.5 ml), and *p*-toluenesulfonic acid (10 mg) was heated at reflux for 26 hr. The crude product was isolated and acetylated essentially as summarized above for the preparation of acetals **4b** and **4c**. Following acetylation, a thin layer chromatogram ($CHCl_3$ mobile phase) showed two components. Purification by preparative layer chromatography in $CHCl_3$ gave the faster moving acetal **10a** as an oil which crystallized from methanol as large prisms (52 mg): mp 103–105°; $[\alpha]_D$ +91.5° (*c* 0.71); RD (c 0.71) $[\alpha]_{300}$ +416°, $[\alpha]_{350}$ +289°, $[\alpha]_{400}$ +212°, $[\alpha]_{450}$ +162°, $[\alpha]_{500}$ +130° $[\alpha]_{589}$ +91.5°, and $[\alpha]_{600}$ +91.5°; pmr δ 0.96 and 1.29 (C-18 and -19 methyls), 2.02 (C-3 acetate), 3.25 (C-21 methoxyl), 3.66 (methyl ester), 4.84 (doublet, J = 5 Hz, H-21), and 5.05 (H-3α).

Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 69.69; H, 9.30.

The more polar isomer acetal **10b** (30 mg) was isolated as an oil that resisted all attempts at crystallization. However, a thin layer chromatogram ($CHCl_3$ mobile phase) indicated presence of only one component: pmr δ 0.99 and 1.26 (C-18 and -19 methyls), 2.04 (C-3 acetate), 2.48, (C-22 methylene) 3.28 (C-21 methoxyl), 3.62 (methyl ester), 4.72 (H-21β), and 5.07 (H-3α).

Conversion of Acetals 10a and 10b into C-Norcardanolide 9 and C-Norcardenolide 6.—Preparation of acetals **10a** and **10b** was repeated on a somewhat larger scale. A solution of acetal **10a** (0.24 g) in benzene (60 ml) containing *p*-toluenesulfonic acid (0.05 g) was distilled until 20 ml of solvent was removed. Heating was continued at reflux for 2 hr and the solution was cooled, diluted with diethyl ether, and washed successively with water, dilute sodium bicarbonate solution, and water. Solvent was removed and the residual oil (0.17 g) was purified by preparative layer chromatography with 9:1 chloroform–ethyl acetate. The product separated into three zones with the most polar corresponding to cardanolide **9**. Crystallization from methanol provided 0.069 g, mp 195–196°. The product was identical[20] with an authentic specimen of cardanolide **9**. The next most polar zone corresponded to cardenolide **6**. Crystallization from methanol gave needles (36 mg), mp 165–166°, identical[20] with an authentic sample. The least polar zone provided 0.13 g of oil that resisted crystallization. Repeated purification by preparative layer chromatography failed to yield a crystalline product.

A solution of acetal **10b** (0.112 g) in dry benzene (30 ml) containing *p*-toluenesulfonic acid (20 mg) was heated at reflux for 14.5 hr until tlc showed that no starting material was present. The crude product was isolated and purified by preparative layer chromatography as summarized in the preceding paragraph. The most polar zone again corresponded to cardanolide **9** (25 mg), mp 187–193°. Recrystallization from methanol gave a sample, mp 194–196°, identical[20] with an authentic specimen. Again, cardenolide **6** (10 mg), mp 151–154°, was isolated from the middle zone. Recrystallization from methanol gave a specimen, mp 160–162°, identical[20] with authentic material. The least polar zone corresponded on the basis of thin layer mobility to the analogous zone obtained from acetal **10a** and could not be persuaded to crystallize.

Registry No.—**4b**, 14892-11-6; **4c**, 14892-12-7; **4f**, 17150-44-6; **4g**, 23353-49-3; **5a**, 23353-50-6; **5b**, 17150-43-5; **6**, 23353-51-7; **7**, 23353-52-8; **8**, 23353-53-9; **9**, 23353-54-0; **10a**, 23353-55-1.

Bufadienolides. 9. Isobufalin[1]

GEORGE R. PETTIT, T. R. KASTURI,[2] JOHN C. KNIGHT, AND KNUT A. JAEGGI

Department of Chemistry, Arizona State University, Tempe, Arizona 85281, and Department of Chemistry, University of Maine, Orono, Maine 04473

Received February 11, 1969

Isobufalin methyl ester (**4a**) was prepared by methanolysis of bufalin (**3**) in the presence of sodium methoxide, and saponification of the 3β-acetoxy derivative **4b** readily afforded isobufalin (**4c**). In each case, the configuration of the side-chain olefin was shown to be *trans* at positions 22 and 23 by proton magnetic resonance measurements. Isodigitoxigenin (**7**), acetal **8e**, and dihydropyran **12a** were prepared from digitoxin by way of digitoxigenin (**6**) as described in part 8. By a four-step reaction sequence *via* intermediates **12b–12d** and **11a**, both methyl esters **8e** and **12a** were converted into methyl 3β-acetoxy-14β,21-epoxy-5β-chol-20(21)-enate (**11b**). Dehydrogenation of methyl ester **11b** employing 2,3-dichloro-5,6-dicyanobenzoquinone completed total synthesis of 3β-acetoxyisobufalin methyl ester and therefore isobufalin.

At an early stage in the extensive and definitive structural investigation of scillaren A by Stoll and colleagues,[3,4] a derivative scillaridin A (**1**) upon contact with potassium hydroxide in methanol was found to yield the methyl ester of an isomeric substance designated isoscillaridin A (**2**).[5] Analogous methanolysis of bufalin[6] (**3**) readily afforded isobufalin methyl ester (**4a**). That a *trans* relationship now existed between the 22 and 23 protons was indicated by proton magnetic resonance signals at δ 5.63 (23 proton) and 7.23 (22 proton) which appeared as a set of doublets with J = 15 Hz. Acetylation of alcohol **4a** gave 3β-acetoxyisobufalin methyl ester (**4b**). Platinum-catalyzed hydrogenation of iso-

(1) (a) This investigation was supported by Public Health Service Research Grants CA-04074-05 to CA-04074-06 and CA-10115-01 to CA-10115-02 from the National Cancer Institute. Part 8: G. R. Pettit, T. R. Kasturi, J. C. Knight, and J. Occolowitz, *J. Org. Chem.*, **35**, 1404 (1970). (b) A preliminary report of the present study was summarized: T. R. Kasturi, G. R. Pettit, and K. A. Jaeggi, *Chem. Commun.*, 644 (1967).

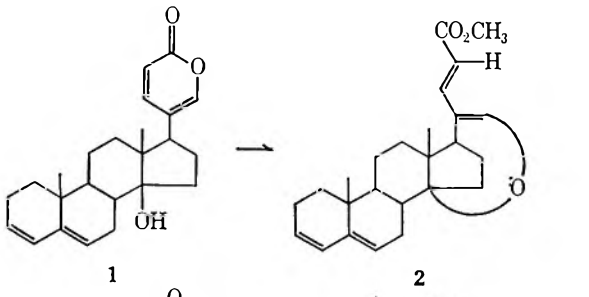
(2) On sabbatical leave from the Indian Institute of Science, Bangalore, India.

(3) A. Stoll, A. Hofmann, and A. Helfenstein, *Helv. Chim. Acta*, **17**, 641 (1934).

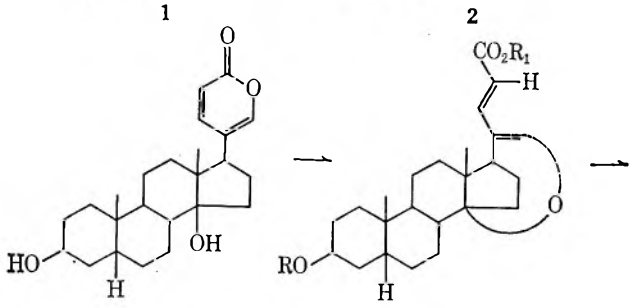
(4) Other pertinent references have been summarized: G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(5) The *trans* side-chain geometry presented in structure **2** for isoscillaridin A is based upon results of a proton magnetic resonance study of isobufalin summarized in the sequel. The assignment presumes comparable energy relationships in the olefin systems of isoscillaridin A and isobufalin.

(6) *Cf.* A. von Wartburg and J. Renz, *Helv. Chim. Acta*, **42**, 1620 (1959).

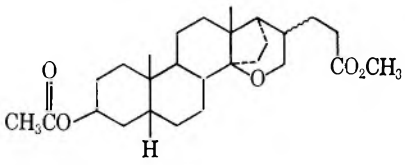


1 2

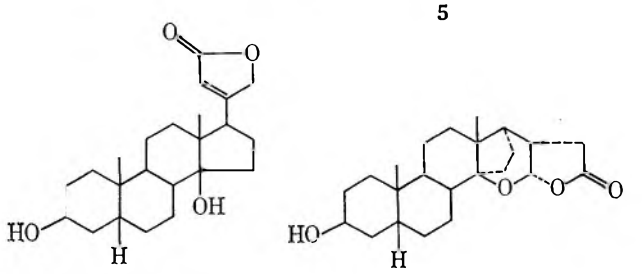


3

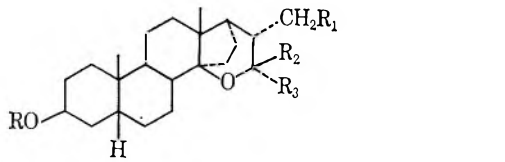
4a, R = H; R_1 = CH_3
b, R = $COCH_3$; R_1 = CH_3
c, R = R_1 = H



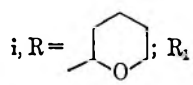
5



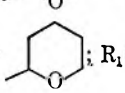
6 7



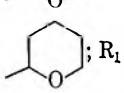
8a, R = H; R_1 = CO_2H; R_2 or R_3 = OH
b, R = $COCH_3$; R_1 = CO_2CH_3; R_2 = $OCOCH_3$; R_3 = H
c, R = $COCH_3$; R_1 = CO_2CH_3; R_2 = R_3 = O
d, R = $COCH_3$, R_1 = CO_2CH_3; R_2 = H; R_3 = OCH_3
e, R = $COCH_3$; R_1 = CO_2CH_3; R_2 = OCH_3; R_3 = H
f, R = H; R_1 = CO_2H; R_2 = R_3 = O
g, R = $COCH_3$; R_1 = CO_2H; R_2 = R_3 = O
h, R = $COCH_3$; R_1 = COCl; R_2 = R_3 = O



i, R = ; R_1 = CH_2OH; R_2 = OCH_3; R_3 = H



j, R = ; R_1 = $CH_2OSO_2CH_3$; R_2 = OCH_3; R_3 = H



k, R = ; R_1 = CH_2CN; R_2 = OCH_3; R_3 = H

bufalin methyl ester provided tetrahydropyran **5**. Saponification of methyl ester **4b** with sodium hydroxide in ethanol essentially as described[3] for isoscillaridin A gave isobufalin (**4c**). The H-22–H-23 coupling constant in each case (**4a**–**4c**) remained at 15 Hz. To further confirm the structure and D-ring stereochemistry of isobufalin and in turn that of bufalin, total[7] synthesis of isobufalin was undertaken.

The initial plan was first to protect hemiacetal acetate **8b**, prepared (**6** → **7** → **8a** → **8b**) from digitoxigenin as already described,[1] by oxidation to lactone **8c** as reported by Schindler and Reichstein.[8] Following extension of the side chain by one methylene group and conversion into acid chloride **9b**, diborane reduction of the δ lactone was expected[9] to result in formation of isodigitoxigenin homolog **10**. The 14β,21-epoxybufanolide **10** was to serve as springboard to both isobufalin and bufalin. In practice, chromium trioxide–glacial acetic acid oxidation of diacetate **8b** gave lactone **8c**, and the same substance was more easily obtained by analogous oxidation of acetal **8d** or **8e**.[1] Ester **8c** was saponified and the product was acetylated to give acid **8g**. This was neutralized with an equivalent amount of sodium methoxide in methanol to give the corresponding sodium salt. After drying, the salt was converted into the acid chloride and treated successively with diazomethane and silver benzoate in dry methanol–triethylamine. Completion of the Arndt–Eistert[10] sequence and purification by column and preparative layer chromatography gave a pure specimen of lactone **9c**. Methyl ester **9c** was transformed into acid chloride **9b** as already noted with acid chloride **8h**. Several attempts to reduce lactone **9b** using diborane in tetrahydrofuran followed by intramolecular cyclization to lactone **10** were unrewarding. In a typical instance, following dilution with water three neutral and two acidic products were obtained. While lactone **10** was not detected, one of the acidic products seemed (by thin layer chromatographic behavior) to be vinyl ether **11a**. Before this route to lactone **10** or acid **11a** could be improved, a more efficient alternative became available.

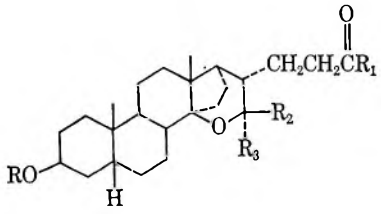
Equatorial acetal **8e**[1] was converted into alcohol **8i** by saponification, methylation, reaction with dihydropyran, and reduction with lithium aluminum hydride in 88% yield. The crystalline alcohol, upon reaction with methanesulfonyl chloride in pyridine, gave oily mesylate **8j**. Nucleophilic displacement of mesylate by reaction with sodium cyanide in dimethylformamide provided crystalline nitrile **8k** in 89% yield. On saponification in ethylene glycol containing potassium hydroxide followed by acidification, nitrile **8k** afforded acid **9d**, which in refluxing acetic acid–water was converted almost completely into vinyl ether **11a**. Elimination of methanol from acetal **9d** was also realized using *p*-toluenesulfonic acid in benzene. However, the acetic acid–water procedure was preferred. An alternative pathway to acid **11a** proceeded from dihydropyran **12a**.[1] The alcohol (**12b**) → mesylate (**12c**) → nitrile (**12d**) →

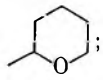
(7) Total synthesis of digitoxigenin (**6**) from, *e.g.*, 3β-acetoxy-17-oxo-5β-androstane, has been described by Sondheimer and colleagues; for leading references see ref 4.

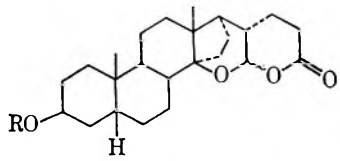
(8) O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **39**, 1876 (1956).

(9) Consult G. R. Pettit, B. Green, G. L. Dunn, P. Hofer, and W. J. Evers, *Can. J. Chem.*, **44**, 1283 (1966), footnote 6, and G. R. Pettit, J. C. Knight, and W. J. Evers, *ibid.*, **44**, 807 (1966), for pertinen treferences to the unreactivity of acid halides toward diborane and reduction of lactones to hemiacetal derivatives by diborane.

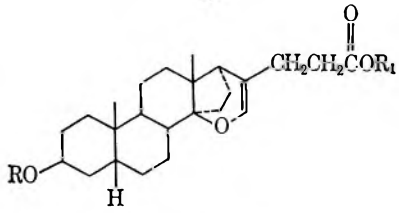
(10) See, *e.g.*, M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5163 (1950); J. Klein and E. D. Bergmann, *J. Org. Chem.*, **22**, 1019 (1957).



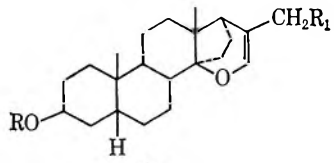
9a, R = $COCH_3$; $R_1 = OCH_3$; $R_2 = R_3 = O$
b, R = $COCH_3$; R_1 = Cl; $R_2 = R_3 = O$
c, R = $COCH_3$; $R_1 = OCH_3$; $R_2 = R_3 = O$
d, R =  ; R_1 = OH; $R_2 = OCH_3$; R_3 = H
e, R =  ; $R_1 = OCH_3$; $R_2 = OCH_3$; R_3 = H
f, R = $COCH_3$; $R_1 = OCH_3$; $R_2 = OCH_3$; R_3 = H

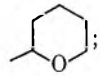
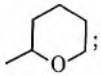


10



11a, R = R_1 = H
b, R = $COCH_3$; $R_1 = CH_3$
c, R = H; $R_1 = CH_3$
d, R = $COCH_3$; R_1 = H



12a, R =  ; $R_1 = CO_2CH_3$
b, R =  ; $R_1= CH_2OH$
c, R =  ; $R_1 = CH_2OSO_2CH_3$
d, R =  ; $R_1 = CH_2CN$
e, R = H; $R_1 = CH_2CN$

carboxylic acid (**11a**) procedure again proved effective, and the corresponding 3β-acetoxy methyl ester **11b** was crystallized and characterized.

The final step necessary for interrelating digitoxigenin with bufalin through isobufalin was performed[11] by heating methyl ester **11b** and 2,3-dichloro-5,6-dicyano-benzoquinone in refluxing dioxane. After purification by chromatography, 36 mg of methyl ester **11b** yielded 25 mg of 3β-acetoxyisobufalin methyl ester (**4b**) identical with an authentic specimen prepared from bufalin. The total synthesis of isobufalin (**4c**) was thereby completed.

Experimental Section[12]

3β-Acetoxyisobufalin Methyl Ester (4b).—To a solution of bufalin (**3**, 0.10 g) in dry methanol (5 ml) was added 5% sodium methoxide in methanol (5 ml). The clear solution was allowed to stand at room temperature for 12 hr. Following acidification with 1 *N* hydrochloric acid and dilution with water, the mixture was extracted with chloroform. The combined extract was washed with water. Removal of solvent gave a solid residue (**4a**, 0.10 g) which crystallized as needles, mp 210–213°, from acetone–diethyl ether. An analytical specimen with unchanged melting point displayed the following data: $[\alpha]_D$ −71° (*c* 0.41); RD (*c* 0.20) $[\alpha]_{350}$ −1000°, $[\alpha]_{400}$ −350°, $[\alpha]_{450}$ −210°, $[\alpha]_{500}$ −130°, $[\alpha]_{589}$ −100°, and $[\alpha]_{600}$ −100°; $\lambda_{max}^{cyclohexane}$ 293 mμ (ε 27,520); λ_{max}^{Nujol} 2.82, 5.90, 6.2, 6.26, 11.35, and 11.8 μ; pmr δ 1.0 (C-18 and -19 methyls), 3.73 (methyl ester), 4.13 (H-3α), 5.63 (doublet, *J* = 15 Hz, H-23), 6.58 (H-21), and 7.23 (doublet, *J* = 15 Hz, H-22).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 76.96; H, 9.06; O, 15.98. Found: C, 74.48; H, 8.91; O, 16.42.

Isobufalin methyl ester (**4a**, 0.46 g) was acetylated and the crude product was chromatographed on basic alumina (12 g). Elution with 1:1 hexane–benzene gave **3β-acetoxyisobufalin methyl ester (4b)**. Crystallization from methanol–acetone afforded 0.40 g as small plates: mp 173–175°; RD (*c* 0.48) $[\alpha]_{350}$ −1219°, $[\alpha]_{400}$ −403°, $[\alpha]_{450}$ −252°, $[\alpha]_{500}$ −149°, $[\alpha]_{589}$ −83°, and $[\alpha]_{600}$ −83°; $\lambda_{max}^{cyclohexane}$ 293 mμ (ε 27,120); $\lambda_{max}^{CHCl_3}$ 5.78, 5.81, 6.24, 7.91, and 8.59 μ; pmr δ 1.0 (C-18 and -19 methyls), 2.05 (C-3 acetate), 3.73 (methyl ester), 5.09 (H-3α), 5.63 (d, *J* = 15 Hz, H-23), 6.59 (H-21), and 7.23 (d, *J* = 15 Hz, H-22).

Anal. Calcd for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65; O, 18.07. Found: C, 73.52; H, 8.68; O, 17.19.

Isobufalin (4c).—To isobufalin methyl ester (**4a**, 0.18 g) in warm ethanol (45 ml) was added hot 2 *N* sodium hydroxide solution (45 ml). The mixture was heated on the steam bath for 10 min, water (90 ml) was added, and heating was continued for another 10 min. After cooling, the mixture was acidified to *ca.* pH 6 with 1 *N* sulfuric acid. The crystals, mp 200–210°, which separated were collected and washed with water. Recrystallization from dioxane gave a pure sample of isobufalin as large needles: mp 212–215° (sintering from 205°); $[\alpha]_D$ −63° (*c* 0.32); RD (*c* 0.48) $[\alpha]_{350}$ −1000°, $[\alpha]_{400}$ −438°, $[\alpha]_{450}$ −250°, $[\alpha]_{500}$ −156°, $[\alpha]_{589}$ −125°, and $[\alpha]_{600}$ −125°; λ_{max}^{KBr} 2.94 (broad), 5.86, 6.17, 8.5, 9.57, and 11.76 μ; pmr δ 1.00 (C-18 and -19 methyls), 5.21 (2 H),[13] 5.63 (doublet, *J* = 15 Hz, H-22), 6.63 (H-21), and 7.31 (doublet, *J* = 15 Hz, H-23).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.56. Found: C, 74.10; H, 9.11; O, 16.62.

Methylation of isobufalin using ethereal diazomethane gave exclusively isobufalin methyl ester (**4a**).[14]

Methyl 3β-Acetoxy-14β,21-epoxy-20 ζ-nor-5β-cholanate (5).—A mixture of isobufalin methyl ester (**4a**, 0.15 g) in methanol (15 ml)–tetrahydrofuran (5 ml) containing suspended platinum from platinum oxide (0.075 g) was stirred under a slight positive pressure of hydrogen for *ca.* 8 hr. The solution was filtered and collected catalyst was washed with diethyl ether. Removal of solvent from the filtrate gave an oily residue which was partially purified by filtration in benzene through basic alumina (5 g). Attempts to induce crystallization were unsuccessful and an

(11) We wish to thank Dr. A. D. Cross and Dr. J. A. Edwards for kindly providing us, prior to publication, with the experimental details of their procedure for dehydrogenating lactones with DDQ. In this regard refer to A. D. Cross, U. S. Patent 3,296,278 (1967); *Chem. Abstr.*, **66**, 6203 (1967); D. Bevlos, L. Cuellan, R. Grezemkovsky, M. V. Avila, and A. D. Cross, *Proc. Chem. Soc.*, 215 (1964); D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(12) Bufalin was used as received from Aldrich Chemical Co., Milwaukee, Wis. Unless otherwise stated, the introduction to the Experimental Section of part 8[1] provides necessary general information for the following experimental summaries.

(13) The δ 5.21 signal disappears upon shaking the deuteriochloroform solution with deuterium oxide. In three different determinations the signal shifted from δ 5.91 to 6.47 and therefore appeared concentration dependent. As no signal corresponding to the carboxyl proton appeared in the spectrum from δ 8 to 15 the signal at δ 5.21 was tentatively assigned to the 3β-hydroxy and carboxyl proton.

(14) Confirmation of identical composition was obtained by results of thin layer chromatographic, proton magnetic resonance, and infrared spectral (in potassium bromide) comparison.

analytical sample was prepared by preparative layer chromatography with 1:1 hexane–ethyl acetate mobile phase and evaporative distillation at 140–150° (bath temperature) and 0.3 mm: $[\alpha]_D$ +25° (*c* 0.52); λ_{max}^{neat} 5.78, 8.0, 8.13, 8.59, and 9.80 μ; pmr δ 0.99 and 1.09 (C-18 and -19 methyls), 2.02 (C-3 acetate), 3.65 (methyl ester), and 5.09 (H-3α).

Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48; O, 17.91. Found: C, 72.93; H, 9.16; O, 17.88.

Methyl 3β-Acetoxy-14β,21-epoxy-21-oxonor-5β-(20*S*)-cholanate (8c). Method A.—The digitoxigenin (6) → isodigitoxigenin (7) → isodigitoxigeninic acid (8a) → methyl 3β-(21*S*)-diacetoxy-14β,21-epoxynor-5β-(20*S*)-cholanate (**8b**) sequence was repeated as previously reported.[1] Diacetate **8b** in 0.20-g portions was oxidized with 2% chromium trioxide in glacial acetic acid essentially as summarized by Schindler and Reichstein.[8] A solution of the crude product in chloroform was passed through a column of basic alumina (20 g). Following removal of solvent, the residue was recrystallized from diethyl ether–acetone–hexane to yield lactone **8c** (70%), mp 135–138° (lit.[8] mp 145–148°). Several attempts to perform chromium trioxide oxidation of diacetate **8b** on a scale larger than 0.20 g afforded lesser yields of lactone **8c**. Accordingly, larger quantities of lactone **8c** prepared using methods A or B were obtained using a series of 0.20-g scale oxidations.

Method B.—Isodigitoxigenin (**7**) was transformed to equatorial acetal **8d** as previously summarized.[1] A solution of acetal **8d** (0.15 g) in glacial acetic acid (2 ml) was treated with 2% chromium trioxide in glacial acetic acid (2 ml) and the mixture was allowed to remain at room temperature for 4 hr. Excess oxidizing agent was destroyed in the violet solution by adding methanol. After a 12-hr period at room temperature, most of the solvent was removed *in vacuo* at 35° and the residue was diluted with 0.1 *N* sulfuric acid (50 ml) and chloroform (30 ml). The mixture was extracted with chloroform and the combined solvent extract was washed successively with water, dilute sodium bicarbonate, and water. Passage of the chloroform solution through a column of basic alumina (10 g) and removal of solvent gave 0.13 g of semisolid. Preparative layer chromatography with 1:4 hexane–ethyl acetate mobile phase gave 0.08 g of lactone **8c**. Recrystallization from diethyl ether–acetone–hexane provided needles: mp 137–139° (a mixture melting point with lactone **8c** prepared by method A was 138–140°); pmr δ 1.02 and 1.12 (C-18 and -19 methyls), 2.05 (C-3 acetate), 3.72 (methyl ester), and 5.09 (H-3α).

By using the procedure just described, equatorial acetal **8e** (0.10 g) was also oxidized to lactone **8c**. Purification by preparative layer chromatography afforded 0.02 g, mp 136–138°. Specimens of lactone **8c** obtained by methods A and B were mutually identical.[14]

Methyl 3β-Acetoxy-14β,21-epoxy-21-oxo-5β-(20*S*)-cholanate (9a).—In a typical experiment, methyl 3β-acetoxy-14β,21-epoxy-21-oxonor-5β-(20*S*)-cholanic acid was saponified with 5% potassium hydroxide in methanol (5 hr at reflux) and the crude product was acetylated with 1:5 acetic anhydride–pyridine overnight at room temperature. The acetylation mixture was poured onto ice and the pH was adjusted to *ca.* 5 with 2 *N* hydrochloric acid. Before extraction with chloroform, the mixture was allowed to remain at room temperature for 15 min to hydrolize mixed anhydride. By removal of solvent *in vacuo* and recrystallization of the crude product from diethyl ether, a sample of 3β-acetoxy acid **8f**, mp 238–240°, was obtained. A 0.40-g specimen of acid **8f** in methanol was neutralized with an equivalent quantity of sodium methoxide in methanol. Solvent was removed at room temperature and the residue was dried for 16 hr at 80° (20 mm), powdered, and redried for 3 hr at 100° (0.1 mm). A suspension of the sodium salt in dry benzene was stirred in a nitrogen atmosphere and cooled until part of the solvent crystallized. At this point, oxalyl chloride[15] (10% excess) in benzene was added over a period of 30 min, while the reaction temperature was maintained at 5–10° so that the benzene phase was partially frozen. Before addition of dry collidine (4 μl) and additional oxalyl chloride (0.1 ml), stirring was continued at room temperature for 30 min. Fifteen minutes later, solvent was evaporated at 25°. A solution of acid chloride **8h** in benzene was slowly added to excess diazomethane in diethyl ether. The reaction mixture was allowed to remain at *ca.* 0° for 36 hr. Evaporation of the solvent and excess diazomethane gave a residue which was dissolved in superdry methanol (10 ml), and a solution of freshly prepared (and dry) silver benzoate (0.3 g) in dry triethylamine (3 ml) was added. After a lapse of 45 min, 23 ml of nitrogen was evolved. Stirring was continued for a total of 1 hr, at which time evolution of nitrogen appeared complete. Solvent was removed at 30° and the residue in benzene was passed through a column of neutral alumina (20 g, E. Merck, Darmstadt). Elution with either benzene or diethyl ether gave a fraction (0.35 g), which was further purified by preparative layer chromatography with 1:4 hexane–ethyl acetate mobile phase. The least polar zone was eluted with chloroform to yield 0.26 g of semisolid, which crystallized from acetone–hexane. Recrystallization from the same solvent gave 0.19 g, mp 118–121°. Final purification was achieved by chromatography of the ester in diethyl ether on basic alumina (1 g) and recrystallization of a fraction eluted with the same solvent from hexane–diethyl ether. By this means a crystalline, analytical sample of lactone **9a**, mp 130–132°, was prepared: pmr δ 0.98 (C-18 methyl), 1.04 (C-19 methyl), 1.98 ($OCOCH_3$), 2.28 (multiplet, C-22 and C-23 methylene), 3.56 (OCH_3), and 4.92 (H-3α).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.39; H, 8.75. Found: C, 70.28; H, 9.02.

Methyl 3β-Tetrahydropyranyloxy-14β,21-epoxy(21*S*)-methoxy-23-hydroxy-5β-(20*S*)-norcholane (8i).—A solution of methyl 3β-tetrahydropyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norcholanate (7.55 g)[1] in dry diethyl ether (100 ml) was added over a 30-min period to a cold (ice bath) mixture of lithium aluminum hydride (3.0 g) and dry diethyl ether (600 ml). Stirring at ice-bath temperature was continued for 2.5 hr. Excess lithium aluminum hydride was removed by cautious addition of ice-water and the ethereal layer was separated. The aqueous phase was extracted with diethyl ether and the combined etheral extract was washed with water. Evaporation of the ether gave a colorless oil which slowly solidified. Recrystallization of the residue from acetone–ligroin afforded alcohol **8i** as large prisms (4.34 g). Concentration of mother liquors provided 3.2-g of a pale brown oil. The mother liquor residue in benzene was chromatographed on basic alumina (200 g). Elution with the same solvent gave an additional 1.8 g of alcohol **8i**. An analytical specimen recrystallized from acetone–pentane as thick, rectangular plates: mp 149–151°, $[\alpha]_D$ + 187° (c 0.24); $\lambda_{max}^{CHCl_3}$ 2.06 μ; pmr δ 0.98 and 1.06 (C-18 and -19 methyls), 3.50 (C-21 methoxy), 4.0 (pyranyl ether acetal proton), 4.30 (doublet, J = 8 Hz, H-21), and 4.66 (H-3α).

Anal. Calcd for $C_{29}H_{48}O_5$: C, 73.07; H, 10.15; O, 16.78. Found: C, 73.34; H, 10.13; O, 16.27.

Methyl 3β-Tetrahydropyranyloxy-14β,21-epoxy-(21*S*)-methoxy-23-cyano-5β-(20*S*)-norcholane (8k).—To a solution of alcohol **8i** (6.0 g) in pyridine (20 ml) was added at 0° with stirring methanesulfonyl chloride (3.0 g) in pyridine (5 ml). Before dilution with diethyl ether, stirring was continued for 3 hr at ice-bath temperature. The ethereal solution was repeatedly washed with water and concentrated to a pale yellow oil with no appreciable infrared hydroxyl absorption. A solution of the oily residue in 1:1 ligroin–benzene was chromatographed on basic alumina. Elution with the same solvent gave 5.85 g of mesylate **8j** as a colorless oil that crystallized on standing. Without further purification the mesylate (5.85 g) was dissolved in dimethylformamide (100 ml). The solution was stirred at room temperature and sodium cyanide (2.4 g) was added. Stirring was continued for 22 hr and the pale yellow solution was diluted with water, cooled, and filtered. The white solid was crystallized from acetone–water to give nitrile **8k** as colorless needles (4.6 g): mp 175–177° after three recrystallizations from the same solvent; $[\alpha]_D$ +35° (*c* 1.05); RD (*c* 1.40) $[\alpha]_{400}$ +54°, $[\alpha]_{450}$ +43°, $[\alpha]_{500}$ +36°, $[\alpha]_{589}$ +22°, $[\alpha]_{600}$ +22°; $\lambda_{max}^{CHCl_3}$ 4.42 μ; pmr δ 0.98 and 1.08 (C-18 and -19 methyls), 3.48 (C-21 methoxyl), 4.0 (tetrahydropyranyl acetal proton), 4.26 (doublet, J = 8 Hz, H-21), and 4.68 (H-3α).

Anal. Calcd for $C_{30}H_{47}NO_4$: C, 74.19; H, 9.75; N, 2.88; O, 13.18. Found: C, 74.41; H, 9.81; N, 3.02; O, 12.77.

3β-Tetrahydropyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-cholanic Acid (9d).—A solution of nitrile **8k** (4.56 g) and potassium hydroxide (14 g) in ethylene glycol (140 ml) was heated at reflux and stirred in a nitrogen atmosphere for 3 hr. Upon cooling, the clear, pale yellow solution was diluted with water and acidified with concentrated hydrochloric acid. The aqueous mixture was extracted with diethyl ether and the combined extract was concentrated to an oil. Trituration with acetone caused slow crystallization to yield 4.25 g of acid **9d**: pmr δ 0.98

(15) Commercial oxalyl chloride was heated at reflux for 10 min and then distilled from freshly fused and powdered potassium carbonate. The redistilled oxalyl chloride was stored over anhydrous potassium carbonate.

and 1.06 (C-18 and -19 methyls), 3.48 (C-21 methoxyl), 4.0 (tetrahydropyranyl acetal proton), 4.27 (doublet, J = 8 Hz, H-21), 4.70 (H-3α), and 9.33 (carboxylate proton). The acid (0.15 g) was characterized as the methyl ester, prepared using diazomethane. The resulting ester **9e** was purified by chromatography in hexane on basic alumina (4 g). Elution with 1:3 hexane–benzene gave a solid fraction (0.1 g). Recrystallization from acetone–hexane afforded methyl ester **9e** as needles: mp 123–125°; $[\alpha]_D$ +88° (c 0.50); $\lambda_{max}^{CHCl_3}$ 5.78 μ; pmr δ 0.97 and 1.03 (C-18 and -19 methyls), 3.44 (C-21 methoxyl), 3.66 (methyl ester), 3.96 (tetrahydropyranyl acetal proton), 4.26 (doublet, J = 8 Hz, H-21), and 4.67 (H-3α).

Anal. Calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.72; O, 18.51. Found: C, 71.66; H, 9.42; O, 19.02.

Tetrahydropyranyloxy methyl ester **9e** was converted into the 3β-acetate **9f** as follows. To a solution of ester **9e** (1.1 g) in methanol (50 ml) was added water (1 ml) and *p*-toluenesulfonic acid (0.10 g). After having been stirred at room temperature for 3.25 hr, the solution was diluted with water and extracted with diethyl ether. Concentration of the ether layer gave an oil which was held *in vacuo* for 2 hr at 60° and then dissolved in a mixture of acetic anhydride (5 ml)–pyridine (5 ml). The solution was allowed to stand at room temperature overnight, diluted with ice–water, and extracted with ether. The ethereal layer was washed with 2 *N* hydrochloric acid and saturated sodium bicarbonate solution and evaporated. Crystallization of the residue from aqueous methanol gave **3β-acetoxy methyl ester 9f** as fine needles (first crop 0.32 g), mp 108–110°, $[\alpha]_D$ +20.7° (c 1.11).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.58; H, 9.34.

3β-Tetrahydropyranyloxy-14β,21-epoxy-23-cyano-5β-norchol-20(21)-ene (**12d**).—A sample of methyl 3β-tetrahydropyranyloxy-14β,21-epoxy-5β-norchol-20(21)-enate (**12a**, 3.5 g) prepared as noted in part 8[1] was reduced in diethyl ether (600 ml) solution with lithium aluminum hydride (1.5 g) as summarized above for obtaining alcohol **8i**. The colorless, oily sample of alcohol **12b** weighed 3.3 g and exhibited a single spot upon thin layer chromatography with 1:4 ethyl acetate–chloroform mobile phase: pmr 0.98 (C-18 methyl), 1.04 (C-19 methyl), 3.98 (THP-yl acetal H), 5.16 (H-3), and 5.94 (H-21). Allowing the oily alcohol (**12b**, 3.3 g) in pyridine (20 ml) to react with methanesulfonyl chloride (1.6 g) in benzene (10 ml) as summarized in the case of sulfonate **8j** afforded mesylate **12c** as a pale yellow, viscous oil (3.4 g) displaying no hydroxyl absorption in the infrared spectrum. As with alcohol **12d**, further purification of mesylate **12c** by column chromatography on basic alumina again gave a product resistant to crystallization. However, the now colorless oily mesylate was sufficiently pure for conversion into nitrile **12d**. Mesylate **12c** (3.4 g) in dimethylformamide (50 ml) was treated with sodium cyanide (1.5 g) as summarized above for the preparation of nitrile **8k**. In this experiment the crude product in ligroin was chromatographed on silica gel. A 1.0-g fraction eluted by 19:1 ligroin–ethyl acetate corresponded to nitrile **12d** and displayed one spot on a thin layer chromatogram with 1:39 ethyl acetate–chloroform mobile phase. A pure sample recrystallized from acetone–water or from pentane as platelets: mp 136–138°; $[\alpha]_D$ −46° (c 0.30); λ_{max}^{Nujol} 4.44 and 6.24 μ; pmr δ 1.0 and 1.04 (C-18 and -19 methyls), 2.32 (multiplet, C-22 and C-23 methylenes), 4.0 (tetrahydropyranyl acetal proton), 4.14 (H-3α), and 6.0 (H-21).

Anal. Calcd for $C_{29}H_{43}NO_3$: C, 76.78; H, 9.55; N, 3.09; O, 10.58. Found: C, 76.94; H, 9.71; N, 3.23; O, 10.42.

Further elution of the silica gel column with ethyl acetate provided the corresponding 3β-hydroxy derivative **12e** (0.50 g): λ_{max}^{neat} 2.90–2.98, 4.42, and 6.02 μ; pmr δ 1.02 and 1.06 (C-18 and -19 methyls), 4.15 (H-3α), and 5.99 (H-21). Removal of the pyranyloxy group from nitrile **12d** (1.0 g) was achieved by dissolution in methanol (80 ml)–water (1 ml) containing *p*-toluenesulfonic acid (0.10 g). After the solution had been stirred for 3 hr at room temperature, essentially quantitative conversion into alcohol **12e** was realized. The glassy alcohol **12e** was combined with the 0.5-g quantity and hydrolyzed to hydroxy acid **11a** as outlined in the following experiment.

Methyl 3β-Acetoxy-14β,21-epoxy-5β-chol-20(21)-enate (**11b**).—A solution of hydroxy nitrile **12e** (1.55 g) was hydrolyzed with potassium hydroxide (4.5 g) in ethylene glycol (50 ml, redistilled from potassium hydroxide) as summarized above with nitrile **8k** (see **9c**). A colorless, viscous, oily specimen of acid **11a** (1.38 g) was obtained: pmr δ 0.98 and 1.02 (C-18 and -19 methyls), 2.28 (multiplet, C-22 and C-23 methylene), 4.16 (H-3α), 5.90 (H-21), and 5.90 (broad) (carboxylate disappeared on addition of D_2O). No signals appeared further downfield.

Hydroxy acid **11a** was methylated with ethereal diazomethane and acetylated. The product was chromatographed on basic alumina (5 g). Elution with hexane–benzene (3:1) led to oily methyl ester **11b** (0.1 g), which crystallized from methanol as prisms: mp 104–106°; $[\alpha]_D$ −17.4° (c 0.86); RD (c 1.05) $[\alpha]_{300}$ −119°, $[\alpha]_{350}$ −76°, $[\alpha]_{400}$ −52°, $[\alpha]_{450}$ −38°, $[\alpha]_{500}$ −26°, $[\alpha]_{589}$ −21°, and $[\alpha]_{600}$ −21°; γ_{max}^{KBr} 1742, 1662, and 1255 cm^{-1}; pmr δ 1.07 (C-18 and -19 methyls), 2.07 (C-3 acetate), 3.67 (methyl ester), 5.1 (H-3α), and 5.89 (H-21).

Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; O, 17.99. Found: C, 72.54; H, 9.18; O, 18.06.

Conversion of Methyl 3β-Tetrahydropyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-cholanate (**9d**) **into Derivatives of 3β-Hydroxy-14β,21-epoxy-5β-chol-20(21)-enic Acid** (**11a**).—A solution of acetal **9d** (0.10 g) in benzene (10 ml) containing *p*-toluenesulfonic acid (0.02 g) was heated at reflux for 1.5 hr. After cooling, the solution was diluted with diethyl ether and washed with water, dilute sodium bicarbonate, and water. Following removal of solvent the brown oily residue was purified by preparative layer chromatography with 1:9 ethyl acetate–chloroform mobile phase. Several bands were detected, three of which appeared dark under ultraviolet light. The largest zone did not absorb ultraviolet light, and upon elution with diethyl ether gave 0.016 g of oily dihydropyran **11c**. Vinyl ether **11a** could be conveniently prepared by heating for 30 min at reflux a solution prepared from acid **9d** (3.09 g) and acetic acid (100 ml)–water (50 ml). Acid **11a** was isolated by ether extraction as an oil, which was acetylated using 1:1 acetic anhydride–pyridine (20 ml) at steam-bath temperature for 15 min to give acetoxy acid **11d** (2.78 g). Methylation with diazomethane gave acetoxy methyl ester **11b** which was in every way identical[14] with the product prepared from the nitrile **12e** as described above.

Conversion of Methyl 3β-Acetoxy-14β,21-epoxy-5β-chol-20(21)-enate to 3β-Acetoxyisobufalin Methyl Ester (**4b**).—A solution of ester **11b** (0.036 g) and 2,3-dichloro-5,6-dicyanobenzoquinone (0.030 g) in dry dioxane (5 ml) was heated at reflux for 20 hr. Following cooling the mixture was diluted with methylene chloride and the solid phase was collected and washed with additional methylene chloride. The combined filtrate was passed through a column of neutral alumina (3 g). Removal of solvent from the methylene chloride eluate provided an 0.025-g residue which crystallized as needles, mp 172–174°, from methanol–acetone. A mixture melting point with an authentic sample prepared from bufalin (see **4b**) of 3β-acetoxyisobufalin methyl ester was undepressed. The mutual identity of both specimens was confirmed by comparing ultraviolet, infrared, optical rotatory dispersion, and proton magnetic resonance spectra. In each case, spectra of the methyl ester **11b** dehydrogenation product were superimposable upon those of 3β-acetoxyisobufalin methyl ester prepared from bufalin.

Registry No.—**4a**, 23337-64-6; **4b**, 23337-65-7; **4c**, 23337-66-8; **5**, 23337-67-9; **8c**, 23337-68-0; **8i**, 23337-69-1; **8k**, 23337-70-4; **9a**, 23337-71-5; **9e**, 23337-72-6; **9f**, 23359-80-0; **11b**, 17150-46-8; **12d**, 23337-73-7; **12e**, 23337-74-8.

Bufadienolides. 10. 3β-Acetoxy-14β,21-epoxy-5β-bufanolide and Related Lactones[1,2a]

JOHN C. KNIGHT, GEORGE R. PETTIT,[2b] AND PETER BROWN

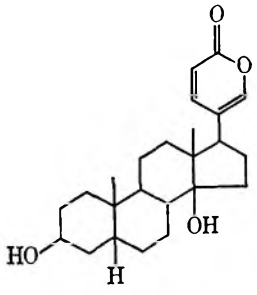
Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received February 11, 1969

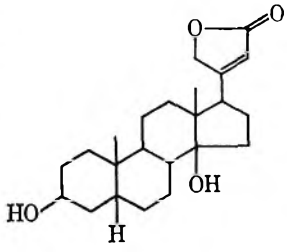
Methyl 3β-pyranyloxy-(21*S*)-methoxy-14β,21-epoxy-5β-(20*S*)-norcholanate (**6a**) and the axial acetal **6b** each gave isodigitoxigenin (**3a**) on treatment with hydrochloric acid in aqueous acetic acid. Extension of this reaction to cholanate ester **7b** gave 3β-acetoxy-14β,21-epoxy-5β-bufanolide (**4**). The epoxide **9** prepared from 3β-acetoxy-14β,21-epoxy-5β-chol-20(21)-enic acid (**8b**) spontaneously cyclized to give γ-lactones of type **11** rather than δ-lactone derivatives. In another potential approach to bufadienolides, 3β-pyranyloxy-23-mesyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norcholane (**7d**) was converted into 3β-acetoxy-14β,21-epoxy-20-formylpregn-20(21)-ene (**15a**). Condensation of aldehyde **15a** with malonic acid took an unexpected course which culminated in formation of olefin **18**.

Two important considerations in a potentially useful synthesis of bufalin (**1**) are protection of the 14β-hydroxyl group and prevention of isomerization at position 17. In attempting to prepare bufalin from digitoxigenin (**2**) it seemed that both obstacles could be avoided by utilizing the cyclic acetal isodigitoxigenin (**3a**). Expansion of the lactone ring to give 14β,21-epoxybufanolide **4** followed by conversion into unsaturated lactone **5** and cleavage of the acetal linkage would then give bufalin (**1**).

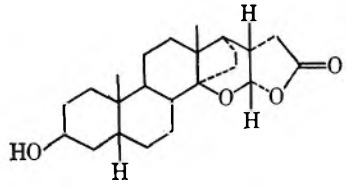
The previous two papers in this series[2,3] described conversion of isodigitoxigenin into acetals **6a** and **6b** and homologation of compound **6a** to acetal **7a**. Model experiments determined that **6a** could be recyclized to isodigitoxigenin (**3a**) in excellent yield by treatment with hydrochloric acid in aqueous acetic acid.[4] Similar treatment of acetal **7b** gave a mixture of products, which after remethylation and reacetylation could be separated by column chromatography into three principal components. Vinyl ether **8a**[2] was present in largest amount (42%) together with a substance (28%) which showed two pmr acetate signals at δ 2.06 and



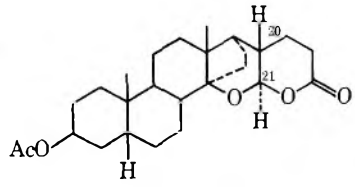
1



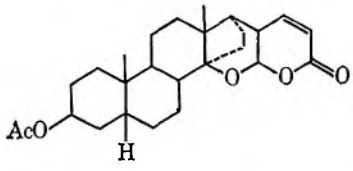
2



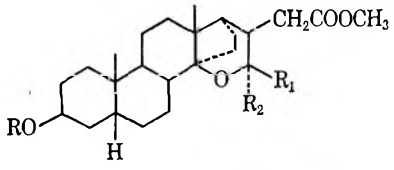
3a, R = H
b, R = $COCH_3$



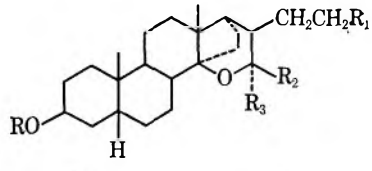
4



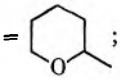
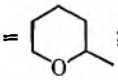
5



6a, R = tetrahydropyranyl; $R_1 = OCH_3$; $R_2 = H$
b, R = $COCH_3$; $R_1 = H$; $R_2 = OCH_3$



7a, R =  ; $R_1 = COOCH_3$; $R_2 = OCH_3$; $R_3 = H$

b, R = $COCH_3$; $R_1 = COOCH_3$; $R_2 = OCH_3$; $R_3 = H$
c, R = $COCH_3$; $R_1 = COOCH_3$; $R_2 = OCOCH_3$; $R_3 = H$
d, R =  ; $R_1 = OSO_2CH_3$; $R_2 = OCH_3$; $R_3 = H$
e, R =  ; $R_1 = I$; $R_2 = OCH_3$; $R_3 = H$
f, R =  ; $R_1 = OH$; $R_2 = OCH_3$; $R_3 = H$

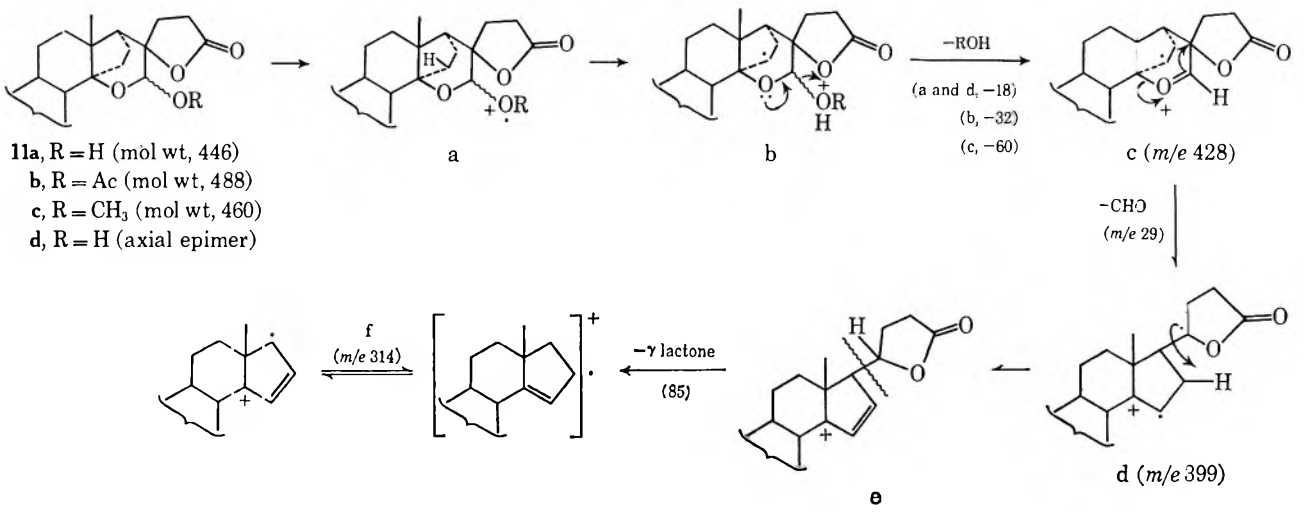
(1) This investigation was supported by Public Health Service Research Grants CA-10115-01 and CA-10115-02 from the National Cancer Institute. Purchase of the Atlas CH-4B and SM-1B mass spectrometers was made possible through Grants GB-4939 and GP-6979, respectively, from the National Science Foundation.

(2) (a) Preceding contribution: G. R. Pettit, T. R. Kasturi, J. C. Knight, and K. A. Jaeggi, *J. Org. Chem.*, **35**, 1410 (1970). (b) To whom inquiries should be addressed.

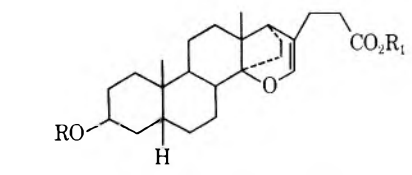
(3) G. R. Pettit, T. R. Kasturi, J. C. Knight, and J. Occolowitz, *J. Org. Chem.*, **35**, 1404 (1970).

(4) G. Buchi, D. M. Foulkes, M. Kurono, G. D. Mitchell, and R. S. Schneider, *J. Amer. Chem. Soc.*, **89**, 6745 (1967).

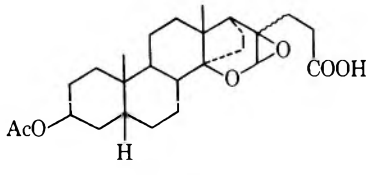
SCHEME I
FRAGMENTATION OF γ LACTONES 11a–11d



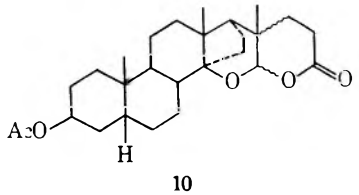
2.12. The mass spectrum also indicated the presence of two acetate groups, and the new compound was assigned structure **7c**. The most polar product, and that present in the smallest yield (1.6%), was the desired 3β-acetoxy-14β,21-epoxybufanolide **4**. Lactone **4** showed a pmr doublet at δ 5.08 for H-21 (acetal). The 8-Hz coupling constant indicated a *trans* fusion of the δ-lactone and tetrahydropyran rings, *i.e.*, a 20*S*,21*R* configuration.



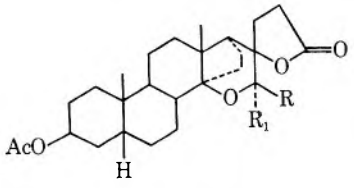
8a, R = $COCH_3$; R_1 = CH_3
b, R = $COCH_3$; R_1 = H
c, R = R_1 = H



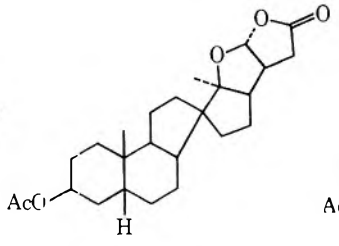
9



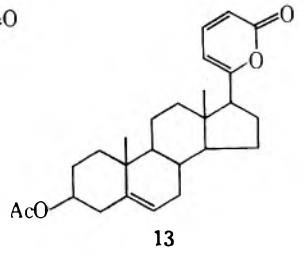
10



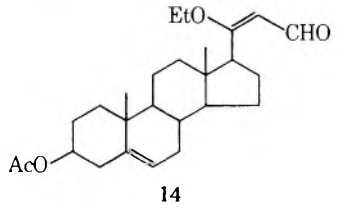
11a, R = OH; R_1 = H
b, R = $OCOCH_3$; R_1 = H
c, R = OCH_3; R_1 = H
d, R = H; R_1 = OH



12



13



14

The low yield in the cyclization step leading to lactone **4** was not encouraging, and other more promising approaches were considered. For example, by analogy with the ready formation of tetrahydropyranyl esters from dihydropyran and carboxylic acids, acid **8b** should undergo intramolecular cyclization to lactone **4**. However, no observable lactone formation could be demonstrated under conditions normally used for this reaction.[5]

In view of the work of Stevens and coworkers on formation and reactions of epoxy ethers,[6] we expected that an epoxypyran such as **9**, formed by *m*-chloroperbenzoic acid oxidation of dihydropyran **8b**, would undergo rapid intramolecular cyclization yielding lactone **10**. The rate of intramolecular reaction would presumably be much faster than the competing intermolecular reaction with *m*-chlorobenzoic acid present in the reaction mixture. Experimentally, reaction rapidly occurred, and after a few minutes acid **8b** was consumed. The product was separated into neutral and sodium hydroxide soluble fractions. The neutral material was a high-melting solid which showed the expected molecular ion at *m/e* 446 ($C_{26}H_{38}O_6$) and a sharp pmr signal at δ 5.32 for an acetal-type proton, but the infrared spectrum showed absorption at 1760 cm^{-1} more typical of a γ-lactone than a δ-lactone. Structure **11a** therefore seemed probable and is supported by mass spectral evidence (Figure 1). A possible scheme which accounts for prominent fragmentation is shown in Scheme I. Empirical formulae of the major fragments were checked by high-resolution mass spectrometry (Table I).

(5) See, *e.g.*, W. S. Johnson, R. C. Christiansen, and R. E. Ireland, *J. Amer. Chem. Soc.*, **79**, 1995 (1957).

(6) C. L. Stevens and J. Tazuma, *ibid.*, **76**, 715 (1954). We wish to thank Professor M. E. Munk for a valuable discussion concerning such epoxy ether reactions.

TABLE I
HIGH-RESOLUTION MASS SPECTRAL DATA

Empirical formula	Calcd mass	Measured mass	
		Lactone **11a**	Lactone **11b**
$C_{24}H_{31}O_2$	339.2323	339.2339	339.2352
$C_{22}H_{31}O_3$	343.2273	343.2269	...
$C_{25}H_{35}O_4$	399.2535	399.2523	...
$C_{26}H_{36}O_5$	428.2562	428.2577	428.2559
$C_{26}H_{38}O_6$	446.2668	446.2711	...

Additional evidence was obtained by examining the acidic fraction. Although it had been extractable by strong base, isolation by acidification and reextraction gave a neutral substance, presumably a lactone, which readily opened and recyclized. As an infrared spectrum of the crude product indicated loss of the 3β-acetate, the alcohol was reacetylated and purified by chromatography. The pmr spectrum showed signals for two acetate groups at δ 2.02 and 2.12, and infrared peaks at 1790 (γ lactone), 1762 (acetal acetate), and 1734 cm^{-1} (acetate) were consistent with a structure such as **11b**. The mass spectrum showed a molecular ion at *m/e* 488, and exhibited the same fragmentation as found in that of hemiacetal lactone **11a**. The major peak at *m/e* 339 in each spectrum is presumably due to further loss of acetic acid from the 3-acetate group of the ions at *m/e* 399 (d).

The γ-lactone **11a** tended to open readily, and even on heating with aqueous methanol was converted into a complex mixture. Two compounds could be isolated by preparative layer chromatography, mp 209–222° and 266–271°, respectively. The former (**11c**) showed typical infrared γ-lactone absorption at 1782 cm^{-1}, a pmr methyl ether peak at δ 3.40, and a molecular ion at *m/e* 460, which indicated methylation of the hemiacetal hydroxyl. In addition, ions at *m/e* 428 (c), 399 (d), 339 (d − 60), and 314 (f) indicated a close structural similarity to starting material **11a** (see Scheme I).

The higher melting compound, of which only a few milligrams was obtained, showed typical γ-lactone infrared absorption at 1772 cm^{-1} and hydroxyl absorption at 3500 cm^{-1}. Therefore the substance with a melting point of 266–271° may be hemiacetal lactone **11d**, the C_{21} epimer of **11a**. The mass spectrum did not show a molecular ion, but prominent ions at *m/e* 428, 399, 339, and 314 were present. Lack of a molecular ion is noteworthy in view of the strong molecular ion shown by **11a**. If a mechanism such as that in Scheme I is operative, then hydrogen transfer (a → b) with subsequent loss of water might be expected to take place much more readily in the isomer with the axial OH-21.

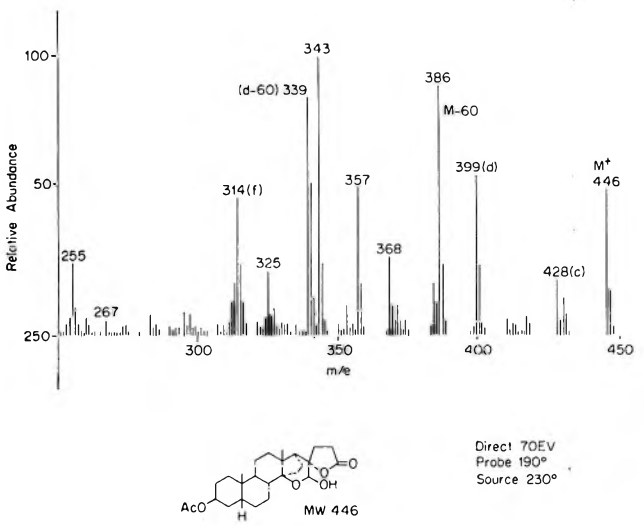
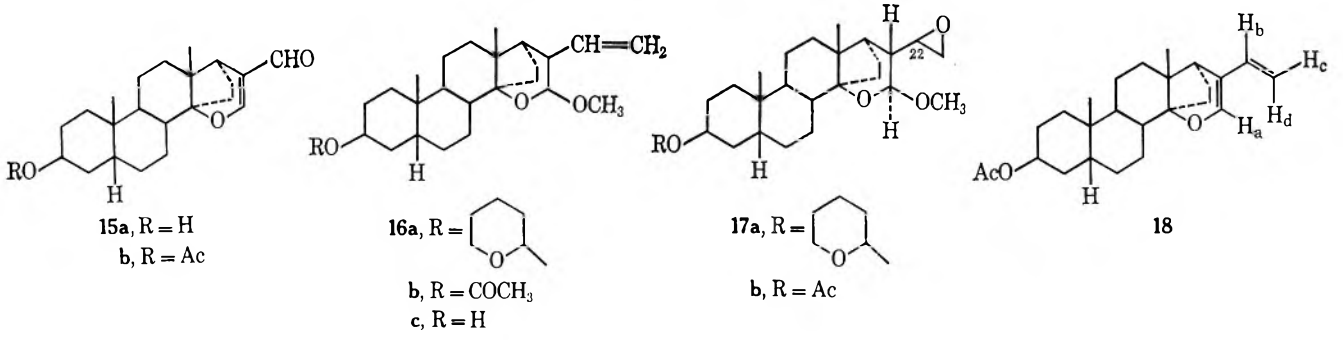


Figure 1.

At this stage, model experiments designed to cleave the 14β,21-epoxy linkage in isodigitoxigenin (**3**) showed that acidic conditions were prone to generate a carbonium ion at C-14, resulting in rearrangement to C-norcardenolides[3] such as **12**. Thus considerable difficulty was expected in effecting conversion of unsaturated lactone **5** into bufalin (**1**), and an alternative approach was investigated. An earlier contribution of this series[7] summarized synthesis of isobufadienolides such as 6′-substituted 2-pyrone **13** from unsaturated aldehyde **14** by condensation with malonic acid in pyridine–piperidine solution. With these experiments in mind we decided to explore an analogous transformation with unsaturated aldehyde **15**. Similar reaction leading to formation of a 5′-substituted 2-pyrone would give bufalin or the 14-dehydro derivative. Aldehyde **15** was prepared as follows. The previously described mesylate **7d**[2] was converted into **7e** with sodium iodide in refluxing acetone, and the product was dehydrohalogenated to olefin **16** with potassium *t*-butoxide in dimethyl sulfoxide.[8] The structure of olefin **16a** was confirmed by the pmr spectrum which showed a complex pattern in the olefinic proton region at δ 4.8–6.2, integrating for three protons and strongly resembling in overall appearance the spectra of compounds with an allylic grouping –CHRCH=CH_2.[9a] Ozonolysis of



(7) G. R. Pettit, J. C. Knight, and C. L. Herald, *J. Org. Chem.*, **35**, 1393 (1970).

(8) N. F. Wood and F. C. Chang, *ibid.*, **30**, 2054 (1965).

(9) (a) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian N.M.R. Spectra Catalog," Varian Associates, 1962, Spectra No. 26, 32, 38, and 136; (b) Spectrum No. 32.

olefin **16** followed by treatment with zinc–acetic acid did not give very satisfactory yields of aldehyde **15a**. Another approach was more effective. Epoxidation of olefin **16a** using *m*-chloroperbenzoic acid gave oily epoxide **17a**, but analogous oxidation of **16b** gave crystalline acetate **17b**. Both epoxides showed a complex three-proton pattern in the pmr spectrum at δ 2.5–3.0 resembling that of propylene oxide.[9b] The 60-MHz spectra were difficult to resolve, and at 100 MHz it was apparent that **17b** was a 1:1 mixture of two epimeric (at C-22) epoxides. For instance, what appeared to be a doublet with J = 8.5 Hz at δ 4.56 in the 60-MHz spectrum (owing to H-21) appeared in the 100-Mz spectrum as a pair of closely spaced doublets with coupling constants of 8.8 and 9.5 Hz. Cleavage of the epoxide with periodic acid[10] and simultaneous loss of methanol from the acetal grouping gave aldehyde **15**. Unfortunately, the aldehyde could not be induced to react under conditions developed for conversion of aldehyde **14** into pyrone **13**. More severe conditions, *i.e.*, refluxing pyridine–piperidine for extended periods, gave complex mixtures, and the only crystalline product isolated was diene **18**. Structure **18** was deduced mainly from the pmr spectrum, which was reminiscent of a compound containing an isolated vinyl group. The splitting pattern was complicated by presence of signals owing to the olefinic H-21 (H_a) and H-3α, but coupling constants of the expected magnitude could still be assigned. Fine splitting owing to allylic coupling was not observed in the 60-MHz spectrum. Structure **18** was further supported by the mass spectrum, which showed a molecular ion at m/e 384, correct for $C_{25}H_{36}O_3$.

Meanwhile other approaches to bufalin began showing greater promise than those summarized above. Further efforts to utilize lactone **4** and aldehyde **15** were discontinued when a useful synthesis of bufalin was achieved employing another route[11].

Experimental Section

Low-resolution mass spectra were secured by E. S. Bebee using an Atlas CH-4B mass spectrometer equipped with "molecular beam" direct probe inlet system and operating under the following conditions: electron energy 70 eV, trap current 19 μA, source temperature 230°, probe temperature 120–190°, accelerating voltage 3 kV. High-resolution measurements were made with an Atlas SM-1B instrument, again using a direct probe inlet system. Other operational parameters follow: electron energy 70 eV, trap current 290 μA, source temperature 230°, probe temperature 120–190°, accelerating voltage 8 kV, apparent resolution 12,500. The mass reference compound was perfluorokerosene.

Unless otherwise stated, introduction to the Experimental Section of part 9[2] provides other necessary general information for the following experimental summaries.

Recyclization of Methyl 3β-Pyranyloxy-(21*S*)-methoxy-14β,21-epoxy-5β-(20*S*)-norcholanate (6a) and Methyl 3β-Acetoxy-(21*R*)-methoxy-14β,21-epoxy-5β-(20*S*)-norcholanate (6b) to Isodigitoxigenin Acetate (3b).—To a solution of acetal **6a** (0.16 g) in acetic acid (10 ml) was added water (5 ml) and concentrated hydrochloric acid (0.5 ml). The clear solution was stirred overnight at room temperature, and the resulting cloudy suspension was diluted with water (20 ml) and filtered. The precipitate (0.11 g) was dried and purified by preparative layer chromatography on one 20 × 20 cm plate with 4:1 chloroform–ethyl acetate. Two distinct zones were eluted. The least polar material (64 mg) crystallized from methanol–chloroform, giving shining needles (60 mg) of isodigitoxigenin acetate (**3b**), mp 258–260°. The more polar material (24 mg) crystallized from the same solvent, providing isodigitoxigenin (**3a**) as small flakes (17 mg), mp 265–267°. The specimens thus prepared were identical[12] with authentic samples of isodigitoxigenin and acetate derivative.

Similar treatment of acetal **6b** (0.21 g) gave a solid product (0.148 g), which was separated into isodigitoxigenin acetate (0.10 g) and isodigitoxigenin (12.5 mg) as above.

Cyclization of Methyl 3β-Acetoxy-(21*S*)-methoxy-14β,21-epoxy-5β-(20*S*)-cholanate (7b) to 3β-Acetoxy-14β,21-epoxybufanolide (4).—To acetal **7b** (1.0 g) dissolved in acetic acid (45 ml) was added water (5 ml) containing concentrated hydrochloric acid (2.5 ml). The mixture was stirred for 2 days at room temperature, diluted with water, and extracted with chloroform. An infrared spectrum of the crude product suggested the presence of free carboxylic acid groups and deacetylation at C-3. Therefore, a solution of the product in diethyl ether was treated for 2 hr with diazomethane at 0°. Excess reagent was destroyed by adding a few drops of acetic acid. The solution was evaporated to dryness and the residue was reacetylated with 10 ml of 1:1 acetic anhydride–pyridine overnight at room temperature. Chromatography of the crude product in ligroin on silica containing increasing amounts of ethyl acetate gave three fractions, which follow in order of increasing polarity. (a) **Methyl 3β-acetoxy-14β,21-epoxy-5β-chol-20(21)-enate (8a)** was eluted by 9:1 ligroin–ethyl acetate and crystallized from methanol as large prisms (0.50 g), mp 105–107°, identical[12] with an authentic specimen. (b) **Methyl 3β-(21*R*)-diacetoxy-14β,21-epoxy-5β-(20*S*)-cholanate (7c)** was eluted by 4:1 ligroin–ethyl acetate and crystallized from ligroin–ethyl acetate as long needles (0.30 g), mp 154–162°, mol wt, 504 (mass spectrum). On crystallization, ester **7c** tended to decompose to unsaturated ester **8a** and elemental analysis was not performed, but the mass and other spectral data support the assigned structure: pmr δ 1.0 (C-18 methyl), 1.10 (C-19 methyl), 2.06 (C-3 O acetate), 2.12 (C-21 O acetate), 3.70 (–$COOCH_3$), 5.10 (H-3α), 5.66 (doublet, J = 8.5 cps, acetal –OCHO–). (c) **3β-Acetoxy-14β,21-epoxybufanolide (4)** was eluted by 1:1 ligroin–ethyl acetate and crystallized from ligroin–ethyl acetate as small prisms (13 mg): mp 207–218°; ν_{max}^{KBr} 1745 and 1735 cm^{-1}; RD (c 0.583, dioxane) $[\alpha]_{600}$ −60°, $[\alpha]_{589}$ −67°, $[\alpha]_{500}$ −94°, $[\alpha]_{400}$ −163°, $[\alpha]_{350}$ −240°, $[\alpha]_{300}$ −420°, $[\alpha]_{250}$ −960°, and $[\alpha]_{234}$ −1561°; pmr δ 0.94 (C-18 methyl), 1.08 (C-19 methyl), 2.0 (O acetate), 2.64 (triplet, J = 7 Hz, –CH_2CO–), 5.06 (H-3α), and 5.08 (doublet, J = 8 Hz, –OCHO–).

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; mol wt, 430. Found: C, 72.79; H, 8.94; mol wt, 430 (mass spectrum).

Attempted Cyclization of 3β-Hydroxy-14β,21-epoxy-5β-chol-20(21)-enic Acid (8c).—Acid **8c** (0.11 g) was dissolved in benzene (12 ml), and *p*-toluenesulfonic acid (11 mg) was added. The solution was stirred at room temperature for 73 hr and examined periodically by tlc without any observable reaction. Also, 24 hr at reflux followed by 48 hr at room temperature had no effect. The benzene solution was washed with water, dried, and evaporated to yield an oil with the same infrared and pmr spectrum as those of the starting material.

Peracid Oxidation of 3β-Acetoxy-14β,21-epoxy-5β-chol-20(21)-enic Acid (8b).—To cholenic acid **8b** (2.78 g) dissolved in chloroform (50 ml) was added *m*-chloroperbenzoic acid (1.4 g). After 15 min at room temperature the solution was washed with saturated sodium bicarbonate solution to remove *m*-chlorobenzoic acid, then with 2 *N* sodium hydroxide solution. Neutral material, obtained by evaporation of the washed and dried chloroform solution, was an amorphous solid (1.96 g). The alkaline extract was acidified and precipitated material was extracted with diethyl ether, washed with water, dried, and evaporated to give a crystalline solid (0.67 g).

The neutral material (0.75 g) was chromatographed on silica, and elution with 4:1 benzene–ethyl acetate gave γ lactone **11a** as a solid which crystallized from chloroform–ligroin as minute needles (0.11 g): mp 251–253°; ν_{max} 1758 (γ lactone), 1725, and 1260 cm^{-1} (acetate); $[\alpha]_D$ +63° (*c* 0.44); pmr δ 1.02 (C-18 methyl), 1.18 (C-19 methyl), 2.04 (O acetate), 5.10 (H-3α), and 5.32 (–OCHO–).

Anal. Calcd for $C_{26}H_{38}O_6$: mol wt, 446.266822. Found: mol wt, 446.271129 (mass spectrum).

(10) (a) G. Maerker and E. T. Haeberer, *J. Amer. Oil Chem. Soc.*, **43**, 97 (1966); (b) S. G. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968).

(11) G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Brushweiler, *Chem. Commun.*, 93 (1970); *J. Org. Chem.*, in press.

(12) Mutual identity was confirmed by comparison of infrared spectra and thin layer chromatography R_f values.

An ir and pmr spectrum of the base-soluble material indicated deacetylation and the presence of small amounts of *m*-chlorobenzoic acid. The crude product was redissolved in diethyl ether and the ethereal solution was washed with sodium bicarbonate solution and evaporated. The resultant crystalline solid was acetylated with 1:1 acetic anhydride–pyridine overnight at room temperature and chromatographed on silica gel. Elution with 4:1 ligroin–ethyl acetate gave γ lactone **11b**, which crystallized from chloroform–ligroin as short needles (0.15 g): mp 224–232°; ν_{max}^{KBr} 1790, 1762, 1734, and 1240 cm^{-1}; $[\alpha]D$ +29.5° (c 3.15); $\nu_{max}^{CHCl_3}$ 1780 and 1740 cm^{-1}; pmr δ 1.00 (C-18 methyl), 1.10 (C-19 methyl), 2.04 (C-3β O acetate), 2.12 (C-21 O acetate), 5.12 (H-3α), and 5.89 (–OCHO–).

Anal. Calcd for $C_{28}H_{40}O_7$: mol wt, 488. Found: mol wt, 488 (mass spectrum).

When crystallization of lactone **11a** from aqueous methanol was attempted, a viscous oil was obtained which showed many spots on tlc examination. The oil from 0.32 g of lactone **11a** was chromatographed in 9:1 ligroin–ethyl acetate on silica gel. Elution with 2:1 ligroin–ethyl acetate gave a crystalline solid (50 mg), mp 208–220°, which was separated into two components by preparative layer chromatography with 1:4 ethyl acetate–chloroform. The major component was lactone **11c**, crystallized from methanol as long needles (30 mg): mp 209–222°; ν_{max}^{KBr} 1782 (γ lactone), 1738, and 1240 cm^{-1} (acetate); $\nu_{max}^{CHCl_3}$ 1785 (γ lactone), 1735, and 1270 cm^{-1} (acetate); pmr δ 1.02 (C-18 methyl), 1.08 (C-19 methyl) 2.06 (O acetate), 3.40 (acetal OCH_3), 4.65 (acetal –OCHO–), and 5.10 (H-3α).

Anal. Calcd for $C_{27}H_{40}O_6$: mol wt, 460. Found: mol wt, 460 (mass spectrum).

The minor component was lactone **11d**, which crystallized also from methanol as short, sparkling needles (7 mg): mp 266–271° dec; ν_{max}^{KBr} 1750, 1740, and 1235 cm^{-1}; $\nu_{max}^{CHCl_3}$ 1772 (γ lactone), 1735, and 1270 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_6$: mol wt, 446. Found: mol wt, 446 (mass spectrum).

3β-Pyranyloxy- and 3β-Acetoxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norchol-22(23)-ene (16a and 16b).—To a solution of 3β-pyranyloxy-23-mesyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norcholane (**7d**, 1.3 g) in redistilled acetone (50 ml) was added sodium iodide (0.7 g). The solution was heated at reflux for 5 hr, by which time tlc showed no starting material. After cooling, dilution with water, and extraction with diethyl ether, the ethereal solution was washed with water and evaporated, yielding iodide **7e** as a colorless glass (1.33 g). Without further purification, the iodide was dissolved in benzene (10 ml) and added to a stirred 1 *N* solution of potassium *t*-butoxide (2.24 g) in dimethyl sulfoxide (20 ml). The yellow solution was stirred at room temperature for 15 min, poured into ice–water, and extracted with ether. The ether solution was evaporated to a yellow gum (1.03 g) which was applied in ligroin to a column of silica gel. Elution with 19:1 ligroin–ethyl acetate gave olefin **16a** as a colorless oil: pmr δ 0.98 (C-18 methyl), 1.09 (C-19 methyl), 3.50 (–OCH_3), 4.0 (THP –OCHO–), 4.44 (doublet, J = 8 Hz, –OCHO), 4.66 (H-3α), 5.0 (multiplet), 5.22 (sharp singlet), and 5.5–6.1 (multiplet).

The oily tetrahydropyranyl ether was converted into the crystalline acetate **16b** in the following manner. To a solution of ether **16a** (0.40 g) in methanol (20 ml)–water (0.4 ml) was added *p*-toluenesulfonic acid (40 mg). The solution was stirred at room temperature for 1.25 hr. Alcohol **16c** was isolated by dilution with water followed by extraction with ether. Following acetylation with 1:1 acetic anhydride–pyridine (5 ml) overnight at room temperature, acetate **16b** was obtained as an oil that crystallized on standing, and recrystallized from methanol as well-formed prisms (0.25 g): mp 146–148°; ν_{max}^{KBr} 1738, 1240 (acetate), and 1640 cm^{-1} (weak, C=C); $[\alpha]D$ +35.8° (c 1.54); pmr δ 1.02 (C-18 methyl), 1.10 (C-19 methyl), 2.06 (O-acetate), 3.50 (–OCH_3), 4.44 (doublet, J = 8 cps, –OCHO–), 5.10 (H-3α), and 4.90–6.10 (complex 3 H region).

Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68; mol wt, 416. Found: C, 74.94; H, 9.59; mol wt, 416 (mass spectrum).

In both tetrahydropyranyl ether **16a** and acetate **16b**, the region in the pmr spectrum between δ 4.90 and 6.10 integrated for three protons and bore a strong resemblance to that shown by compounds containing an allylic grouping.

3β-Pyranyloxy- and 3β-Acetoxy-14β,21;22,23-diepoxy-(21*S*)-methoxy-5β-(20*S*)-norcholane (17a and 17b).—A solution of 3β-pyranyloxy-14β,21-epoxy-(21*S*)-methoxy-5β-(20*S*)-norchol-22-(23)-ene (**16a**, 0.10 g) in chloroform (5 ml) was stirred with *m*-chloroperbenzoic acid (35 mg) at room temperature for 18.5 hr. As reaction was still incomplete by tlc with 39:1 chloroform–ethyl acetate, a further 35 mg of peracid was added and stirring was continued for a total of 45 hr. No starting material remained and the mixture was washed with sodium bicarbonate solution and water and evaporated to a colorless oil which was purified by preparative layer chromatography on one plate (40 × 20 × 0.2 cm) in 19:1 ligroin–ethyl acetate. Epoxide **17a** was obtained as an oil (91 mg) which did not crystallize: pmr δ 0.96 (C-18 methyl), 1.00 (C-19 methyl), 2.5–3.00 (complex 3 H region, protons α to oxide), 3.48 (OCH_3), 4.00 (THP acetal H), 4.56 (doublet, J = 8 Hz, –OCHO–), and 4.65 (H-3α).

Since the tetrahydropyranyl ether **17a** did not crystallize, acetate **17b** was prepared by epoxidation of 3β-acetoxy olefin **16b**. The olefin (0.27 g) was stirred at room temperature in chloroform (10 ml) with *m*-chloroperbenzoic acid (0.15 g) for 97 hr, and the product was isolated as described above. Epoxide **17b** crystallized from methanol as well-formed prisms (0.16 g): mp 182–184°; $[\alpha]D$ +19° (c 1.84); pmr δ 1.02 (C-18 methyl), 1.06 (C-19 methyl), 2.06 (O acetate), 2.55–3.00 (complex 3 H region, protons α to oxide), 3.52 (–OCH_3), 4.56 (doublet, J = 8 Hz, –OCHO–), and 5.12 (H-3α).

Anal. Calcd for $C_{26}H_{40}O_5$ (mol wt, 432): C, 72.19; H, 9.32. Found: C, 72.30; H, 9.15. The mass spectrum showed a peak at m/e 400 for loss of 32 (CH_3OH) from the molecular ion at m/e 432.

The pmr spectra at δ 2.5–3.00 of tetrahydropyranyl ether **17a** and the acetate **17b** resembled that of propylene oxide.

Condensation of 3β-Acetoxy-14,21-epoxy-20-formylpregn-20(21)-ene (15a) with Malonic Acid.—To a solution of epoxide **17b** (0.16 g) in acetone (15 ml) was added a solution of periodic acid (0.45 g) in acetone (8 ml)–water (1.5 ml). The mixture was heated at reflux for 1 hr, cooled, diluted with water, and extracted with diethyl ether. The extract was washed well with water and evaporated to a yellow, acrid-smelling, lacrymatory oil. The oil was held at 60° (0.1 mm) for 1 hr and chromatographed on silica gel. Elution with 9:1 ligroin–ethyl acetate gave some unchanged epoxide, followed by a more polar oily fraction (99 mg) identified by spectral characteristics as aldehyde **15a**: ν_{max}^{film} 1720, 1650, and 1600 cm^{-1}; pmr δ 0.94 (C-18 methyl), 1.02 (C-19 methyl), 2.06 (O acetate), 2.66 (multiplet, H-17), 5.12 (H-3), 7.08 (H-21), and 9.32 (–CHO).

Aldehyde **15a** (0.10 g) was dissolved in pyridine (3 ml) and morpholine (0.10 g), and malonic acid (0.10 g) was added. The mixture was warmed on a steam bath for 1 hr, cooled, acidified with 2 *N* hydrochloric acid, and extracted with diethyl ether. Removal of solvent gave an oil with an infrared spectrum superimposable on that of starting material. Extending the reaction time had no effect. Recovered aldehyde was redissolved in pyridine (3 ml) with morpholine (0.20 g) and malonic acid (0.20 g), and the solution was heated at reflux for 1 hr. The product was isolated as noted directly above. Tlc with 7:3 ligroin–ethyl acetate indicated the presence of relatively nonpolar diene **18**, which was isolated by preparative thin layer chromatography with 4:1 ligroin–ethyl acetate mobile phase and crystallized from methanol as needles (15 mg): pmr δ 1.02 (combined C-18 and -19 methyls), 2.06 (O acetate), 4.7 (J_{bc} = 10 Hz, J_{cd} = 2 Hz, H_c), 4.94 (J_{bd} = 17 Hz, J_{cd} = 2 Hz, H_d), 5.1 (H-3α), 6.22 (H_a), and 6.24 (J_{bd} = 17 Hz, J_{bc} = 10 Hz, H_b).

Registry No.—**3a**, 464-82-4; **3b**, 23337-56-6; **4**, 23337-57-7; **7c**, 23359-75-3; **11a**, 23359-76-4; **11b**, 23337-58-8; **11c**, 23337-59-9; **11d**, 23359-77-5; **15a**, 23359-78-6; **16a**, 23337-60-2; **16b**, 23337-61-3; **17a**, 23337-62-4; **17b**, 23337-63-5; **18**, 23359-79-7.

The Structure of Pactamycin[1]

PAUL F. WILEY, HEINZ K. JAHNKE, FORREST MACKELLAR, R. B. KELLY, AND ALEXANDER D. ARGOUDELIS

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received September 22, 1969

The structure of the antibiotic, pactamycin, has been shown to be that represented by I by physical studies and chemical degradation.

The isolation of the antibiotic, pactamycin, and its characterization were reported some years ago by Argoudelis, Jahnke, and Fox.[2] The present paper discusses the determination of the structure of pactamycin and of some of its degradation products and presents evidence that the structure is as represented in I in which the hydroxyl groups at C-4 and C-5 are *trans* to each other and the two nitrogen atoms at C-1 and C-2 are *cis* to each other and *trans* to the anilino system.

The originally reported molecular formula for pactamycin was $C_{28}H_{40}N_4O_8$.[2] As a result of mass spectra derived from degradation products it has been necessary to revise the molecular formula to $C_{28}H_{38}N_4O_8$. As mentioned earlier[2] pactamycin exhibits ultraviolet absorption having a strong maximum at 239 mμ with a shoulder at 264 mμ and weak maxima at 313 and 356 mμ. There is almost no change in dilute acid solutions, but the 313 mμ maximum moves to 320 mμ in alkaline solutions. The infrared spectrum is quite complex showing bands indicative of OH–NH, carbonyl, and aromatic rings. However, it was found that in rigorously purified pactamycin the band reported[2] at 1718 cm^{-1} is absent. A basic function is present (pK_a' 7.25) as is a weakly acidic function (pK_a' 9.35) with the basic function presumably being due to a primary amino group indicated to be present by a Van Slyke nitrogen determination. Pactamycin has been reported[2] to have a rotation of +79° in ethanol changing to +23° on standing. It has been found that pactamycin upon standing in acetone changes its rotation from +25° at zero time to +76° after 24 hr. Pactamycin which has been exposed to acetone has two new singlets in the nmr spectrum at δ 2.00 and 2.26 with each singlet representing a C-methyl group. Solution of such material in ethanol followed by reisolation gives pactamycin having the usual nmr spectrum. From these results it is concluded that pactamycin reacts with acetone to form a complex having a rotation of +79° in ethanol, and that the complex is readily destroyed to give pactamycin which has a rotation of +23° in the same solvent. This acetone product was studied only to clarify the discrepancy in rotation and no attempt was made to determine its structure. The chemical shifts of the protons on carbon of pactamycin are shown in Table I. The significance of the data shown will be discussed exhaustively in connection with the nmr spectra of degradation products. At this point it is sufficient to point out that four methyl groups attached to carbon are present with only one having a proton on an adjacent carbon atom. The singlet appearing at δ 2.94 indicates that two N-methyl groups are present.

A solution of pactamycin in 2 *N* hydrochloric acid heated on the steam bath for a short time gives rise to two products. One of these was identified as dimethylamine by reaction with phenyl isothiocyanate to form N-phenyl-N′-dimethylthiourea. The second product was a new compound designated pactamycate (II) and having the molecular formula $C_{26}H_{31}N_3O_8$ differing from pactamycin in its molecular formula by the elements of dimethylamine. Analyses of pactamycate and its diacetyl derivative and a molecular weight determination of the latter compound by mass spectrum established the molecular formula. In contrast to pactamycin, pactamycate is crystalline and is only slightly soluble in most common organic solvents. Its rotation, pK_a values, and ultraviolet spectrum are almost the same as those of pactamycin. However, the infrared spectrum has a band at 1739 cm^{-1} which was not present in the pactamycin spectrum. The 1739-cm^{-1} band indicates, in view of the reaction conditions, that a new carbonyl system has been created concomitant with expulsion of dimethylamine. The primary amino group is still present.

Mild basic hydrolysis of pactamycate formed a further degradation product, desalipactamycate (IIIa). The same product was readily formed by base treatment of pactamycin. In addition there was formed 6-methylsalicyclic acid from both pactamycin and pactamycate. The acid was identified by conversion into its methyl ether and comparison of the physical properties of the two compounds with those reported in the literature. The molecular formula of desalipactamycate was established as $C_{18}H_{25}N_3O_6$ by analysis and high resolution mass spectra. Desalipactamycate is an amorphous material, highly soluble in water and methanol but sparingly soluble or insoluble in less polar solvents. No titratable groups are present in desalipactamycate suggesting that the acidic function of the preceding compounds is the phenolic hydroxyl group and that reaction had occurred at the basic group originally present. The ultraviolet spectrum of desalipactamycate is similar to those of pactamycin and pactamycate except that the maximum at 313 mμ is no longer present. The infrared spectrum differs significantly in the carbonyl region from those of pactamycin and pactamycate. A new band previously lacking appears at 1705 cm^{-1}, and the 1739-cm^{-1} band is absent. Three derivatives of desalipactamycate (IIIb, IIIc, and IIId) were prepared by standard procedures. Characterization data are provided in Table II.

The presence of an infrared band at 1705 cm^{-1} and the absence of a primary amino group in desalipacta-

(1) A portion of this material was presented at the 4th International Symposium on the Chemistry of Natural Products, Stockholm, Sweden, June 26–July 1, 1966. This work was supported by Contract PH43-68-1023, Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md.

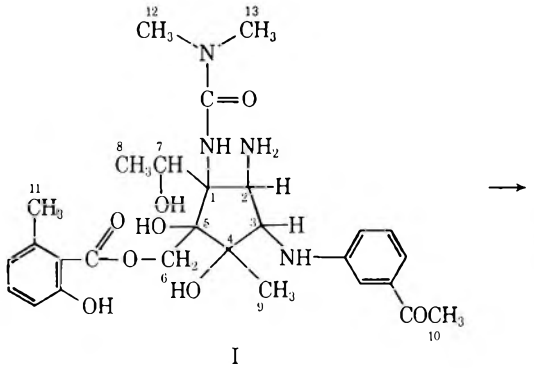
(2) A. D. Argoudelis, H. K. Jahnke, and J. A. Fox, *Antimicrobiol. Agents Chemother.*, 191 (1961).

TABLE I

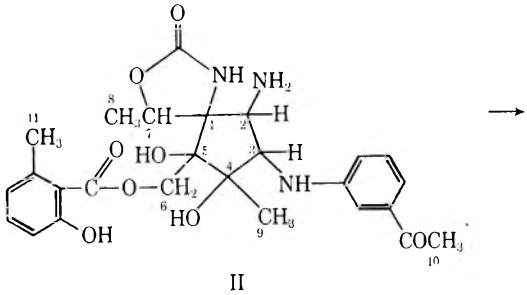
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA[a]

Proton	Pactamycin (I)	Pactamycate (II)	Desalipactamycate (IIIa)	Diacetyldesalipactamycate (IIIe)
H-8	0.98 (3 H, d)	1.54 (3 H, d)	1.21 (3 H, d)	1.20 (3 H, d)
H-9	1.49 (3 H, s)	1.38 (3 H, s)	1.52 (3 H, s)	1.57 (3 H, s)
H-11	2.20 (3 H, s)	2.24 (3 H, s)		
H-10	2.50 (3 H, s)	2.46 (3 H, s)	2.53 (3 H, s)	2.55 (3 H, s)
H-12, H-13	2.94 (6 H, s)			
H-3	3.97 (1 H, s)	3.73 (1 H, d)	3.85 (1 H, s)	4.04 (1 H, s)
H-2	4.00 (1 H, s)	3.56 (1 H, d)	3.41 (1 H, s)	3.59 (1 H, s)
H-7	4.03 (1 H, q)	4.73 (1 H, q)	4.21 (1 H, q)	5.48 (1 H, q)
H-6	4.54, 4.78 (2 H, dd)	4.65, 4.39 (2 H, dd)	3.98, 3.72 (2 H, dd)	4.30, 4.49 (2 H, d)
Aromatic	6.7–7.3 (7 H, m)	6.72–7.12 (7 H, m)	6.98–7.3 (4 H, m)	6.9–7.45 (4 H, dm)
O ‖ CCH_3				1.90 (3 H, s) 2.02 (3 H, s)

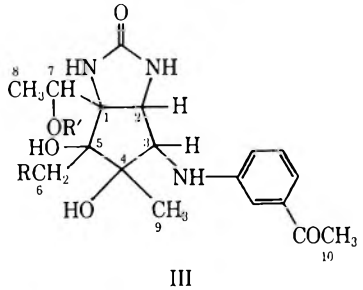
[a] Chemical-shift values are expressed in δ units (parts per million) relative to internal tetramethylsilane. The solutions are approximately 10% by weight in d_7-DMF with D_2O added for exchange. All spectra were run at 100 MHz.



I



II



III

a, R = OH; R′ = H

b, R = CH_3—(p-phenylene)—SO_3; R′ = H

c, R = O_2N—(p-phenylene)—SO_3; R′ = H

d, R = I; R′ = H

e, R = CH_3COO; R′ = CH_3CO

mycate are consistent with the reaction of a carbonyl group already present to form a cyclic amide.[3] Treatment of desalipactamycate with 5 *N* sodium hydroxide under reflux forms carbon dioxide establishing that the cyclic amide is either a cyclic urea or a 2-oxazolidone.

(3) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 47.

TABLE II

Compd	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
IIIb	155 dec	56.27	5.86	7.87	56.42	6.09	7.86
IIIc		51.07	5.00	9.92	50.72	5.40	9.87
IIId	211 dec	44.18	4.95	8.59	44.53	5.24	8.47

That it is probably a cyclic urea is indicated by the infrared band at 1705 cm^{-1} which would be expected for such compounds.[4]

Oxidation of desalipactamycate with performic acid formed two products, *m*-nitroacetophenone and *m,m′*-diacetoazoxybenzene. Such products can arise only from a *m*-acetoanilino moiety. The presence of such a moiety is also indicated by the similarity of the ultraviolet spectrum of desalipactamycate to that of *m*-aminoacetophenone which also has a strong maximum at a low wavelength (231 mμ in methanol), a shoulder (257), and a weak maximum at a longer wavelength (330). The nmr signal appearing as a singlet at δ 2.53 would be as expected for the methyl group of such a system.

The nmr spectrum of desalipactamycate (Table I) shows the presence of two C-methyl groups (δ 1.21 and 1.52) in addition to the one in the *m*-acetoanilino moiety. The higher field signal is coupled with a proton at δ 4.21 (J = 6.4 Hz). Such a pattern establishes that one C-methyl group is attached to a carbon atom having a single proton and most probably an oxygen substituent. Desalipactamycate forms a diacetate (IIIe) whose nmr spectrum has a quartet centered at δ 5.48 arising from a proton adjacent to C-methyl. The 1.27-ppm downfield shift of the quartet chemical shift upon acetylation indicates acetylation of a hydroxyl group on the same carbon atom. There, then, must be a $CH_3C(OH)H$ system in desalipactamycate.

Periodate oxidation of desalipactamycate results in very rapid consumption of 2 mol of periodate/mol with a slow overoxidation to a total of a little more than 3 mol of periodate. The only product isolated was formaldehyde although electrometric titration of the reaction mixture indicated formation of a carboxyl group. The absence of acetaldehyde formation shows that the secondary alcohol was not involved in the oxi-

(4) (a) Biotin and dehydrobiotin have infrared bands in the region of 1700 ± 15 cm^{-1}. These data were provided by Mr. Paul Meulman of The Upjohn Co. (b) J. Altman and D. Ben-Ishai, *J. Heterocycl. Chem.*, **5**, 679 (1968).

TABLE III

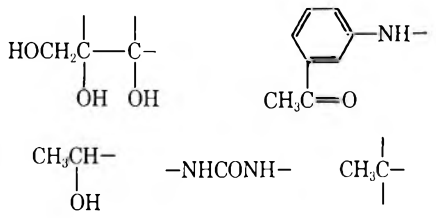
HIGH RESOLUTION MASS MEASUREMENTS[a]

Desalipactamycate			Diacetyldesalipactamycate		
Measured *m/e*	Calcd *m/e*	Composition	Measured *m/e*	Calcd *m/e*	Composition
379.1744	379.1743	$C_{18}H_{25}N_3O_6$	463.1957	463.1955	$C_{22}H_{29}N_3O_8$
334.1401	334.1403	$C_{16}H_{20}N_3O_5$	403.1735	403.1743	$C_{20}H_{25}N_3O_6$
276.1342	276.1348	$C_{14}H_{18}N_3O_3$	358.1396	358.1403	$C_{16}H_{20}N_3O_5$
250.1090	250.1079	$C_{13}H_{16}NO_4$	298.1193	298.1192	$C_{16}H_{16}N_3O_3$
190.0873	190.0868	$C_{11}H_{12}NO_2$	292.1155	292.1185	$C_{15}H_{18}NO_5$
135.0690	135.0684	C_8H_9NO	232.0976	232.0974	$C_{13}H_{14}NO_3$
120.0446	120.0449	C_7H_6NO	190.0864	190.0868	$C_{11}H_{12}NO_2$
			135.0682	135.0684	C_8H_9NO

[a] Not all of the data are included.

dation. As the nitrogen atoms are neutral and no products expected from oxidation involving the nitrogen atoms present were isolated, it appears that these too were not involved in the periodate oxidation. Since the speed of the reaction is consistent only with a normal periodate oxidation, the only remaining explanation is that a 1,2,3-trihydroxy system is present in desalipactamycate, and none of the three hydroxyls can be the secondary hydroxyl adjacent to the C-methyl group. The formation of formaldehyde must be due to the presence of one primary carbinol. The nmr spectrum of desalipactamycate and that of its diacetate are also indicative of the presence of such a primary hydroxyl. The signals centered at δ 3.72 and 3.98 in desalipactamycate and at 4.26 and 4.54 in its acetate are characteristically those of a primary carbinol which has then been acetylated. The AB pattern of doublets indicates the absence of a hydrogen atom adjacent to the methylene protons. The other two hydroxyl groups must be tertiary as there is no nmr evidence for hydrogen on carbon bearing a hydroxyl group and the two groups are not acetylatable.

The previous discussion leads to the conclusion that the following moieties are present in desalipactamycate and that no other functional groups can be present.



This information in conjunction with the molecular formula of desalipactamycate requires the presence of two ring systems, in addition to the aromatic ring, one of which must contain the urea system. These two rings are necessarily formed from six carbon atoms and two nitrogen atoms since twelve carbon atoms, one nitrogen atom, and all of the oxygen atoms have been shown to be outside any ring system.

The high resolution mass spectra of desalipactamycate and its diacetate (Table III) demonstrated that the moieties already indicated can only be combined to lead to the structure represented by IIIa or its isomer in which the CH_3CHOH substituent is at C-2. A choice between these two structures will be presented later in this paper. Desalipactamycate fragments with loss of $C_5H_9N_2O_2$ (379.1744 $\xrightarrow{m^*}$ 250.1090) followed by loss of $C_2H_4O_2$ (250.1090 $\xrightarrow{m^*}$ 190.0873) to give a $C_{11}H_{12}NO_2$ ion, both paths being established by the presence of metastable ion peaks in the spectrum. The composition of the eleven-carbon fragment is only consistent with retention of the aromatic system. The diacetate exhibits a completely parallel pathway except that the loss at each stage is C_2H_2O larger

$$C_{22}H_{29}N_3O_8 \xrightarrow[m^*]{-C_7H_{11}N_2O_3} C_{15}H_{18}NO_5 \xrightarrow[m^*]{-C_4H_5O_3} C_{11}H_{12}NO_2$$

again established by metastable ions. The five-carbon fragment must contain an acetylated group in the acetate as does the two-carbon fragment. The $C_2H_4O_2$ includes the primary hydroxyl group as the secondary hydroxyl could not be lost in a fragment of this composition. The three-carbon sequence which has three hydroxyl groups can only be attached to a carbon substituted by the *m*-acetoanilino moiety as evidenced by the thirteen-carbon ion. The eleven-carbon fragment would necessarily include the C-methyl group on the ring to have eleven carbon atoms. Desalipactamycate also fragments by a different pathway with loss of $C_4H_7O_3$ (379.1744 → 276.1348). This loss establishes that the ring C-methyl group is on one of the carbon atoms bearing a hydroxyl group, and the loss of $C_2H_4O_2$ means that the C-methyl cannot be on the carbon atom adjacent to the primary carbinol. Otherwise a three-carbon fragment would be lost. Since the four-carbon fragment and the eleven-carbon fragment both contain the C-methyl group on the carbocyclic ring, and, in view of the presence of the primary hydroxyl group in the four-carbon fragment, the C-methyl group must be attached to a carbon atom which is attached to a carbon atom bearing the *m*-acetoanilino moiety. The remaining part of the desalipactamycate molecule is the five-carbon fragment which includes the secondary carbinol and the cyclic urea system. There are only two ways in which the five-carbon and the thirteen-carbon fragment can be combined. The two ways are as in IIIa or as the isomer of IIIa previously mentioned.

Pactamycate (II) is converted into desalipactamycate with addition of the elements of water and loss of 6-methylsalicyclic acid. However, changes other than hydrolysis occur, as shown by loss of the 1739-cm^{-1} infrared band and appearance of a 1705-cm^{-1} band in desalipactamycate. Such a change indicates that one of the carbonyl systems in pactamycate has been converted into the cyclic urea system of desalipactamycate. Also consistent with this interpretation is the presence of the primary amino function in pactamycate. An examination of the nmr spectrum of pactamycate shows that the chemical shifts due to the methylene group and the single proton on carbon of the secondary

carbinol system are downfield from the signals of desalipactamycate (Table I) indicating esterification of both the primary and secondary carbinols. Therefore, 6-methylsalicyclic acid must be attached to one of these groups and the 1739-cm^{-1} carbonyl group must be esterified with the other hydroxyl group. That the 1739-cm^{-1} carbonyl system is actually a 2-oxazolidone, although such a ring system could involve either the primary or the secondary oxygen, is indicated by loss of carbon dioxide by strong base hydrolysis of pactamycate. The 1739-cm^{-1} infrared band is typical of substituted 2-oxazolidones such as 5-(*m*-trifluoromethylphenoxymethyl)-2-oxazolidone (1737 cm^{-1}) and 5-(3,4-dimethylphenyl)-2-oxazolidone (1735 cm^{-1}).[5] Pactamycate forms a neutral diacetyl derivative indicating that the acidic function is the phenolic hydroxyl group. Reduction of pactamycate with sodium borohydride gives a dihydro derivative which can be acetylated to a triacetate. Such behavior indicates reduction of a ketonic carbonyl, and the nmr spectrum of the triacetyl derivative shows that the carbonyl reduced was the carbonyl of the *m*-acetoanilino group. The signal in pactamycate representing the *m*-acetoanilino methyl appears at δ 2.46 (s), but this signal no longer appears after reduction while a new doublet representing three hydrogen atoms appears at δ 1.42. The free phenolic hydroxyl group indicating absence of an ether linkage, the absence of a ketonic carbonyl in the salicoyl moiety as shown by failure of the salicoyl carbonyl to reduce with sodium borohydride, and the nmr data showing that the protons on C-6 of pactamycate are downfield from the C-6 protons of desalipactamycate establish that 6-methylsalicyclic acid is present in pactamycate as an ester. Although the two hydrogen atoms (H-2 and H-3) giving chemical shifts of δ 3.41 and 3.85 in the nmr of desalipactamycate show no coupling, the same two hydrogen atoms in pactamycate (3.56 and 3.73) have a coupling constant of 8.5 Hz. This can only be interpreted to mean that they are adjacent. Consequently, the secondary carbinol system must be attached at C-1 in desalipactamycate and IIIa is the correct expression for the structure since the only possible isomer would necessitate a 1,3 relationship for these hydrogen atoms. The failure of pactamycate to consume periodate is somewhat surprising as there is no indication that the adjacent tertiary hydroxyl groups of desalipactamycate are no longer present. This will be discussed further.

In view of the data already discussed, it has been established that pactamycin has been converted into pactamycate by loss of the elements of dimethylamine with incorporation of a carbonyl group into a 2-oxazolidone system. Such a transformation would be consistent with the attachment of the dimethylamine group to a carbonyl, and such a linkage is confirmed by the signal at δ 2.94 in the nmr due to the dimethylamino moiety. However, the presence of an N,N-dimethylamide should give rise to a doublet while the signal at δ 2.94 is a singlet. It would seem more probable that the dimethylamino group was part of a urea system as the nmr spectrum of tetramethylurea has a singlet at δ 2.85 representing all the methyl groups. Such a supposition was confirmed by hydrolysis of pactamycin with either strong acid or strong base to form carbon dioxide. The urea system must be attached at C-1 since attachment at C-2 would require a molecule which could be readily oxidized with periodate to form acetaldehyde. Such reaction does not occur. Furthermore, urea attachment at C-2 would not give an oxazolidone. The nmr signal due to hydrogen adjacent to methyl (C-8) has moved back upfield from its position in pactamycate. Therefore the hydroxyl on the same carbon atom must be free in pactamycin and part of the oxazolidone ring in pactamycate. In such case the 6-methylsalicoyl group can only be attached at the oxygen which becomes a primary carbinol in desalipactamycate.

The two single hydrogen atoms (H-2 and H-3) which show coupling in the nmr spectrum of pactamycate and fail to show such coupling in desalipactamycate again are not coupled in pactamycin. Pactamycin shows only slow and nonspecific oxidation with periodate although two tertiary hydroxyl groups are present. These rather unusual phenomena can be explained on the basis of stereochemistry. The large $J_{H\text{-}2,H\text{-}3}$ shown in pactamycate is usually taken as an indication that such hydrogen atoms are *cis*. However, in pactamycin the coupling constant is 0 Hz indicating a dihedral angle of about 90°, and the maximum angle possible with *cis* hydrogen atoms would be about 45°.[6,7] However, a *trans* arrangement of H-2–H-3 could give the coupling constant observed if the dihedral angle were large enough (about 160°), and such coupling constants have been observed in very rigid systems.[8] When the five-membered carbocyclic ring is part of a less rigid system, conformational change could result in an H-2–H-3 dihedral angle giving rise to H-2 and H-3 signals which exhibit no vicinal coupling. In view of the usually accepted mechanism for periodate oxidation involving a cyclic ester,[9] it appears that *trans* hydroxyl groups would be oxidized with difficulty. Such a view is supported by experiment.[10] Furthermore, it has been shown that in some *trans* five-membered-ring diols oxidation is very slow, and, in certain cases involving extremely rigid bicyclic systems, oxidation does not occur.[11] In the case of pactamycin, periodate oxidation is slow and nonspecific. If the *vic*-diol system were *trans*, the slow periodate oxidation of such a system could allow oxidation at other sites resulting in the mixture of products obtained with pactamycin and the slow rate of reaction. In pactamycate the great rigidity of the spirobicyclic system and its conformation could result in a *trans* system in which two adjacent hydroxyl groups are so far apart that oxidation is precluded. Desalipactamycate is readily oxidized, but, when the primary hydroxyl is no longer present (IIIb,

(5) (a) These data were provided by Mr. Paul Meulman of The Upjohn Co. (b) J. E. Herweh, *J. Heterocycl. Chem.*, **5**, 687 (1968).

(6) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, a Division of John Wiley & Sons, Inc., New York, N. Y., 1965, p 203.

(7) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., p 87.

(8) (a) K. L. Rinehart, Jr., W. S. Chilton, and M. Hichens, *J. Amer. Chem. Soc.*, **84**, 3216 (1962); (b) H. W. Heine, R. Peary, and A. J. Dubetaki, *J. Org. Chem.*, **31**, 3924 (1966); (c) M. E. Munk, C. S. Sodano, R. L. McLean, and L. H. Haskil, *J. Amer. Chem. Soc.*, **89**, 4158 (1967); (d) B. K. Tidd, *J. Chem. Soc., C*, 218 (1967).

(9) R. Breslow, "Organic Reaction Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1966, p 198.

(10) R. Criegee, E. Buchner, and W. Walther, *Chem. Ber.*, **73**, 571 (1940).

(11) H. H. Wasserman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 385.

IIIc, and IIId), no oxidation occurs. This can happen because with structure IIIa oxidation first leads to a ketone which could then be oxidized further quite readily as the *trans*-diol system would have been destroyed. In those cases (IIIb, IIIc, and IIId) in which the only periodate oxidizable system present is a *trans*-diol, the situation would be very similar to that in pactamycate.

These considerations lead to the assignment I for the structure of pactamycin with the proviso that the stereochemistry of C-4 and C-5 relative to the other carbocyclic carbon atoms is not known, and the absolute stereochemistry is unknown.

Experimental Section[12]

Acetone Complex with Pactamycin.—A sample of pactamycin was prepared by the Florisil chromatography procedure of Argoudelis, Jahnke, and Fox.[2] The nmr spectrum of the Florisil sample, which had been exposed to acetone, was run in d_6-acetone. The spectrum was identical with that of pactamycin except for the presence of two new signals, each representing three protons, at δ 2.00 and 2.26. In the same system acetone gave a signal at δ 2.17.

A solution of 1 g of the acetone complex in 25 ml of 95% ethanol was allowed to stand at room temperature for 4 days. The ethanol was removed by evaporation, and an nmr was run on the residue. The peaks at δ 2.00 and 2.26 were absent.

Rotation of Pactamycin in Various Solvents.—The rotation of pactamycin was run in acetone, 95% ethanol, and chloroform each at a concentration of 1%. The rotations were run immediately and after 24 hr (Table IV).

TABLE IV

Solvent	$[\alpha]_D$ at 0 hr, degree	$[\alpha]_D$ at 24 hr, degree
Acetone	25	76.1
95% ethanol	22	17.8
Chloroform	36.5	41.1

Pactamycate (II).—Concentrated hydrochloric acid (2 ml) and 10 ml of water were added to a solution of 1 g of pactamycin in 1 ml of absolute ethanol. The solution was heated on the steam bath for 2 hr. A precipitate which formed during heating was dissolved by adding methanol. The clear solution was adjusted to pH 8.0 with sodium hydroxide solution. After a short period of standing, a light yellow precipitate formed. The precipitate was removed by filtration and recrystallized from ethanol. The yield of crystalline pactamycate, mp 207–210°, was 425 mg: $[\alpha]_D$ +26° (c 0.84, DMF); λ_{max}^{EtOH} 239.5 mμ (ϵ 26,800), 313 (2016), and 356 (1744); λ_{sh}^{EtOH} 264 mμ (ϵ 7870); ν_{max} 3390, 1739, 1660, 1635, 1595, 1320, 1265, 1250, 1205, 1165, 1125, 1105, 1068, 1040, 980, 948, 884, 805, 775, 728, 704, and 683 cm^{-1}; pK_a = 6.00 and 8.83.

Anal. Calcd for $C_{26}H_{31}N_3O_8$ (dried at 150°): C, 60.81; H, 6.09; N, 8.18. Found: C, 60.72; H, 5.83; N, 8.16.

Dimethylamine from Pactamycin.—One gram of pactamycin was dissolved in 5 ml of methanol, and 20 ml of 10% sodium hydroxide was added. The solution was heated on a steam bath in a stream of nitrogen which was bubbled through 50 ml of 0.1 *N* hydrochloric acid. The acidic solution was evaporated to dryness, 1.03 g. The residue was dissolved in 2 ml of ethanol, and 0.7 ml of phenyl isothiocyanate and 1.5 ml of 1 *N* sodium hydroxide were added. After the mixture had stood for 10 min, water was added, and the mixture was extracted with ethyl acetate. The organic phase was evaporated to dryness, and the crystalline residue was recrystallized from ethanol, mp 132–134° (lit. mp 135° for N-phenyl-N′,N′-dimethylurea). The infrared spectrum was identical with that of an authentic sample.

Diacetylpactamycate.—One gram of pactamycate was dissolved in 30 ml of acetic anhydride and 60 ml of pyridine. After the solution had stood at room temperature for 24 hr, it was evaporated to dryness under reduced pressure. The residue was dissolved in 15 ml of absolute ethanol at 70°, and water was added until the solution was cloudy. Slow cooling resulted in a precipitate which was collected and dried, yield 950 mg. Recrystallization in the same way gave a 90% recovery: mp 173–176°; $[\alpha]_D$ +31° (c 0.97, 75% EtOH); λ_{max}^{EtOH} 240 mμ (ϵ 25,900) and 359 (1900); λ_{sh}^{EtOH} 265 mμ; ν_{max} 3540, 3400, 3310, 1755, 1710, 1675, 1605, 1590, 1520, 1295, 1275, 1235, 1200, 1115, 1100, and 1070 cm^{-1}. Potentiometric titration showed the absence of titratable groups.

Anal. Calcd for $C_{30}H_{35}N_3O_8$: C, 60.35; H, 6.90; N, 7.03; O, 26.78; acetyl (2), 14.4; mol wt, 597.6. Found: C, 60.42; H, 6.58; N, 6.95; O, 27.27; acetyl, 15.38; mol wt (mass spectrum), 597.

Triacetyldihydropactamycate.—A solution of 450 mg of pactamycate in 150 ml of absolute methanol was mixed with a solution of 200 mg of sodium borohydride in 10 ml of water and 5 ml of saturated sodium bicarbonate solution. After the reaction mixture had stood at room temperature for 3 hr, it was adjusted to pH 1.5 with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of methanol and hydrochloric acid and again evaporated to dryness under reduced pressure followed by three repetitions. The final residue was dissolved in a mixture of 20 ml of acetic anhydride and 40 ml of pyridine, and the solution was allowed to stand at room temperature overnight. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was partitioned between water and chloroform. The chloroform solution was concentrated to a small volume, and the solute was precipitated by the addition of Skellysolve B. The precipitate was collected and dried, yield 320 mg. The product was chromatographed on 20 g of alumina pretreated with ethyl acetate and packed in Skellysolve B. The material was added in the minimum amount of chloroform, and the column was developed using 10 ml of each of the following solvent systems: benzene–Skellysolve B (4:6), benzene–Skellysolve B (8:2), benzene, benzene–ethyl acetate (8:2), benzene–ethyl acetate (6:4), benzene–ethyl acetate (4:6), benzene–ethyl acetate (2:8) and 30 ml of ethyl acetate. Twelve 10-ml fractions were collected. On the basis of a weight analysis, the last four fractions were combined and evaporated to dryness under reduced pressure. The residue was crystallized from a mixture of chloroform and Skellysolve B: yield 200 mg; mp 148–153°; λ_{max}^{EtOH} 250 mμ (ϵ 14,750) and 300 (1920); ν_{max} 3370, 1740, 1655, 1605, 1590, 1525, 1245, 1200, 1100, 1065, and 1025 cm^{-1}. Potentiometric titration showed the absence of titratable groups.

Anal. Calcd for $C_{32}H_{39}N_3O_{11}$: C, 59.90; H, 6.12; N, 6.54; O, 27.43; acetyl (3), 20.1. Found: C, 59.03; H, 6.29; N, 6.74; O, 26.96; acetyl, 17.9.

Desalipactamycate (IIIa). A. From Pactamycin.—A solution of 25 g of pactamycin in 500 ml of saturated barium hydroxide was heated on the steam bath under nitrogen for 1 hr. The reaction mixture was refrigerated and filtered, and the insoluble material was washed with 25 ml of cold water. The Ba^{2+} was precipitated by the addition of 1 *N* sulfuric acid. The precipitate was removed by centrifugation and washed in the same way. The combined supernatant and washings were washed with two 200-ml portions of ether, and the aqueous solution was freeze dried. The yield of crude material was 11.2 g. The product was chromatographed on 525 g of silica gel packed in ethylene dichloride–methanol (8:2) and washed with 500 ml of the same solvent mixture and then with 500 ml of ethylene dichloride. The sample was added in ethylene dichloride–methanol (9:1) and eluted with 600 ml of the same solvent system and then with ethylene dichloride–methanol (8:2) until a total of 125 20-ml fractions had been collected. On the basis of an ultraviolet spectrum analysis, fractions 70–120 were combined and evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml of 50% *t*-butyl alcohol, and the solution was freeze dried, yield 1.3 g.

Five grams of material prepared as above was purified by countercurrent distribution in a cyclohexane–*n*-butyl alcohol–water (1:9:10) system for 450 transfers. Tubes 250–320 were combined and concentrated under reduced pressure to an aqueous residue which was freeze dried: yield 3.76 g; mp 125–145° $[\alpha]^{25}_D$ −14° (c 0.64, H_2O); $\lambda_{max}^{H_2O}$ 238 mμ (ϵ 26,550) and 350 (1700); $\lambda_{sh}^{H_2O}$ 264 mμ; ν_{max} 3300, 1705, 1680, 1600, 1583, 1510, and 1100 cm^{-1}. Potentiometric titration showed the absence of titratable groups.

(12) Infrared spectra were run as Nujol mulls on a Perkin-Elmer 421 instrument. Nmr spectra were taken on a Varian A-60A instrument. The melting points are corrected.

Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.65; N, 11.08; mol wt, 379.1743. Found: C, 57.06; H, 6.93; N, 10.45; mol wt (mass spectrum), 379.1744.

B. From Pactamycate.—A solution of 203 mg of pactamycate in a mixture of 1 ml of ethanol and 4 ml of 10% sodium hydroxide was heated on a steam bath under nitrogen for 2 hr. The solution was adjusted to pH 2 with hydrochloric acid and extracted with ether. The aqueous phase was evaporated to dryness under reduced pressure. The residue was extracted with 500 ml of hot absolute ethanol. Evaporation of the ethanol gave 382 mg of residue which was extracted with pyridine. The pyridine extract was evaporated to give 190 mg of crude desalipactamycate identified by paper chromatography and infrared spectrum.

6-Methylsalicyclic Acid from Pactamycate.—The ether extract from the above experiment was evaporated to dryness, yield 61 mg. The product was purified by sublimation at 130° under reduced pressure, mp 164–168° (lit.[3] mp 168°). The melting point and infrared spectrum established that the product was 6-methylsalicyclic acid. A sample was converted into its methyl ether by the procedure of Anslow and Raistrick.[13] The melting point was 137–138° (lit.[13] mp 139°).

Diacetyldesalipactamycate (IIIe).—Desalipactamycate (500 mg) was dissolved in 15 ml of dry pyridine, and 5 ml of acetic anhydride was added. The solution was allowed to stand at room temperature overnight, diluted with 5 ml of methanol, and allowed to stand 0.5 hr. The solution was concentrated under reduced pressure to a volume of about 3 ml, and 20 ml of water was added. The mixture was extracted with three 10-ml portions of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in water, acidified with 1 *N* hydrochloric acid, and again extracted in the same way with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The residue was crystallized from ethanol: yield 190 mg; mp 147–151°; $[\alpha]^{26}D$ −7° (c 0.37, ethyl alcohol); λ_{max}^{EtHO} 239 mμ (ε 26,350) and 354 (1850); λ_{sh}^{EtOH} 260 mμ (ε 9050); ν_{max} 3400, 1755, 1745, 1705, 1685, 1600, 1580, 1510, 1265, 1240, 1115, 1095, 1075, 1055, 1050, and 1030 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}N_3O_8$: C, 57.03; H, 6.32; N, 9.07; acetyl (2), 18.93; mol wt, 463.1955. Found: C, 57.02; H 6.90; N, 8.87; acetyl, 16.77; mol wt (mass spectrum), 463.1957.

Performic Acid Oxidation of Desalipactamycate.—One gram of desalipactamycate was added slowly with stirring to a mixture of 6 ml of 97% formic acid and 3 ml of 30% hydrogen peroxide. After the reaction mixture had cooled, it was diluted with 9 ml of water. Filtration gave 33 mg of product A, mp 124–126°. The filtrate was cooled in an ice bath and kept below 40° while the pH was adjusted to 6 with cold 50% sodium hydroxide. The crystalline precipitate was cooled and dried, yield 165 mg, mp 62–69°, designated product B. Repeated recrystallization of both products from ethy alcohol gave A melting at 136–137° and B melting at 73–76°. Product A had an infrared spectrum identical with that of *m,m*-diacetoazoxybenzene,[14] and the mixture melting point showed no depression. Product B had an infrared spectrum identical with that of *m*-nitroacetophenone, and the mixture melting point showed no depression.

Carbon Dioxide from Acid Hydrolysis of Pactamycin.—A solution of 2 g of pactamycin in 50 ml of 12 *N* sulfuric acid was refluxed for 6 hr while the gases from the reaction were led into 50 ml of saturated barium hydroxide solution. The precipitate was collected, washed thoroughly with water, and dried under reduced pressure at 130°. The yield was 508 mg, 78%. The product was identified as barium carbonate by its infrared spectrum.

Carbon Dioxide from Pactamycin, Pactamycate, and Desalipactamycate from Base Hydrolysis.—All three of the compounds were run in the same fashion. Starting material (0.5 g) dissolved in 10 ml of 5 *N* sodium hydroxide was refluxed for 48 hr. Nitrogen, which had been passed through barium hydroxide solution, was used to sweep out the reaction mixture while 10 ml of 6 *N* hydrochloric acid was added and then for 4 hr afterward. The nitrogen was bubbled through 100 ml of saturated barium hydroxide solution. The precipitate was isolated by centrifugation, washed thoroughly in the same way, and dried under reduced pressure at 140°. In each case the product was identified as barium carbonate by its infrared spectrum. The yields follow: pactamycin, 90 mg (52%); pactamycate, 78 mg (41%); and desalipactamycate, 74 mg (38%).

Periodate Oxidation of Pactamycin (I).—Pactamycin was titrated by the Fleury–Lange procedure[15] using a solution of 280 mg in 100 ml of a 1:1 mixture of dioxane and 0.1 *M* sodium periodate and titrating with 10-ml aliquots. The consumption of periodate in hours (moles) follows: 0 (0.2), 0.15 (0.3), 1 (0.6), 4 (0.6), and 8 (0.9).

No acetaldehyde was detected by the procedure reported in Dyer.[15]

Periodate Oxidation of Desalipactamycate (IIIa). A. Titration.—Desalipactamycate was titrated by the Fleury–Lange procedure[15] using a solution of 80 mg in 40 ml of 0.05 *M* sodium periodate and titrating 4-ml aliquots. The consumption of periodate in hours (moles) follows: 0 (0.75), 0.5 (2.0), 1 (2.25), 2 (2.62), 4 (3.0), 6 (3.0), and 10 (3.62). Titration with periodic acid in the same way gave very similar results except that 2 mol of periodate was consumed in less than 10 min.

B. Determination of Formaldehyde.—A solution of 400 mg of desalipactamycate in 100 ml of 0.05 *M* sodium periodate was allowed to stand for 4 hr. The solution was adjusted to pH 7 with 0.1 *N* sodium hydroxide and 150 ml of 0.05 *M* sodium arsenite was added. One-half of the solution was adjusted to pH 5.5 with 2 *N* acetic acid. The solution was mixed and 170 ml of 1:1 2 *N* sodium acetate and 1 *N* hydrochloric acid and 175 ml of 0.4% dimedon solution were added. After the solution had stood for 3 days, 71 mg of precipitate was collected. After two recrystallizations from ethyl alcohol, the product melted at 187–192°. The infrared spectrum and mixture melting point identified the product as the dimedon derivative of formaldehyde.

A periodate oxidation in the same way followed by the chromotropic acid procedure for determining formaldehyde[16] indicated 0.653 mol of formaldehyde/mol of desalipactamycate.

C. Determination of Acetaldehyde.—The other half of the solution from B was adjusted to pH 5.5 with 2 *N* acetic acid, and nitrogen was bubbled through it and then through 200 ml of 2,4-dinitrophenylhydrazine solution. After 4 hr no precipitate was obtained.

D. Electrometric Titration.—A solution of 380 mg of desalipactamycate in 100 ml of 0.05 *M* sodium periodate was allowed to stand at room temperature in the dark for 24 hr. Ethylene glycol (0.4 ml) was added. After 1 hr the mixture was titrated with 0.1 *N* sodium hydroxide. The first end point required 7.60 ml of sodium hydroxide indicating that a carboxyl group had been formed by the oxidation.

E. Determination of Volatile Acid.—The procedure reported by Dyer[15] was used on 190 mg of desalipactamycate. Only a trace (0.03 mmol) of volatile acid was detected.

Periodate Oxidation of Pactamycate, Diacetylpactamycate, Desalipactamycate *p*-Nitrobenzenesulfonate, and 6-Deoxy-6-iododesalipactamycate.—These were all run by the Fleury–Lange procedure.[15] No oxidation was detected after 4 hr.

Registry No.—I, 23668-11-3; II, 23754-55-4; IIIa, 23668-12-4; IIIb, 23754-56-5; IIId, 23668-13-5; IIIe, 23668-14-6.

Acknowledgment.—The authors would like to express their appreciation for the invaluable assistance of Dr. Kenneth L. Rinehart, Jr., on this problem. We also thank Dr. Marvin F. Grostic for assistance in obtaining and interpreting mass spectra.

(13) W. K. Anslow and H. Raistrick, *Biochem. J.*, **25**, 39 (1931).

(14) H. W. Galbreath, E. F. Degering, and E. F. Gitch, *J. Amer. Chem. Soc.*, **73**, 1323 (1951).

(15) J. R. Dyer, "Methods of Biochemical Analysis," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1956, p 111.

(16) D. A. MacFadyen, *J. Biol. Chem.*, **158**, 107 (1945).

The Conversion of Cholesterol into 10α-Cholesterol

J. T. EDWARD AND N. E. LAWSON

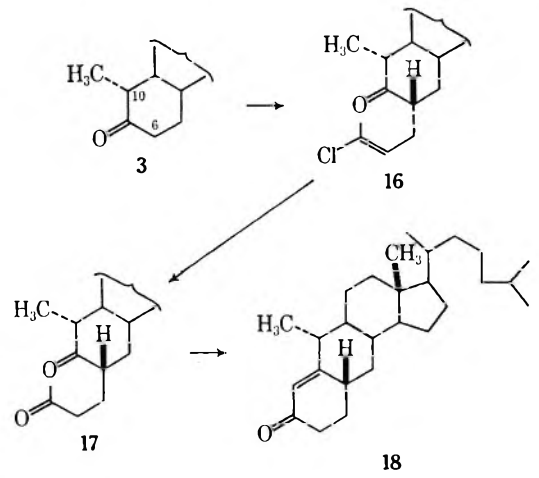
Department of Chemistry, McGill University, Montreal, Canada

Received July 17, 1969

Cholesterol was degraded by a sequence of five reactions to the known BCD intermediate de-A-cholest-9-en-5-one (**5**). Ring A was then restored by methyl vinyl ketone annelation to give 10α-cholest-9(11)-en-5α-ol-3-one (**8**). Hydrogenation of the 9(11) double bond and elimination of the 5α-hydroxyl group generated a mixture of 10α-cholest-4-en-3-one (**12**) and 10α-cholest-5-en-3-one (**13**), which were both converted into the same enol acetate **14**. Reduction with sodium borohydride yielded 10α-cholesterol.

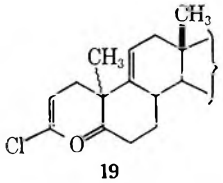
The discovery of the interesting clinical effects of some of the 9β,10α- ("retro") steroids[1] has stimulated interest in steroids of unnatural configuration, and several papers[2-11] have recently described the conversion of steroids into 10α-steroids. We now report the conversion of cholesterol (**1**) into 10α-cholesterol (**15**) by the 11-step sequence shown in Scheme I in a overall yield of 6.4%. While our work was in progress, Uskoković, *et al.*,[6] reported in a preliminary note a synthesis of 10α-progesterone by a route closely similar to ours. This similarity is pointed out at relevant points in our discussion below.

The first objective, the removal of ring A, was accomplished by conversion of cholesterol (**1**) into cholest-4-en-3-one[12] and thence into Windaus' keto acid (**2**)[13] and Inhoffen's ketone (**3**).[14-16] We then attempted to re-form ring A by a preferential condensation at the 10 position without blocking the 6 position. Unfortunately, our results parallelled those of Pinder and Robinson,[17] who had previously found that **3** was alkylated only at C-6. When **3** was treated with 1,3-dichlorobut-2-ene[18,19] in the presence of sodium *t*-amylate,[20] an oily product was obtained in 43% yield which was shown by its nmr spectrum (doublet for the C-10 methyl group) to be the 6-substituted ketone **16**, and not the desired 10-substituted ketone. The configuration of the chlorobutenyl group was assumed to be the more stable α, since alkylation took place under equilibrating conditions. The chloro ketone **16** was converted by treatment with cold, concentrated sulfuric acid[19] into the diketone **17**, and the latter was cyclized in acetic acid–hydrochloric acid[19] to the anthra steroid **18**. This represents a novel route to the anthra steroids.[21,22]



We next decided to try to direct the condensation to the 10 position by introducing a double bond to give the unsaturated ketone **5**, since a rather similar ketone had been found by Barkley, *et al.*,[23] to condense preferentially at C-10. (A further example came from the synthesis of 10α-progesterone by Uskoković, *et al.*,[6] while our work was in progress.)

The unsaturated ketone **5**[16] was prepared by brominating **3** with N-bromosuccinimide to give **4** (a more convenient method than that of Hartshorn and Jones[16]) and dehydrobrominating the latter by lithium chloride in dimethylformamide. The 1,3-dichlorobut-2-ene method of ring formation[18-20] failed completely when applied to **5**, since the initial adduct (or mixture of adducts) **19** could not be further transformed into the desired intermediates.



(1) For a brief review see D. Taub and T. B. Windolz in "Encyclopedia of Chemical Technology," Vol. 18, R. E. Kirk and D. F. Othmer, Ed., John Wiley & Sons, Inc., New York, N. Y., 1969, pp 880–883; E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kessenaar, E. Diczfalusy, and K. C. Tillinger, *Nature*, **186**, 168 (1960); A. M. Krubiner, G. Saucy, and E. P. Oliveto, *J. Org. Chem.*, **33**, 3548 (1968).

(2) R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 2420 (1962).

(3) R. Ginsig and A. D. Cross, *J. Amer. Chem. Soc.*, **87**, 4629 (1965); *J. Org. Chem.*, **31**, 1761 (1966).

(4) J. A. Settepani, M. Torigoe, and J. Fishman, *Tetrahedron*, **21**, 3661, 3669, 3677 (1965).

(5) B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *ibid.*, **21**, 2973 (1965).

(6) M. Uskoković, J. Iacobelli, R. Philion, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966).

(7) G. Saucy, H. Els, F. Miksh, and A. Furst, *Helv. Chim. Acta*, **49**, 1529 (1966).

(8) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron*, **20**, 2473 (1960).

(9) J. Castells, E. R. H. Jones, G. D. Meakins, and S. Palmer, *J. Chem. Soc.*, 2907 (1962).

(10) J. A. Edwards, P. Crabbé, and A. Bowers, *J. Amer. Chem. Soc.*, **85**, 3313 (1963).

(11) P. Crabbé and A. Bowers, *J. Org. Chem.*, **32**, 2921 (1967).

(12) J. F. Eastham and R. Teranishi, *Org. Syn.*, **35**, 39 (1955).

(13) J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Can. J. Chem.*, **39**, 599 (1961).

(14) H. H. Inhoffen and Huang-Minlon, *Chem. Ber.*, **72**, 1686 (1939).

(15) S. A. Julia, A. Eschenmoser, H. Heusler, and N. Tarkoy, *Helv. Chim. Acta*, **36**, 1885 (1953).

(16) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962).

(17) A. R. Pinder and R. Robinson, *ibid.*, 1224 (1952).

(18) O. Wichterle, *Collect. Czech. Chem. Commun.*, **12**, 93 (1947).

(19) R. Bucourt, J. Tessier, and G. Nominé, *Bull. Soc. Chim. Fr.*, 1923 (1963); L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960); L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, and A. Pierdet, *Compt. Rend.*, **250**, 1084 (1960).

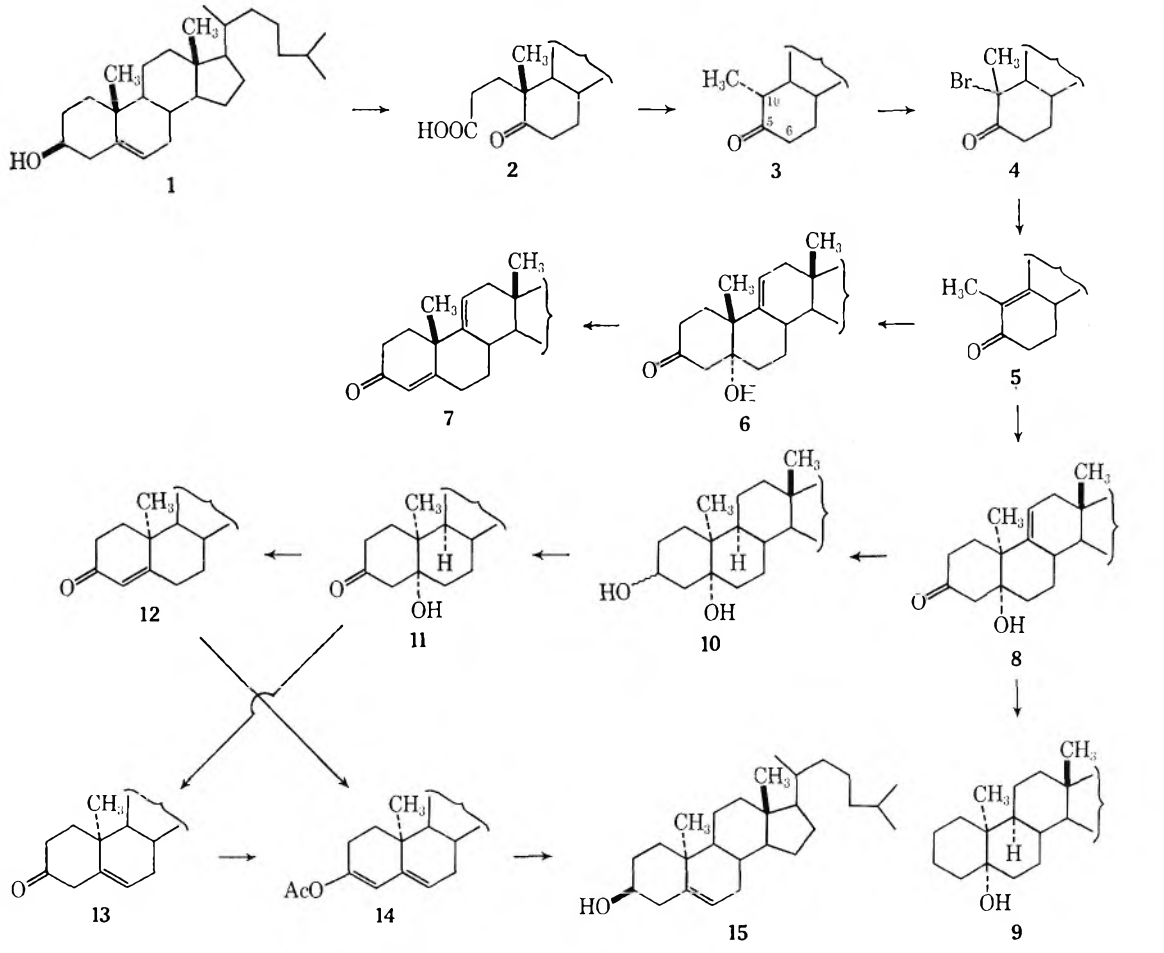
(20) S. Julia, *Bull. Soc. Chim. Fr.*, 780 (1954).

(21) W. R. Nes, R. B. Kostic, and E. Mosettig, *J. Amer. Chem. Soc.*, **78**, 436 (1956).

(22) A. van der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron*, **20**, 2521 (1964).

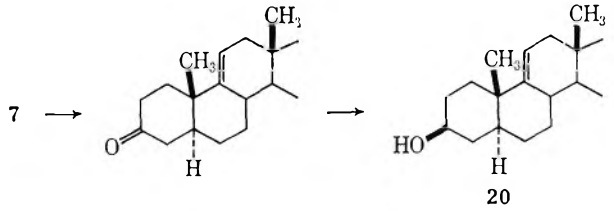
(23) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Amer. Chem. Soc.*, **78**, 4111 (1956).

SCHEME I



However, the unsaturated ketone **5** did react with methyl vinyl ketone in the presence of sodium ethoxide to give two compounds in the ratio of *ca.* 5:1 (by tlc), which were probably the 10α epimer **8** and the 10β epimer **6**, respectively.[24] It was also found that when the reaction mixture was left for several days at 5°, the 10β isomer **6** suffered base-catalyzed elimination of water[25] so that a mixture of only **8**, **7**, and unreacted **5** remained; these compounds were easily separated by column chromatography on alumina.

Compound **7** (5% yield) was eluted from the column after the unreacted starting material. The assigned structure for this compound is in harmony with its



combustion analysis and infrared, ultraviolet, and nmr spectra. The latter was almost identical with that of cholest-4-en-3-one with the addition of a broad peak at 5.45 ppm owing to the vinyl proton at C-11. Further proof for the structure **7** was provided by converting it into the known 5α-cholest-9(11)-en-3β-ol (**20**)[26] by hydrogenation and reduction. Two products were obtained. Both appeared from their infrared spectra to be unsaturated alcohols, but only the major product could be crystallized. The melting point (134–135°) differed from that reported for **20** (123°), although the optical rotations were almost the same; it is possible that it had a different crystalline form, because the acetate was shown to be identical by melting point and mixture melting point with a sample of 5α-cholest-9(11)-en-3β-ol acetate[26] generously provided by Professor L. F. Fieser.

Compound **8** (37% yield) was next eluted from the column. Its structure was supported by its combustion analysis, infrared spectrum, and nmr spectrum (a singlet at 0.82 ppm for the C-19 protons, a singlet at 1.98 ppm for the OH, removed by D_2O, and a broad peak at 5.63 ppm for the C-11 vinyl proton). The tertiary character of the alcohol was indicated by the nmr spectrum (no peak at 3.4–4.5 ppm[27]) and by the resistance to oxidation with Jones reagent.[28] Hydrogenation of **8** over platinum in acetic acid gave a saturated alcohol **9** (20% yield) and a diol **10** (80% yield). The alcohol was believed to have the tertiary structure **9** because it was not oxidized by Jones

(24) The major product was expected to be the 10α isomer from consideration of the "principle of perpendicular attack" discussed by L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965). See also ref 23.

(25) It is shown later that cholest-4-en-3-one of the 10α series is more strained than that of the 10β series; it is possible that this greater strain is reflected in the transition states leading to them, so that β elimination takes place less readily from **8** than from **6**.

(26) L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.*, **75**, 5356 (1953).

(27) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 55.

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

reagent.[28] Several other catalysts and solvents were investigated in an attempt to minimize the hydrogenolysis leading to **9**, but they were not effective in reducing the 9(11) double bond.

The oily diol was not purified but was immediately oxidized by Jones reagent[28] to 10α-cholestan-5α-ol-3-one (**11**) in 74% overall yield from **8**. The infrared spectrum of the ketol **11** was essentially the same as that of **8**, except that the bands of the double bond had disappeared. Hydrogenation of the double bond of **8** would be expected to take place from the less hindered underside of the molecule to give the 9α configuration shown for **10** and thence **11**. The 5α and 10α configurations of **11** are in accord with its negative Cotton effect according to the octant rule,[29] assuming a chair conformation for ring A.

Subjected to refluxing benzene containing a trace of *p*-toluenesulfonic acid, ketol **11** lost water, and the two unsaturated ketones **12** and **13** were separated from the product mixture by chromatography. The major product, 10α-cholest-4-en-3-one (**12**), was an oil whose infrared and ultraviolet spectra showed it to be an α,β-unsaturated ketone. The crystalline 2,4-dinitrophenylhydrazone had an ultraviolet spectrum closely similar to that of the same derivative of natural cholest-4-en-3-one.[30]

The minor product was obtained as a crystalline solid, for which the β,γ-unsaturated structure **13** was indicated by its infrared spectrum. Both **12** and **13** were converted by treatment with perchloric acid–acetic anhydride[31] into the same enol acetate **14**, having an ultraviolet spectrum (uv max 236 mμ) very similar to that of the 10β epimer (uv max 236 mμ), which was prepared in a similar manner from cholest-4-en-3-one.

Alkaline hydrolysis of **14** gave a mixture of **12** and **13** in the ratio (presumably thermodynamically controlled) of 2:1. Ginsig and Cross[3] found that equilibration of 10α-testosterone with potassium *t*-butoxide gave the α,β- and β,γ-unsaturated ketones in the ratio of 1:2. In both cases the proportion of unconjugated ketone in the equilibrium mixture is vastly greater than in the equilibrium mixture of the corresponding 10β compounds.[32] Molecular models show that in **12** ring B is forced to exist in a skew-boat conformation, whereas in **13** it can exist in a more stable half-chair conformation; this effect will destabilize the otherwise more stable conjugated ketone and cause **12** and **13** to be more equally stable.

Reduction of the enol acetate **14** with sodium borohydride in aqueous methanol (a modification of the procedure of Belleau and Gallagher[33]) gave 10α-cholesterol (**15**). Oxidation of this compound under mild conditions[28] gave **13**, thus proving the position of the double bond. The β configuration of the C-3 hydroxyl group was deduced from the nmr spectrum. This showed a fairly broad peak at 3.35 ppm which was due to both the hydroxyl and C-3 protons; after treatment with deuterium oxide the peak became smaller by removal of the hydroxyl proton and much sharper ($W_{1/2}$ = 2.5 Hz). This is characteristic of an equatorial proton α to a hydroxyl group.[34] By comparison, the natural 10β-cholesterol showed a very broad peak at *ca.* 3.4 ppm which was due to the axial α-carbinol proton. The formation of the axial alcohol **15** is probably a case of "steric approach control" in the reduction of the intermediate **13** (from the hydrolysis of **14** during the process) by the bulky solvated borohydride ion,[35] the "convex" α face of **13** being more accessible than the "concave" β face.[36]

The overall nmr spectra of natural and 10α-cholesterol were very similar (except for the hydroxyl and α-carbinol peaks). Surprisingly, the C-19 protons group showed the same chemical shift (0.817 ppm) for both compounds; it might be expected to be at lower field for the 10α isomer, since it does not seem to be able to "see" as much of the steroid ring system.[37]

10α-Cholesterol at a concentration of 10^{-4} *M* failed to prevent the *in vitro* formation of natural cholesterol from 2[^{14}C]-acetate in albino rat liver homogenate.[38]

Experimental Section[39]

10α-De-A-cholestan-5-one (3).—The following procedure is elaborated from that of Hartshorn and Jones,[16] who gave few experimental details.

A 6.7-g portion of sodium methoxide was added to a solution of 23.5 g of **2** in 300 ml of MeOH, and neutralization was completed by adding 0.25 *N* sodium methoxide in MeOH to a phenolphthalein end point. The solution was evaporated to dryness under reduced pressure, and the sodium salt was dried further at 100° for 2 hr. Sodium phenylacetate was similarly prepared from phenylacetic acid. A 25-g portion of the sodium salt of **2**, 100 g of sodium phenylacetate, and 3 g of asbestos fiber were ground together in a mortar, and then pyrolyzed in a 250-ml, round-bottom flask connected by a 90° elbow to a side-arm receiving flask evacuated to 0.05 Torr by a diffusion pump. The flask was heated from 250 to 310° by a bath of molten solder, and kept at the latter temperature for 2 hr. The elbow was heated to 250° by a heating tape, and the receiving flask was cooled with tap water. A pale yellow oil, wt 19.3 g, collected in the receiving flask and was taken up in hexane and chromatographed in two lots on 300-g columns of alumina. The oily solid eluted from the column with hexane was crystallized from petroleum ether (bp 30–60°), giving 6.7 g of **3**, mp 61–62° (lit.[16] mp 62–63°). A further 6.5 g was obtained by chromatography of the mother liquors; total yield 69%. The 2,4-dinitrophenylhydrazone had a melting point of 173–174° (lit.[16] mp 177–178°).

(29) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(30) E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945).

(31) B. E. Edwards and B. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(32) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 50, 51.

(33) B. Belleau and T. F. Gallagher, *J. Amer. Chem. Soc.*, **73**, 4458 (1951).

(34) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 79; (b) J. T. Edward and J. M. Ferland, *Can. J. Chem.*, **44**, 1311 (1966); (c) C. P. Rader, *J. Amer. Chem. Soc.*, **88**, 1713 (1966); (d) D. M. S. Wheeler, M. M. Wheeler, M. Fetizan, and W. H. Castine, *Tetrahedron*, **23**, 3909 (1967).

(35) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, J. Jiu, and R. Micheli, *ibid.*, **78**, 3752 (1956).

(36) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstad, *Tetrahedron*, **2**, 1 (1958).

(37) Reference 34a, p 16.

(38) We are grateful to R. D. Dvornik of Ayerst, McKenna, and Harrison, Ltd., Montreal, Canada, for this test.

(39) Infrared spectra were obtained on Perkin-Elmer 337 or 521 grating spectrophotometers using CCl_4 as solvent; nmr spectra were taken on a Varian A-60 spectrometer using CCl_4 or $CDCl_3$ as solvents and tetramethylsilane as an internal standard; ultraviolet spectra were obtained with a Unicam SP-800 spectrophotometer using 95% EtOH as solvent. Melting points are corrected. Optical rotations were taken on a Carl Zeiss 0.005° photoelectric polarimeter using $CHCl_3$ solutions in a 1-dm tube, and the ORD curve was obtained on a JASCO spectropolarimeter. Column chromatography was carried out on Woelm neutral alumina, grade III. All solutions were dried over anhydrous magnesium sulfate before evaporation. Elemental analyses were performed by Dr. C. Daessle, Montreal, Canada, and by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

6α-(3′-Chlorobut-2′-enyl)-10α-de-A-cholestan-5-one (16).—A solution of 3.8 *N* sodium *t*-amylate[20] in 1.25 ml of dry benzene was added at 5° under nitrogen to a stirred solution of 1.50 g of **3** and 0.71 g of freshly distilled 1,3-dichlorobut-2-ene in 10 ml of dry benzene. The mixture was stirred for 1 hr while warming to room temperature, and was then refluxed for 2 hr. It was diluted with ether, washed with water and saturated, aqueous NaCl solution, dried, and evaporated, The oily residue was chromatographed on 80 g of alumina. Elution with hexane–5% ether yielded 0.82 g (43%) of **16** as a clear oil: ir 3040 and 1675 (HC=C) and 1725 cm^{-1} (C=O); nmr 0.71 (s, C-18 protons), 0.80 (d, J = 4.5 Hz, C-19 protons), 2.2 (s, vinyl methyl), and 5.47 ppm (m, vinyl proton). Analysis by vpc using a glass column (10 ft × 4 mm) packed with 3% SE-30 on Chromosorb W at 250° with a N_2 flow of 90 ml/min demonstrated the product purity, t_R 13.5 min.

6α-(3′-Oxobutyl)-10α-de-A-cholestan-5-one (17).—A solution of 0.80 g of **16** in 5 ml of glacial HOAc was added under N_2 to 12 ml of ice-cold, concentrated H_2SO_4. The dark solution was stirred at 0° for 5 min, and then poured over 50 g of crushed ice. The resulting mixture was extracted with ether, and the organic solution was washed with water and with saturated, aqueous $NaHCO_3$, dried, and evaporated. The oily residue, wt 0.677 g, was chromatographed on 20 g of alumina. Elution with benzene yielded 0.283 g (37%) of **17** as a clear oil, ir 1720 cm^{-1} (C=O).

10α,6β-Anthracholest-4-en-3-one (18).[40]—A solution of 0.283 g of **17** in 5 ml of glacial HOAc and 0.5 ml of concentrated HCl was left overnight at room temperature. It was then diluted with water and extracted with ether. The organic extract was washed with water and with saturated, aqueous $NaHCO_3$, dried, and evaporated. The oily residue was chromatographed on 20 g of alumina. Hexane–benzene (1:1) eluted 0.122 g (43%) of the anthra steroid **18**, which was crystallized twice from MeOH: mp 122.5–123.5°; uv max 244 mμ (log ε 4.10); ir 3030 and 1625 (HC=C) and 1680 cm^{-1} (C=O); nmr 0.70 (s, C-18 protons), 0.85 (d, J = 3.5 Hz, C-19 protons), and 5.65 ppm (s, C-4 vinyl proton).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.47; H, 11.33.

The unsaturated ketone formed a red 2,4-dinitrophenylhydrazone, mp 166.5–167.5°.

Anal. Calcd for $C_{33}H_{48}O_4N_4$: C, 70.18; H, 8.57. Found: C, 70.21; H, 8.56.

De-A-cholest-9-en-5-one (5).—A stirred suspension of 6.94 g of **3** and 3.92 g of N-bromosuccinimide in 100 ml of pentane and 350 ml of CCl_4 was illuminated for 45 min by a 500-W photoflood lamp. The flask was cooled by an air stream to prevent overviolent refluxing. The mixture was cooled, filtered, and evaporated at room temperature to yield a oily, brown residue containing the bromide **4**. This was dissolved with 3.4 g of anhydrous LiCl in 35 ml of dimethylformamide, and the mixture was heated on the steam bath for 4 hr with occasional swirling. It was then cooled, diluted with ether, washed with water and saturated, aqueous NaCl, dried, and concentrated under reduced pressure to give 6.85 g of a dark brown oil which was chromatographed on 210 g of alumina. Hexane and hexane–benzene mixtures eluted 2.95 g of **3**, which was recycled, 0.88 g of a mixture, and 2.46 g of **5**, a pale yellow oil: overall yield 55%; ir 3050 and 1610 (HC=C) and 1675 cm^{-1} (C=O); uv max 249 mμ (log ε 4.16) [lit.[16] uv max 248.5 mμ (log ε 4.21)]; nmr 0.80 (s, C-18 protons) and 1.69 ppm (s, C-19 protons) and no olefinic protons.

A dark red 2,4-dinitrophenylhydrazone was formed by **5**, mp 179.0–179.5° (lit.[16] mp 179–181°).

10α-Cholest-9(11)-en-5α-ol-3-one (8).—To 8.30 g of **5** in 60 ml of anhydrous dioxane, a solution of 0.58 g of sodium in 190 ml of absolute EtOH was added. This was cooled to −15° under N_2 and 6.5 ml of freshly distilled methyl vinyl ketone in 50 ml of anhydrous dioxane was dripped in over 9.5 hr with stirring. The reaction was left at 0° under N_2 for 2 days, whereupon an additional 2 ml of methyl vinyl ketone in 2 ml of dioxane was added, and the solution left as before for an additional 2 days. Glacial HOAc (10 ml) was then added, and the solvent was removed at room temperature under reduced pressure. After dilution with water, the mixture was extracted twice with ether, and the organic layer was washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 285 g of alumina to yield 3.73 g (37%) of **8**, eluted by benzene–10% ether. This was recrystallized from petroleum ether: mp 148.5–149.5°; $[\alpha]^{25}D$ −61° (*c* 0.55); ir 3600 (OH), 3050 and 1675 (HC=C) and 1720 cm^{-1} (C=O); nmr 0.59 (s, C-18 protons), 0.82 (s, C-19 protons), 1.98 (s, hydroxyl proton, removed by D_2O), 1.5–3.0 (m, protons α to carbonyl), and 5.63 ppm (broad s, C-11 vinyl proton).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.26; H, 10.96.

Cholesta-4,9(11)-dien-3-one (7).—During the previous chromatography, a brown oil was obtained from the earlier fractions, which was shown by tlc to be mostly unreacted ketone **5** (18% yield) plus a slightly more polar compound. This was obtained crystalline after standing for several weeks, and was recrystallized from petroleum ether and MeOH to give 0.465 g (5%) of **7**: mp 116–116.5°; $[\alpha]^{25}D$ +81° (*c* 1.84); ir 3040 and 1610 (HC=C) and 1680 cm^{-1} (C=O); uv max 241 mμ (log ε 4.18); nmr 0.65 (s, C-18 protons), 0.82 (s, C-19 protons), 5.45 (broad s, C-11 vinyl proton), and 5.73 ppm (s, C-4 vinyl proton).

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.55; H, 11.05.

5α-Cholest-9(11)-en-3β-ol (20).—An 84-mg sample of cholesta-4,9(11)-dien-3-one (**7**) was hydrogenated over 61 mg of prereduced Adams catalyst in 15 ml of HOAc containing 1 drop of concentrated HCl until rapid uptake of H_2 ceased (30 min). After filtration the solution was diluted with ether, washed with water and saturated, aqueous $NaHCO_3$, dried, and concentrated. The residue was dissolved in 50 ml of acetone and oxidized to the ketone(s) with Jones reagent.[28] Excess oxidant was destroyed with 5 ml of MeOH, and the solution was diluted with ether and washed with water and saturated, aqueous $NaHCO_3$. The solvent was evaporated and the residue was dissolved in 10 ml of anhydrous diglyme to which 200 mg of lithium tri-*t*-butoxyaluminum hydride was then added. After the solution had been stirred overnight at 25°, water was added to destroy the excess hydride followed by 10 ml of glacial HOAc. The solution was extracted with ether, and the organic layer was washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 10 g of alumina. Hexane–10% benzene eluted an oil which did not crystallize, and benzene eluted 20 mg of 5α-cholest-9(11)-en-3β-ol (**20**), which was recrystallized from MeOH: mp 134–135°; $[\alpha]^{25}D$ +25° (*c* 0.13) (lit.[26] mp 123°, $[\alpha]D$ +27°); ir 3625 and 3300 (OH) and 3040 and 1675 cm^{-1} (HC=C).

The acetate was prepared by the method of Edwards and Rao:[31] mp 105–108°; $[\alpha]^{25}D$ +24° (*c* 0.17) (lit.[26] mp 105°, $[\alpha]D$ +22.5°).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.21; H, 11.20.

The acetate was shown to be identical by melting point and mixture melting point with a genuine sample of 5α-cholest-9(11)-en-3β-ol acetate.

10α-Cholestan-5α-ol-3-one (11).—A solution of 266 mg of **8** in 20 ml of glacial HOAc was hydrogenated at 1 atm over 196 mg of prereduced Adams catalyst. After 2 equiv of hydrogen was absorbed (4 hr), ether was added and the catalyst was filtered off. The filtrate was washed with water and saturated, aqueous $NaHCO_3$ solution, dried, and concentrated under reduced pressure to give a mixture of the saturated diol **10** and the alcohol **9**, ir 3620 and 3400 cm^{-1} (OH). The crude mixture in 50 ml of acetone was oxidized by Jones reagent,[28] excess oxidant being destroyed by the addition of 5 ml of MeOH. The solution was diluted with ether, washed with water and saturated, aqueous $NaHCO_3$ solution, dried, and concentrated to give a solid which was crystallized from petroleum ether to yield 197 mg of **11** (74% from **8**): mp 170.5–171°; $[\alpha]^{25}D$ +49° (*c* 0.24); ir 3610 and 3400 (OH) and 1710 cm^{-1} (C=O); ORD (*c* 0.10, $CHCl_3$) $[\phi]_{400}$ +30°, $[\phi]_{350}$ +30°, $[\phi]_{327}$ 0°, $[\phi]_{312}$ −80° (max), $[\phi]_{300}$ −35° (inflection), $[\phi]_{302}$ 0°, $[\phi]_{300}$ +45°, $[\phi]_{290}$ +190°, $[\phi]_{280}$ +250°, and $[\phi]_{275}$ +310°.

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.69; H, 11.22.

Palladium or platinum in EtOH or EtOAc, with or without a trace of perchloric acid, and tris(triphenylphosphine)rhodium chloride[41] in benzene with hydrogen pressures of 1–4 atm were all tried in vain attempts to improve the yield of **11**.

10α-Cholestan-5α-ol (9).—The combined mother liquors from the crystallization of **11** were chromatographed on alumina. Hexane–10% benzene eluted **9** (20% yield from **8**), which was

(40) Numbering system suggested in ref 22.

(41) A. J. Birch and K. A. M. Walker, *J. Chem. Soc.*, 1894 (1966).

crystallized from MeOH: mp 79.5–80°; $[\alpha]^{25}D$ +53° (*c* 0.18); ir 3640 and 3350 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.72; H, 12.25.

A solution of 50 mg of **9** in acetone was treated with Jones reagent,[28] but only starting material was isolated.

10α-Cholest-4-en-3-one (12) and 10α-Cholest-5-en-3-one (13).—In 10 ml of dry benzene, 123 mg of **11** was refluxed for 2 hr with a trace of *p*-toluenesulfonic acid. Dilution with ether, washing with saturated, aqueous $NaHCO_3$, drying, and evaporation of the solvent gave a clear oil which was chromatographed on 12 g of alumina. Hexane–25% benzene eluted 27 mg (22%) of of a white solid, which was crystallized from MeOH–H_2O to give **13**: mp 112–112.5°; $[\alpha]^{25}D$ −104° (*c* 0.68); ir 3030 and 1680 (HC=C) and 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.14; H, 11.56.

Hexane–50% benzene eluted 90 mg (73%) of a clear oil which could not be crystallized and was assigned structure **12**: ir 3030 and 1630 (HC=C) and 1680 cm^{-1} (conjugated C=O); uv max 243 mμ (log ε 4.15).

The oil formed a red, crystalline 2,4-dinitrophenylhydrazone: mp 185–185.5°; uv max 260 mμ (log ε 4.23), 293 (4.02), and 392 (4.44). The uv of the analogous 10β compound[30] was 256 mμ (log ε 4.33), 281 (4.20), 292 (4.06), and 393 (4.47).

Anal. Calcd for $C_{33}H_{48}O_4N_4$: C, 70.18; H, 8.57. Found: C, 70.08; H 8.73.

10α-Cholesta-3,5-dien-3-ol Acetate (14).—Both **12** and **13** were convertible into the same enol acetate (**14**) by the method of Edwards and Rao.[31] In later experiments the crude mixture of **12** and **13** derived from 825 mg of the ketol **11** was treated with the following reagent: 10 ml of a solution of 0.05 ml of 72% perchloric acid in 50 ml of absolute EtOAc was poured into a 50-ml volumetric flask containing 30 ml of absolute EtOAc and 4.8 ml of acetic anhydride and the flask was made up to 50 ml with EtOAc. After standing for 10 min the reaction product was diluted with ether and saturated aqueous $NaHCO_3$ was added. The ether phase was washed well with the $NaHCO_3$ solution, dried, and concentrated.

To the residue was added 5 ml of MeOH containing a trace of pyridine, and the whole was evaporated to dryness, and crystallized from MeOH to give 733 mg of the enol acetate **14** (84% overall yield from **11**): mp 93–94°; $[\alpha]^{25}D$ +32° (*c* 0.36); ir 3030 and 1660 (HC=C) and 1755 cm^{-1} (C=O); uv max 236 mμ (log ε 4.18).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.75; H, 10.93.

Alkaline Hydrolysis of 10α-Cholesta-3,5-dien-3-ol Acetate (14).—In 2 ml of MeOH, 5 mg of **14** was dissolved and 0.25 ml of 5% aqueous NaOH was added. The solution was refluxed for several minutes, cooled, diluted with ether, washed with water and saturated, aqueous NaCl, and dried, and the solvent was evaporated. The ir spectrum of the product showed two strong carbonyl peaks: 1720 (unconjugated ketone **13**) and 1680 cm^{-1} (conjugated ketone **12**). Their absorption intensities were in the ratio 1:2, respectively.

10β-Cholesta-3,5-dien-3-ol Acetate.—This compound was made for uv comparison purposes by the same method as the 10α analog: mp 83–84° (clears at 110°) [lit.[42] mp 80° (clears at 105–110°)]; uv max 236 mμ (log ε 4.26).

10α-Cholesterol (15).—A 3-g sample of sodium borohydride in 30 ml of 85% aqueous MeOH was added to a solution of 615 mg of the enol acetate **14** in 400 ml of MeOH at 5°, and the resulting solution was stirred and allowed to warm up to 25°. After 2.5 hr a further 0.5 g of borohydride was added and the solution was stirred overnight. The MeOH was removed under reduced pressure, ether was added, and enough 2 *N* HCl was added to make the aqueous layer slightly acidic, this phase being extracted well with ether. The combined ether extracts were washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 30 g of alumina. Hexane–50% benzene eluted a solid which was crystallized from MeOH to give 468 mg (84%) of **15** as white needles: mp 118.5–119°; $[\alpha]^{25}D$ −46° (*c* 1.14); ir 3620, 3350, 1390, 1375, and 1050 (COH), and 3040 and 1675 cm^{-1} (HC=C); nmr 0.69 (s, C-18 protons), 0.817 (s, C-19 protons), 3.45 (broad s, α-carbinol proton and hydroxyl proton, the latter disappears on D_2O exchange to give a sharp s, $W_{1/2}$ = 2.5 Hz), and 5.44 ppm (d, *J* = 6 Hz, C-6 vinyl proton).

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.76; H, 11.79.

10α-Cholesterol Acetate.—This compound was prepared by acetylation of 10α-cholesterol by the method of Edwards and Rao:[31] mp 124–124.5°; $[\alpha]^{25}D$ −47° (*c* 1.48); ir 3040 and 1675 (HC=C) and 1740, 1375 (d), 1250, and 1040 cm^{-1} (COAc).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.14; H, 11.40.

Oxidation of 10α-Cholesterol (15).—To 20.5 mg of **15** in 5 ml of acetone, Jones reagent[28] was added in slight excess; 2 ml of MeOH was then added, followed by ether and saturated, aqueous $NaHCO_3$. The ether layer was dried and concentrated, and the white solid was crystallized from MeOH to give **13**, identified by melting point and mixture melting point.

Registry No.—**1**, 57-88-5; **3**, 23820-60-2; **5**, 23820-61-3; **7**, 23820-62-4; **8**, 23820-63-5; **9**, 23820-64-6; **11**, 23820-65-7; **12**, 23820-66-8; **12** 2,4-dinitrophenylhydrazone, 23820-67-9; **13**, 23820-68-0; **14**, 23820-69-1; **15**, 23820-70-4; **15** acetate, 23820-71-5; **16**, 23820-72-6; **17**, 23820-73-7; **18**, 23820-74-8; **18** 2,4-dinitrophenylhydrazone, 23820-75-9; **20**, 23820-76-0.

Acknowledgments.—We are grateful to the Medical Research Council of Canada for financial support, to Canada Packers, Ltd., for generous supplies of cholesterol, to Professor Peter Morand for ORD measurements, to Professor L. F. Fieser for a sample of 5α-cholest-9(11)-en-3β-ol acetate, and to McGill University for a University Graduate Scholarship to one of us (N. E. L.)

(42) H. Reich and A. Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).

Partial Synthesis of 25D- and 25L-Cholestanoic Acids from Some Common Bile Acids[1]

THOMAS BRIGGS

Department of Biochemistry and Molecular Biology, The University of Oklahoma Medical Center, Oklahoma City, Oklahoma 73104

Received September 17, 1969

Cholestanoic acids isomeric at C-25 have been partially synthesized by an improved application of the Kolbe electrolytic cross-coupling reaction. Electrolysis was carried out with optically pure methyl 2-methyl-3-carboxypropanoate, *i.e.*, one of the half-esters of methylsuccinic acid, and a C_{24} bile acid. A single step produced the extended-chain 25D- or 25L-bile acid methyl ester, after which the free acid was easily obtained. Cholestanoic acids corresponding to cholic, deoxycholic, chenodeoxycholic, and lithocholic acids were made, in yields of 3–5% (pure crystalline products). The contribution of side-chain extension to molecular rotation is *ca.* −24 in 25D-cholestanoic acids and +47 in the 25L series, when compared with the parent C_{24} cholanoic acid.

Bile acids with 27 carbon atoms are interesting from the standpoint of both comparative biochemistry and metabolism. They occur in the bile of some primitive existing vertebrates, and are also a stage in the formation of cholic acid[2] from cholesterol in more highly evolved forms. The pathway of bile acid biosynthesis in a mammal such as the rat apparently recapitulates the evolutionary history of bile acids in vertebrates.[3]

In partial synthesis of 27-carbon bile acids, introduction of an asymmetric center at C-25 presents a major difficulty. Using the Kolbe electrolytic cross-coupling reaction, Bridgwater[4] converted cholic acid into optically pure 3α,7α,12α-trihydroxy-5β-cholestanoic acids by a procedure which has remained the only unambiguous synthesis of these substances. Others[5] have reported syntheses, but without attempting to produce asymmetry at C-25.

This paper describes the partial synthesis of two known and six new C_{27} bile acids corresponding to some of the common C_{24} acids. Asymmetry has been introduced at C-25 by an electrolytic method based on that of Bridgwater, but with modifications which have simplified the synthesis and improved the yields.

Discussion

The synthesis described here differs from the method of Bridgwater[4] in the asymmetric half-ester used during electrolysis. Owing to the lack of a satisfactory method for preparing optically pure half-esters of methylsuccinic acid, Bridgwater used half-esters of D- or L-β-methylglutaric acid. Electrolysis produced methyl esters of homocholestanoic acids which had to be converted into C_{27} acids by a laborious Barbier–Wieland degradation.

Bridgwater attempted to employ half-esters of methylsuccinic acid, but the method of preparation (from D- or L-methylsuccinic anhydride) actually gave a mixture of $HOOCCH_2CH(CH_3)COOMe$ (A), and $HOOCCH(CH_3)CH_2COOMe$ (B) (both D or both L). Although B theoretically should not have undergone anodic coupling, the mixture gave anomalous results, and the products of electrolysis were not considered reliable with respect to configuration at C-25.

Methylsuccinic acid half-methyl ester prepared by the method of Ställberg[6] exists entirely as A above. Electrolysis conducted with the optically pure form should give unequivocal results. This was verified by preliminary syntheses with cholic acid, which yielded the expected products (**1** and **2**) whose configuration was established by Bridgwater.

Preparing optically pure half-ester is tedious. However, for making 25D- and 25L-cholestanoic acids, the present synthesis has the advantage that electrolysis with C_{24} bile acid yields the product (methyl ester) in one step. Once the half-ester is available, it can easily be used to make a variety of C_{27} acids, since purification in each case is not difficult.

Equimolar amounts of bile acid and half-ester were an arbitrary choice for electrolysis. Excess half-ester would have improved the yield (based on C_{24} bile acid) but wasted precious half-ester. Excess bile acid might have conserved half-ester, but produced larger amounts of steroid impurities which could have hindered recovery of C_{27} acid. With a 1:1 ratio of reactants, the extent of cross coupling which would form the desired compound could not be expected to result in a yield of more than 25%. Yields of pure crystalline products were usually 3–5%.

Rotational Relationships.—Side-chain extension with introduction of a new center of asymmetry changes the optical rotation of bile acids in a manner which causes systematic differences in molecular rotation (M_D). These M_D increments (ΔM_D) should be the same for a series of cholestanoic acids having the same asymmetry at C-25, assuming no vicinal effects since the side-chain terminus is well separated from the rest of the molecule.

With two exceptions, pure synthetic cholestanoic acids have consistent ΔM_D values. Compared with the parent C_{24} bile acids, three C_{27} acids, made from

(1) Supported in part by a general research support grant (NIH) from the University of Oklahoma School of Medicine. The work was begun while the author was in the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn., where it was supported by USPHS Grants FR 00356-01 and HE 03558-10. An abstract has appeared: T. Briggs, *Federation Proc.*, **26**, 3333 (1967).

(2) Systematic names: cholic acid, 3α,7α,12α-trihydroxy-5β-cholanoic acid; chenodeoxycholic acid, 3α,7α-dihydroxy-5β-cholanoic acid; deoxycholic acid, 3α,12α-dihydroxy-5β-cholanoic acid; lithocholic acid, 3α-hydroxy-5β-cholanoic acid. In the nomenclature of cholestanoic acids according to the sequence rule, 25D corresponds to (25*R*) and 25L to (25*S*).

(3) Recent reviews: (a) comparative biochemistry and evolution, G. A. D. Haslewood, *J. Lipid Res.*, **8**, 535 (1967); (b) metabolism, H. Danielsson and T. T. Tchen in "Metabolic Pathways," Vol. 2, D. M. Greenberg, Ed., Academic Press Inc., New York, N. Y., 1968; (c) extended-chain bile acids and alcohols, T. Hoshita and T. Kazuno, *Advan. Lipid Res.*, **6**, 207 (1968).

(4) R. J. Bridgwater, *Biochem. J.*, **64**, 593 (1956).

(5) (a) P. D. G. Dean and R. T. Aplin, *Steroids*, **8**, 565 (1966); (b) N. Hoshita and K. Okuda, *J. Biochem.* (Tokyo), **62**, 655 (1967); (c) K. Morimoto, Y. Kurata, N. Hoshita, and K. Okuda, *Hiroshima J. Med. Sci.*, **17**, 1 (1968).

(6) G. Ställberg, *Arkiv Kemi*, **12**, 79 (1957).

TABLE I

PHYSICAL CONSTANTS OF C_{27} BILE ACIDS

Compd	Parent acid	Isomerism at C-25	Mp, °C	Methyl ester Mp, °C	α_D, deg	MD, deg	MD[a] of parent acid, deg	ΔMD of chain extension
1	Cholic	L	199–201	160–161	+44	198	151	+47
2		D	183–184	153–154	+28	126		−25
3	Chenodeoxycholic	L			+18[b]	79[b]	45	+34[b]
4		D	175–176		+5	21		−24
5	Deoxycholic	L	177–179		+63	274	208	+66
6		D	130, 174–175	92–94	+47	204		−4
7	Lithocholic	L	169–170	112–113	+43	180	132	+48
8		D	155–157	108–109	+26	109		−23

[a] Based on α_D values (EtOH): Cholic +37°; deoxycholic, +53°; chenodeoxycholic, +11.5°; lithocholic, +35°. [b] Noncrystalline product.

cholic, chenodeoxycholic, and lithocholic acids, exhibit ΔMD values close to −24 when configuration at C-25 is D (Table I). Two 25L products, made from cholic and lithocholic acids, show ΔMD about +47. The 25L product made from chenodeoxycholic acid could not be purified by crystallization and has MD lower than the expected value. The presence of 12% impurity (optically inactive) could, however, account for the discrepancy.

Molecular rotations for 25D- and 25L-cholestanoic acids made from deoxycholic acid show increments (−4 and +66) which deviate from the other values (−24 and +47). However, the difference between the 25D and 25L Δ values is nearly the same in all cases (*ca.* 70). Since Δ values are derived in part from α_D of the parent C_{24} acid, a simple explanation for the anomalous figures could be that the accepted α_D value for deoxycholic acid (+53°) is low by about 10%; that is, it should be about +58°. In fact, calculation of the specific rotation of deoxycholic acid from α_D values of other bile acids and MD contributions of various hydroxyl groups gives a figure of +58°. Further, Wieland and Sorge[7] found that deoxycholic acid holds solvents with exceptional tenacity. After careful purification and exhaustive drying, their sample had α_D +57°.

On balance, we may assign, for the MD contribution of side-chain extension in various bile acids, tentative values of −24 for 25D-cholestanoic acids and +47 for the 25L series, when compared with parent C_{24} cholanoic acids.

Biological.—Several 5β-cholestanoic acids occur naturally,[3c,5a,8] but a number remain to be found, which the compounds described in this report will be useful in identifying. A series of 5α-cholestanoic acids, corresponding to the 5α (allo) cholanoic acids, may also occur. One, a C_{27} homolog of allocholic acid, has already been isolated from the bile of the lizard *Iguana iguana*.[9] From MD considerations, the 25D isomer should have α_D *ca.* +16°, and the 25L isomer *ca.* +31° (taking α_D +23° for allocholic acid[10]).

Optically pure cholestanoic acids will also be valuable in metabolic investigations. Mendelsohn and Mendelsohn[11] have shown that rat liver enzymes of cholesterol catabolism exhibit a stereochemical preference in sterol side-chain oxidation. A search for cholestanoic acid as an intermediate *in vitro* revealed mainly the 25D form. Partially synthetic C_{27} acids can be used both as substrates and as reference substances in the analysis of unknown metabolites. Work along these lines is in progress.

Experimental Section

Half-Methyl Esters of Optically Active Methylsuccinic Acid.—Methylallylacetic acid was synthesized, resolved with quinine,[12] and converted into (−)-methyl 2L-methyl-3-carboxypropanoate,[6] α_D (pure substance) −8.52° (lit.[6] α_D −8.71°). The opposite enantiomer of methylallylacetic acid[13] was prepared *via* the (+)-phenylethylamine[14] salt, and converted into (+)-methyl 2D-methyl-3-carboxypropanoate.[6] Since optical purity of the half-ester was unsatisfactory, resolution was completed by means of the cinchonidine salt,[6] giving $\alpha^{20}D$ +9.55° (lit.[6] $\alpha^{20}D$ +9.44°).

Electrolysis.[15]—The two electrodes were of platinum mesh, 3 cm × 8 cm, rolled into cylinders and mounted coaxially 2.5 mm apart on two Teflon rings. A typical electrolysis was conducted in a 150-ml beaker, in which the electrodes were suspended with platinum wire. Sodium (1.7 mg-atoms) was dissolved in redistilled methanol (100 ml, dried by reaction with magnesium). Bile acid (17 mmol) was added; the mixture was stirred and warmed if necessary to promote solution. Optically active half-ester of methylsuccinic acid (17 mmol) was added and the assembly was immersed in an ice bath. Electrolysis was carried out with constant stirring (magnetic bar) at 15–25° using direct current from a 20-V power source. Current polarity was reversed every 15 min. Initially *ca.* 0.9 A, the current decreased after 3–4 hr to *ca.* 0.7 A. The reaction caused a change in pH from *ca.* 4.5 to 6.5.

Purification.—The methanolic solution, which contained products of electrolysis, was poured into water (700 ml), acidified (HCl) to about pH 2, and extracted twice with ethyl acetate (150 ml and 100 ml) and twice with ether (100 ml each). The combined extracts were washed with 5% aqueous $NaHCO_3$ (100 ml), water (50 ml), and saturated NaCl solution (50 ml). The combined washings were extracted with ether (50 ml), which was added to the main ethyl acetate–ether solution and filtered through Na_2SO_4. Evaporation left neutral material, usually about 6.5 g. Acidic material (usually 1 g or less) could be recovered from the aqueous washings.

The neutral fraction, which consisted of a complex mixture including the desired C_{27} bile acid methyl ester, was partially purified by adsorption chromatography on alumina (acid; 80–200 mesh, Fisher Scientific Co., Houston, Texas). Fractions were concentrated and analyzed by thin layer chromatography (tlc). Those with product were combined and saponified by refluxing 1.5 hr with 2 *N* ethanolic KOH (25 ml). After dilution with water (250 ml), ether extraction removed nonsaponifiable material. The aqueous solution was acidified (HCl) and extracted with ethyl acetate (50 ml) and twice with ether (50 ml each); the combined extracts were washed with water (25 ml) and saturated NaCl solution (25 ml). The combined washings

(7) H. Wieland and H. Sorge, *Z. Physiol. Chem.*, **97**, 1 (1916).
(8) T. Briggs, M. W. Whitehouse, and E. Staple, *Arch. Biochem. Biophys.*, **85**, 275 (1959).
(9) K. Okuda, M. G. Horning, and E. C. Horning, *Proc. Int. Congr. Biochem., 7th, Tokyo, IV*, 721 (1967) (Abstracts).
(10) I. G. Anderson and G. A. D. Haslewood, *Biochem. J.*, **85**, 236 (1962).
(11) D. Mendelsohn and L. Mendelsohn, *ibid.*, **114**, 1 (1969).
(12) S. Ställberg-Stenhagen, *Arkiv Kemi, Mineral., Geol.*, **23A**, 1 (1946).
(13) G. Ställberg, *Acta Chem. Scand.*, **11**, 1430 (1957).
(14) A. W. Ingersoll in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943.
(15) The method in general is that of Bridgwater,[4] with modifications. I thank Dr. B. Preiss for help in designing electrodes.

were extracted with ether (15 ml), which was added to the main ethyl acetate–ether solution and filtered through Na_2SO_4. Evaporation left crude C_{27} acid, usually 0.5–0.8 g, which often crystallized readily. Yields, calculated from the total amount of starting material (17 mmol of C_{24} bile acid), are given for pure recrystallized products.

Characterization of Products.—Melting points were determined on a block-type apparatus under a magnifying lens and are uncorrected. Galbraith Laboratories, Inc., Knoxville, Tenn., performed the microanalyses. Optical rotation measurements were made with a Franz Schmidt and Hoensch polarimeter. Unless stated otherwise, all determinations were done at or near 25°, in 2% ethanolic solutions with a 2-dm light path. Methyl esters were made with CH_2N_2. Thin layer chromatography was carried out with silica gel H (E. Merck, A. G., Darmstadt, Germany) in 250-μ layers. Solvent systems were modified from Usui.[16] Spots were made visible with an anisaldehyde spray reagent.[17] Since R_f values varied, analyses always included standards. Cholestanoic acids and their methyl esters migrated farther than the corresponding C_{24} compounds containing the same number of hydroxyl groups (Table II).

TABLE II

THIN LAYER CHROMATOGRAPHY OF BILE ACIDS

	R_f of free acid in system 1[a]	R_f of Me ester in system 2[b]
Cholic	0.04	0.02
1 and 2	0.09	0.04
Chenodeoxycholic	0.25	0.18
3 and 4	0.35	0.27
Deoxycholic	0.28	0.18
5 and 6	0.41	0.31
Lithocholic	0.74	0.72
7 and 8	0.78	0.79

[a] Benzene–acetic acid (80:20). [b] Benzene–ethyl acetate (50:50).

3α,7α,12α-Trihydroxy-5β-25L-cholestanoic Acid (1).—Electrolysis of cholic acid (7.0 g, Mann Research Laboratories, New York) with L half-ester (2.5 g) and Na (40 mg) for 4 hr gave neutrals (5.7 g) and acids (1.8 g). The neutrals were dissolved in ether and applied to a column of alumina (150 g, activity grade I) prepared in ether. Eluting solvents (collected in 250-ml portions) and residues after evaporation follow: ether (0.5 l.) and ether–acetone (1:1) (0.5 l.), 1.44 g; acetone (1 l.), 2.15 g; 2% methanol in acetone (0.5 l.), 0.78 g; 10% methanol in acetone (0.5 l.), 1.33 g; and methanol (0.5 l.), 0.92 g. Substances with the mobility (tlc) expected of methyl trihydroxycholestanoate emerged in fractions eluted by acetone and by 2% methanol in acetone. Saponification yielded neutrals (1.8 g), and an acid (0.72 g), which crystallized on standing with ethyl acetate. Recrystallization from ethyl acetate and from ethanol–water gave 1 (393 mg, 5%), mp 199–201°, α_D +44° (lit.[4] mp 195–196°, α_D +43°).

The methyl ester, crystallized from ether–petroleum ether (bp 30–60°) melted at 160–161°. Komatsubara[18] reported mp 156° for the methyl ester of the acid (mp 195–196°) from the bile of *Rana nigromaculata nigromaculata*, and from partial synthesis.

3α,7α,12α-Trihydroxy-5β-25D-cholestanoic Acid (2).—Electrolysis of cholic acid (7.0 g) with D half-ester (1.5 g) and Na (40 mg) for 2 hr, followed by addition of half-ester (1.0 g) and further electrolysis (total, 4.5 hr), gave neutral material (6.0 g) and acids (1.0 g). Neutrals were separated on alumina as before. Appropriate fractions were combined (2.2 g) and saponified yielding neutrals (1.4 g, discarded) and an acid (0.9 g), which crystallized on standing with ether. Recrystallization from ethyl acetate, acetone (twice), ethanol–water, and acetone gave 2 (357 mg, 4.6%), mp 183–184°, $\alpha^{20}D$ +28° (MeOH) (lit.[4] mp 180–182°, α_D +27°).

The methyl ester, crystallized from ether, melted at 153–154°. Haslewood[19] reported mp 153–155° for the methyl ester of the acid (mp 171–173°) from alligator bile.

3α,7α-Dihydroxy-5β-25L-cholestanoic Acid (3).—Electrolysis of chenodeoxycholic acid (6.7 g, "A" grade, CalBiochem, Los Angeles, Calif.) with L half-ester (1.5 g) and Na (40 mg) for 1.5 hr, followed by addition of half-ester (1.0 g) and further electrolysis (total, 4.25 hr), gave neutrals (6.25 g) and acids (0.5 g). The neutrals were dissolved in ether and applied to a column of alumina (180 g, activity grade I) prepared in ether. Eluting solvents and residues follow: ether (0.5 l.) 0.2 g; ether–acetone (1:1) (0.5 l.), 3.0 g; acetone (1.5 l.), 4.8 g; 2% methanol in acetone (1.0 l.), 0.5 g; and 10% methanol in acetone (0.5 l.), 0.7 g. Substances with the mobility (tlc) expected of methyl dihydroxycholestanoate emerged with the first 0.75 l. of acetone.

The combined fractions (4.5 g), which contained much pungent oil,[20] were dissolved in ether and rechromatographed on a column of alumina (135 g) prepared in ether. Eluting solvents and residues follow: ether (0.25 l.), 0.05 g; 50% acetone in ether (1.0 l.), 7.9 g; 60% acetone in ether (1.0 l.), 3.5 g; 75% acetone in ether (1.0 l.), 0.7 g; and acetone (1.0 l.), 0.7 g. The product was eluted by the last 250 ml of 50% acetone and the first 500 ml of 60% acetone. The combined residues (2.4 g) after saponification yielded neutrals (1.6 g, partially crystalline) and acids (0.75 g), which did not crystallize even after purification by reversed phase column partition chromatography.[21] The amorphous material had α_D +18°.

Attempts to crystallize the methyl ester, the diacetate, and the diacetate methyl ester also failed.

3α,7α-Dihydroxy-5β-25D-cholestanoic Acid (4).—Electrolysis of chenodeoxycholic acid (6.7 g) with D half-ester (2.5 g) and Na (40 mg) for 4 hr yielded a small amount of acid material and neutrals (6.6 g), which were dissolved in benzene and applied to a column of alumina (150 g, deactivated with 6% water), prepared in benzene. Eluting solvents (1.0 l. each, collected in 200-ml portions) and residues follow: benzene, 0.95 g; 20% ether in benzene, 1.9 g; and 50% ether in benzene, 1.1 g. Fractions eluted by the last 600 ml of 20% ether appeared (tlc) to contain most of the product and were combined (0.87 g). Saponification gave neutrals (413 mg) and acids (415 mg). The acid fraction was purified by reversed phase column partition chromatography: stationary phase, chloroform–heptane (9:1, 25 ml) on Reversil 4 (100 g, Applied Science Laboratories, State College, Pa.); moving phase, 58% methanol in water.[21] Fractions (5 ml) were titrated with 0.02 *N* NaOH. The peak emerging at 170–615 ml contained material which was recovered by concentration, acidification, and extraction with ethyl acetate–ether. Evaporation left crystals (198 mg), mp 173–175°. Two recrystallizations from methanol–water yielded 4 (161 mg, 2.2%), mp 175–176°, α_D +5°.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.7; H, 10.8.

The methyl ester did not crystallize from any solvent tried.

3α,12α-Dihydroxy-5β-25L-cholestanoic Acid (5).—Electrolysis of deoxycholic acid (6.7 g, recrystallized "C" grade, CalBiochem) with L half-ester (2.5 g) and Na (44 mg) gave neutrals (6.8 g), which were dissolved in benzene and applied to a column of alumina (150 g, deactivated with 6% water) prepared in benzene. Eluting solvents (0.8 l. each) and residues follow: benzene, 0.75 g; 20% ether in benzene, 3.5 g; and 50% ether in benzene, 1.2 g. Substances with appropriate mobility on tlc emerged in 50% ether and in the last 600 ml of 20% ether. Saponification yielded neutrals (1.5 g) and an acid (0.5 g), which crystallized on standing with ethyl acetate. Recrystallization from methanol–water (three times) gave 5 (229 mg, 3.1%), mp 177–179°, α_D +63°.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.1; H, 10.8.

The methyl ester failed to crystallize.

3α,12α-Dihydroxy-5β-25D-cholestanoic Acid (6).—Electrolysis was carried out with D half-ester and deoxycholic acid exactly as it was with the L form. Neutrals (6.75 g) were dissolved in benzene and applied to a column of alumina (165 g, deactivated with 3% water) prepared in benzene. Eluting solvents (1.0 l. each) and residues follow: benzene, 1.0 g; 20% ether in benzene,

(16) T. Usui, *J. Biochem.* (Tokyo), **54**, 283 (1963).

(17) D. Kritchevsky, D. S. Martak, and G. H. Rothblat, *Anal. Biochem.*, **5**, 388 (1963).

(18) T. Komatsubara, *Proc. Jap. Acad.*, **30**, 618 (1954); *Chem. Abstr.*, **50**, 387 (1956).

(19) G. A. D. Haslewood, *Biochem. J.*, **52**, 583 (1952).

(20) Activated alumina apparently causes condensation or polymerization of acetone; evaporation leaves an oil which interferes with product purification. A better procedure is to deactivate the alumina with 6% water; bile acid methyl esters will then be eluted with benzene or a mixture of ether and benzene.

(21) S. Bergström and J. Sjövall, *Acta Chem. Scand.*, **5**, 1267 (1951); A. Norman, *ibid.*, **7**, 1413 (1953).

1.0 g; 50% ether in benzene, 1.7 g; and 75% ether in benzene, 0.1 g. Substances (2.0 g) with appropriate mobility on tlc were eluted by the last 400 ml of 20% ether, by 50% ether, and by 75% ether. Saponification yielded neutrals (1.55 g) and a crystalline acid (526 mg). Recrystallization from ethyl acetate, methanol–water (containing a little ethyl acetate), and ethyl acetate gave **6** (245 mg, 3.3%), mp 130° with subsequent recrystallization and remelting at 174–175°, α_D +47°.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.6; H, 11.0.

The methyl ester, crystallized from methanol, melted at 92–94°.

3α-Hydroxy-5β-25L-cholestanoic Acid (7).—Electrolysis of lithocholic acid (6.5 g, Nutritional Biochemicals Corp., Cleveland, Ohio) with L half-ester (2.5 g) and Na (40 mg) for 4 hr yielded neutrals (7.1 g), which were dissolved in benzene (10 ml), diluted with petroleum ether (20 ml), and applied to a column of alumina (150 g, deactivated with 6% water) prepared in petroleum ether. Eluting solvents (1.0 l. each) and residues follow: 33% benzene in petroleum ether, 1.9 g; 50% benzene in petroleum ether, 0.8 g; and benzene, 1.2 g. Solvents and residues of further elution follow: 5% ether in benzene (0.4 l.), 0.4 g; 20% ether in benzene (0.6 l.), 0.8 g; and ether (0.4 l.), 0.4 g. Substances (750 mg) with the mobility (tlc) expected of methyl monohydroxycholestanoate were eluted by the first 400 ml of benzene. Saponification yielded no neutrals but an acid (723 mg) which crystallized from ether. Several recrystallizations from ether gave **7** (278 mg, 3.9%), mp 169–170°, α_D +43°.

Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.5; H, 11.1. Found: C, 77.7; H, 11.8.

The methyl ester, crystallized from ether–petroleum ether, melted at 112–113°.

3α-Hydroxy-5β-25D-cholestanoic Acid (8).—A similar electrolysis with lithocholic acid (recrystallized), Na, and D half-ester for 3.75 hr yielded neutrals (6.8 g) and traces of acid. After chromatography the product emerged with the first 800 ml of benzene. Saponification yielded crystalline neutrals (556 mg) and an acid (940 mg) which crystallized on standing with ether–petroleum ether. Recrystallization from methanol–water, ether, and methanol-water gave **8** (392 mg, 5.4%), mp 155–157°, α_D +26°.

Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.5; H, 11.1. Found: C, 77.7; H, 11.6.

The methyl ester, crystallized from ether–petroleum ether, melted at 108–109°.

Registry No.—**1**, 23047-29-2; **1** methyl ester, 23740-21-8; **2**, 23740-14-9; **2** methyl ester, 23740-22-9; **3**, 23740-15-0; **4**, 23740-16-1; **5**, 23740-17-2; **6**, 23740-18-3; **6** methyl ester, 23740-23-0; **7**, 23740-19-4; **7** methyl ester, 23740-24-1; **8**, 23740-20-7; **8** methyl ester, 23829-36-9.

Acknowledgments.—I thank Mrs. Louis J. Bussjaeger for expert technical help during part of this work. Numerous colleagues have been most generous in lending equipment.

The Reaction of 5-Bromouracil Derivatives with Sulfur Nucleophiles, and a Novel Synthetic Route to 5-Sulfur-Substituted Uracils and Nucleotides[1a,b]

L. SZABO, T. I. KALMAN, AND T. J. BARDOS[1c]

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Received October 3, 1969

1-Methyl-5-bromouracil (**1**) reacts with sodium hydrosulfide in dimehtyl sulfoxide at room temperature to give 1-methyl-5-mercaptouracil (**2**, isolated as the disulfide **3**) and 1-methyluracil (**4**). Deuterium-exchange studies are consistent with 1,4 addition of the reagent to **1**, followed by tautomerization, to give two stereoisomeric adducts which, after nucleophilic displacement of the bromine by another anion of the reagent, undergo *trans* elimination reactions leading to **2** and **4**, respectively. Based on this mechanism, a useful, novel synthetic route was developed for the introduction of a 5-sulfur substituent into the pyrimidine ring of uracil derivatives *via* addition of methyl hypobromite to the 5,6 double bond, followed by reaction of the adduct with sodium disulfide. By use of this method, **3** was synthesized in 74% yield, and the disulfide of the nucleotide 5-mercapto-2′-deoxyuridine 5′-phosphate (**15**) was synthesized in an overall yield of 68%.

The synthesis of 5-mercapto-2′-deoxyuridine, a structural analog of thymidine, was recently reported.[2] This compound was found to be an effective antimetabolite in various test systems[3] in which it was apparently converted into its 5′-phosphate (**17**). It appeared of interest to synthesize the nucleotide **17** and some of its derivatives; this prompted the investigation of the feasibility of introducing a thiol group at the 5 position of 1-substituted uracil derivatives, to provide a relatively simple method applicable for the preparation of various 5-sulfur-substituted pyrimidine nucleotides. Although 5-halogenopyrimidines are characterized by low reactivity of the halogen atom,[4] Roth and Hitchings reported[5] that thiophenol salts react readily with with 5-bromouracil in ethylene glycol at 150° to give 40–50% yield of 5-arylthiouracils, in addition to uracil and diaryl disulfides obtained as by-products. The observed side reaction was attributed to electron transfer, resulting in the reductive removal of the halogen.[5]

1-Methyl-5-bromouracil (**1**) was selected as a model compound for the determination of the optimal conditions for the substitution reaction. Preliminary experiments indicated that **1** reacted with excess sodium hydrosulfide only at high temperature when ethylene glycol[5] was used as the solvent, but the reaction proceeded readily at room temperature in dimethylacetamide (DMAA) or dimethyl sulfoxide (DMSO). Although in the latter case the reaction appeared to be essentially complete in 1 hr, the presence of both 1-methyl-5-mercaptouracil (**2**) and its disulfide (**3**) in the reaction

(1) (a) This work was supported by U. S. Public Health Service Research Grant R01-CA06695 from the National Cancer Institute, National Institutes of Health, Bethesda, Md. (b) A preliminary report of this work was presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969. (c) To whom inquiries should be directed.

(2) (a) T. J. Bardos, M. P. Kotick, and C. Szantay, *Tetrahedron Lett.*, 1759 (1966); (b) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, in press.

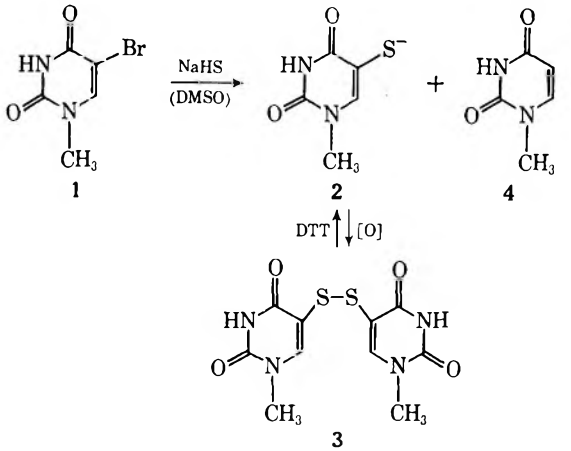
(3) (a) K. Baranski, T. J. Bardos, A. Bloch, and T. I. Kalman, *Biochem. Pharmacol.*, **18**, 347 (1969); (b) T. I. Kalman and T. J. Bardos, *Fed. Proc.*, **27**, 650 (1968).

(4) G. W. Kenner and A. Todd, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., J. Wiley & Sons, Inc., New York, N. Y., 1957, p 301.

(5) B. Roth and G. H. Hitchings, *J. Org. Chem.*, **26**, 2770 (1961).

mixture was indicated by the characteristic absorption maximum of the thiolate ion at 335 mμ and by the increase of the absorbancy at this wavelength upon addition of the reducing agent dithiothreitol (DTT).[6] Therefore, the reaction was continued for 3 days, to permit complete oxidation of 2. Two major products were isolated: 1-methyl-5-mercaptouracil disulfide (**3**), in 54% yield, and 1-methyluracil (**4**), in 41% yield (Scheme I).

Scheme I

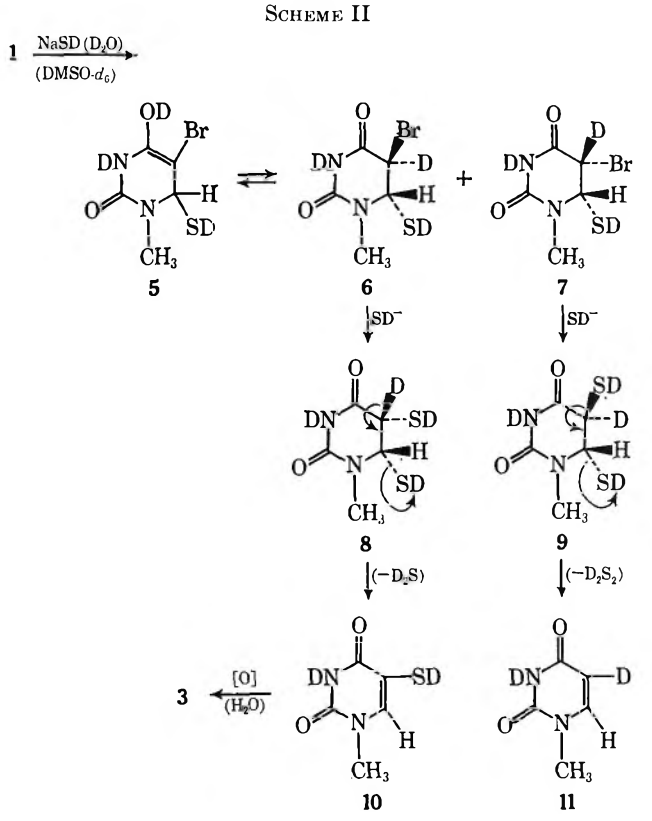


To avoid the reductive replacement of the 5-bromo substituent with hydrogen, leading to the unwanted 1-methyluracil (**4**), the use of other sulfur-containing nucleophilic reagents was attempted, such as potassium thiolacetate, thiourea, sodium disulfide, sodium sulfide, potassium thiocyanate, etc. However, in spite of the effectiveness of these reagents in the preparation of mercaptans from aliphatic and aromatic halides in general, only potassium thiolacetate reacted with **1**, and **4** was obtained also in this case as the second major product.

Recent studies of several investigators[7-9] have demonstrated that in D_2O or MeOD solution a base-catalyzed deuterium exchange occurs at the 5 position of 1-substituted uracil derivatives. It was postulated that the mechanism of this exchange most likely involves a 1,4 addition across the α,β-unsaturated carbonyl system, initiated by a nucleophilic attack of the anion of the base at C-6, followed by an enol–keto tautomeric shift, and then elimination of the C-5 hydrogen atom and the nucleophile.[7] An alternative mechanism, involving the anionic attack at the C-5 position and a 1,2 addition across the 5,6 double bond of the uracil nucleus, was proposed to explain the observed deuterium exchange at the C-6 position in the case of 5-fluorouracil.[9] It occurred to us that the mechanism of the displacement of bromine at C-5 of **1** with sodium hydrosulfide or potassium thiolacetate (or with thiophenol salts in the case of 5-bromouracil[5]) might involve either a 1,2 or a 1,4 addition of the reagent as the necessary first step; this would saturate the 5,6 double bond and thus activate the bromine for nucleophilic displacement by the anion of a second molecule of the sulfur-containing reagent. Such a mechanism would explain the lack of reaction with the other reagents which do not add to the double-bond system.

To study the mechanism of this reaction, **1** was treated with deuterated sodium hydrosulfide in deuterated DMSO as the solvent. Although an intermediate addition product could not be isolated, the final disulfide product (**3**) obtained in this experiment showed no evidence of deuterium exchange at the C-6 position, as indicated by integration of its undiminished C-6 hydrogen peak in the nmr spectrum. Thus, if the reaction did proceed *via* primary addition of the reagent to the double-bond system, then the initial nucleophilic attack by the SD^- anion appears to have occurred at the C-6 position *via* the initial formation of a 1,4 adduct (**5**), as shown in Scheme II. This, then could tautomerize to

Scheme II



the more stable 5,6-saturated adducts, **6** and **7**, in which the bromine (α to the carbonyl group) is readily displaced by the nucleophilic attack of another SD^- anion, with inversion of configuration at C-5, to give **8** and **9**, respectively. *trans* elimination of a molecule of D_2S from **8** would give the 5-mercaptouracil derivative **10** which ionizes to the thiolate anion and undergoes autoxidation to the disulfide. *trans* elimination of D_2S_2 from **9** would give the "reduced" by-product, 1-methyluracil, with deuterium at C-5 (**11**). This product was also isolated from the reaction mixture and showed in its nmr spectrum a singlet for the C-6 hydrogen and no absorption peak for a hydrogen at C-5.

While this proposed mechanism (Scheme II) may not be the only one possible, it certainly provides a satisfactory explanation for the obtained results. If the first reaction step had been a 1,2 addition of sodium deuteriosulfide to the 5,6 double bond of **1**, then (a) in the case that the SD^- anion reacted at C-5, the C-6 posi-

(6) T. J. Bardos, and T. I. Kalman, *J. Pharm. Sci.*, **55**, 606 (1966).
(7) S. R. Heller, *Biochem. Biophys. Res. Commun.*, **32**, 998 (1968).
(8) D. V. Santi, and C. F. Brewer, *J. Amer. Chem. Soc.*, **90**, 6236 (1968).
(9) R. J. Cushley, S. R. Lipsky, and J. J. Fox, *Tetrahedron Lett.*, 5393 (1968).

tion would have been deuterated, and (b) in the case that the SD^- anion reacted at C-6, the expected *trans* addition would give only adduct **7** which according to Scheme II would lead to **11** as the only reaction product. Although the formation of **3** by some different mechanism cannot be excluded, a 1,2-addition mechanism for this reaction is not supported by the results, while a 1,4-addition mechanism could entirely explain the ready formation of both reaction products, **3** and **11**.

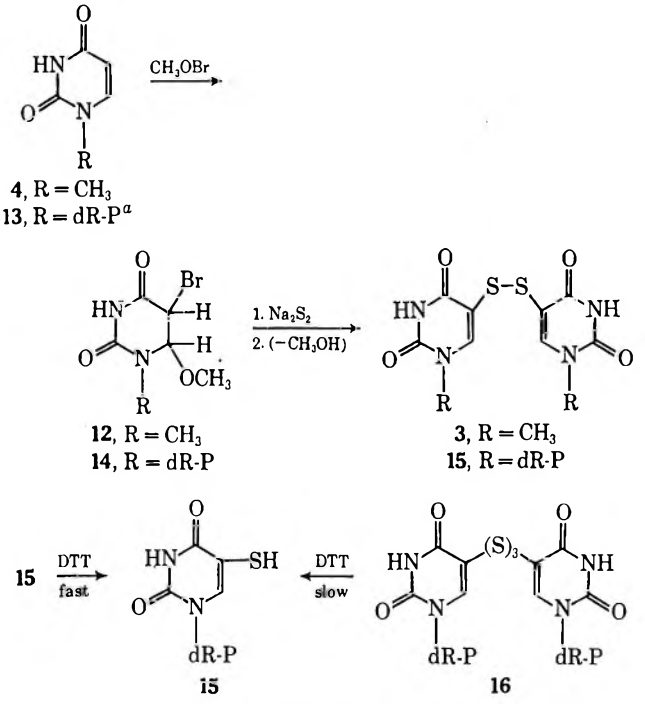
That the intermediate adducts shown in Scheme II could not be isolated is not surprising in view of the expected reactivity of **6** and **7** with a sulfur nucleophile and the understandable lability of the dithiol adducts **8** and **9**. Since the reaction proceeds at room temperature and requires a large excess of the reagent, it is reasonable to assume that the first step is rate limiting, while the nucleophilic displacement and subsequent elimination reactions proceed quite rapidly. Although the "reduced" product **11** could also be formed by direct reduction of either **6** or **7** with sodium deuteriosulfide, this seems unlikely in the presence of the strongly nucleophilic SD^- anion which could most effectively displace the bromine.[10] It is significant that **11** is obtained in nearly the same yield as **3**.

Based on the above mechanistic interpretation of the reaction between **1** and sodium hydrosulfide, we sought to design a better method for the introduction of a sulfur substituent at the 5 position of the uracil nucleus. If the above mechanism is correct, then an adduct of the type **6** should readily react also with those sulfur-containing reagents that did not react with **1** in our initial experiments (presumably because of their inability to form an addition product), and, in the absence of a type **7** stereoisomer, a higher yield of the desired 5-sulfur-substituted product should result. Methyl hypobromite is known to form isolable adducts with various uracil and cytosine derivatives,[11] presumably by *trans* addition to the 5,6 double bond. Thus, these adducts could be expected to have a configuration similar to **6**.

Consequently, methyl hypobromite was treated with **4** according to the general method of Duschinsky, *et al.*,[11] and the adduct **12** was isolated and characterized. It readily reacted at 0° in dimethylacetamide solution with sodium disulfide (one of the reagents that were unreactive toward **1**), to give an overall yield of 75% (based on 1-methyluracil, **4**) of the pure disulfide **3** (Scheme III, R = CH_3). A small amount (12%) of **4** was also isolated; this was probably due to the reversibility of the addition reaction under basic conditions.[11]

This approach was readily applicable also to the synthesis of the desired nucleotide, 5-mercapto-2′-deoxyuridine 5′-phosphate (**17**). The corresponding disulfide, **15**, was obtained from 2′-deoxyuridine 5′-phosphate (**13**) by the above procedure (Scheme III, R = dR-P) in an overall yield of 68% (as the analytically pure barium salt). In addition, a small amount of another sulfur-containing nucleotide was isolated which analyzed for the trisulfide **16**. Both **15** and **16** can be reduced to the 5-mercapto nucleotide **17** with dithiothreitol;[6] however, the reduction proceeds much more slowly in the case of the trisulfide **16** than in the case of **15** or other 5-uracilyl disulfides.[6]

SCHEME III



[a] dR-P = 2-deoxy-β-D-ribofuranosyl 5-phosphate.

Further possible applications of the new synthetic method for the introduction of sulfur substituents at the C-5 position of uracil and cytosine rings of nucleoside triphosphates, oligonucleotides, and nucleic acids are under investigation.

Experimental Section

All melting points were taken on a Mel-Temp apparatus and they are corrected. Infrared spectra were recorded on a Perkin-Elmer Infracord or Beckman IR-8 employing potassium bromide disks. Nmr spectra were recorded on a Varian Model A-60 spectrophotometer in the indicated solvent with TMS as an internal standard. Ultraviolet spectra were obtained on a Beckman DB recording spectrophotometer. Optical rotations were measured in a 1-dm tube using a Perkin-Elmer Model 141 automatic polarimeter at 589 mμ. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-Methyl-5-mercaptouracil Disulfide (3).—To a solution of 1-methyl-5-bromouracil[12] (**1**, 0.60 g, 2.9 mmol) in 10 ml of DMSO, NaSH (0.66 g, 11.8 mmol) was added, and the mixture was stirred for 3 days at room temperature. The progress of the conversion of **1** to the mercapto compound **2**, and of the oxidation of **2** to the disulfide **4**, was followed by tlc and by observing the changes in the uv and nmr spectra. EtOH (5 ml) and Et_2O (100 ml) were then added, and the precipitate was separated by filtration, dissolved in 5 ml of water, and acidified with 10% HCl. The white crystals were filtered, washed with water, and recrystallized from DMF–EtOH, to give 0.25 g (54%) of the product **3**: mp 302–303° dec; uv (pH 7.2) λ_{max} 282 mμ (ε 17,310) and λ_{min} 239 mμ (ε 10,710) [upon addition of DTT, the spectrum changes to that of the thiolate ion[6] (**2**): λ_{max} 335 mμ (ε 10,930) and λ_{min} 291 (ε 4330)]; nmr (DMSO-d_6) δ 3.27 (6 H, s, NCH_3) and 8.15 ppm (2 H, s, 6-CH).

Anal. Calcd for $C_{10}H_{10}N_4O_4S_2$: C, 38.21; H, 3.20; N, 17.82; S, 20.40. Found: C, 38.16; H, 3.20; N, 17.72; S, 20.23.

1-Methyluracil (4).—The DMSO–EtOH–Et_2O mother liquor was evaporated *in vacuo*, and the residue was recrystallized from

(10) We believe that the previously reported reduction of 5-bromo-5-fluoro-6-substituted 5,6-dihydrouracil derivatives with thiols[11] may also proceed *via* nucleophilic displacement of the bromine by the thiolate anion and subsequent displacement of the thiol group by reaction with another molecule of the thiol (disulfide formation). This would explain the observed retention of configuration,[11] as the result of double inversion at C-5.

(11) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grundberg, J. H. Burchenal, and J. J. Fox, *J. Med. Chem.*, **10**, 47 (1967).

(12) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 4585 (1960).

MeOH to give 0.15 g (41%) of 1-methyluracil (**4**), which was identified by uv spectra and mixture melting point with an authentic sample:[13] nmr (DMSO-d_6) δ 3.25 (3 H, s, NCH_3), 5.55 (1 H, d, J = 7.9 Hz, 5-CH), and 7.60 ppm (1 H, d, J = 7.9 Hz, 6-CH).

Reaction of 1 with NaSD in DMSO-d_6.—A solution of NaSH (0.40 g, 7.14 mmol) in D_2O (5 ml) was evaporated *in vacuo* to dryness, and this procedure was repeated four times with four 5-ml portions of D_2O. To the residue, DMSO-d_6 (4 ml) and **1** (0.30 g, 1.46 mmol) were added with stirring at room temperature. Work-up of the reaction products was the same as in the reaction described above. In one experiment, the 5-sulfur-substituted product (0.10 g, 43%), isolated after 2 days, showed in the nmr spectrum two distinct singlets at δ 8.32 and 8.15 ppm for the C-6 hydrogen of the thiol (**2**) and of the disulfide (**3**), respectively. On prolonged standing in the nmr tube, the δ 8.32 peak disappeared and the simultaneously increased 8.15 peak gave an integrated ratio of 1:3 relative to the NCH_3 peak (3.28). In another experiment, the stirring of the reaction mixture was continued for 4 days, and only the disulfide **3** was isolated in pure form.

The second product (**11**) was also obtained in 43% yield (0.08 g) and had the same melting point and uv spectrum as **4** but its nmr spectrum showed absence of the C-5 proton absorption and the C-6 doublet of **4** was replaced by a singlet: nmr (DMSO-d_6) δ 3.25 (3 H, s, NCH_3) and 7.63 ppm (1 H, s, 6-CH).

1-Methyl-5-bromo-6-methoxy-5,6-dihydrouracil (12).—A cold solution of MeOBr, freshly prepared from 0.43 g (5.5 mmol, 0.14 ml) of Br_2 according to the procedure of Duschinsky, *et al.*,[11] was filtered through a Celite filter directly into an ice-cold solution of 1-methyluracil (**4**, 0.25 g, 2 mmol) in 6 ml of MeOH. The stirring and cooling was continued at 0° for 1 hr; then the solution was kept at room temperature for another hour. After addition of Et_2O (50 ml) to the solution, white crystals deposited which were filtered, washed with cold Et_2O, and dried *in vacuo:* yield 0.42 g (90%); mp 144.5°; uv spectrum end absorption only; nmr (CD_3COCD_3) δ 3.18 (3 H, s, NCH_3), 3.55 (3 H, s, $-OCH_3$), 4.66 (1 H, d, J = 2.1 Hz), and 4.92 ppm (1 H, d, J = 2.1 Hz).

Conversion of 12 into 1-Methyl-5-mercaptouracil Disulfide (3).—Crude (unrecrystallized) addition product (**12**, 0.42 g) and $Na_2S_2 \cdot 5H_2O$[14] (0.40 g, 2 mmol) were dissolved in 3.5 ml of ice-cold dimethylacetamide, and the solution was stirred for 2 hr at 0° and then at room temperature for 24 hr. EtOH (2 ml) and Et_2O (50 ml) were added to the solution and the precipitated solids were filtered and then redissolved in 8 ml of water. After the solution stood for 3 hr in the refrigerator, the deposited white crystals were filtered, washed with water, and dried *in vacuo* to yield 0.23 g of pure **3** [74%, based on 1-methyluracil (**4**) as starting material]. The mixture melting point, with a sample of the product **3** obtained previously by the reaction of **1** with sodium hydrosulfide, was not depressed, and the uv, ir, and nmr spectra of the two samples were identical.

After the evaporation of the DMAA–EtOH–Et_2O mother liquor, 0.03 g (12%) of 1-methyluracil (**4**) was isolated and identified.

N_1-(2′-Deoxy-β-D-ribofuranosyl)-5-bromo-6-methoxy-5,6-dihydrouracil 5′-Phosphate (14) Monosodium Salt.—A cold solution of MeOBr, freshly prepared from 0.77 g (9.82 mmol, 0.25 ml) of Br_2 according to the procedure of Duschinsky, *et al.*,[11] was filtered through a Celite filter directly into an ice-cold suspension of 2′-deoxyuridine 5′-phosphate (**13**) disodium salt ($2.5H_2O$) (1.30 g, 3.27 mmol) in 13 ml of MeOH. Stirring and cooling at 0° was maintained for 3 hr; then to the light yellow solution 300 ml of Et_2O was added. The deposited white crystals were filtered and washed with cold Et_2O and recrystallized from MeOH–Et_2O to give 1.40 g of **14** (96%). The uv spectrum showed only end absorption.

Anal. Calcd for $C_{10}H_{16}N_2O_9BrPNa$: C, 27.22; H, 3.42; Br, 18.12; Found: C, 26.61; H, 3.79; Br, 18.21.

N_1-(2′-Deoxy-β-D-ribofuranosyl)-5-mercaptouracil 5′-Monophosphate Disulfide (15) and N_1-(2′-Deoxy-β-D-ribofuranosyl)-5-mercaptouracil 5′-Monophosphate Trisulfide (16).—To a solution of 1.40 g of crude (unrecrystallized) addition product (**14**) in 16 ml of dimethylacetamide, $Na_2S_2 \cdot 5H_2O$[14] (1.08 g, 5.4 mmol) was added at 0°, with stirring. The reaction mixture was then stirred for 5 hr at 0° and at room temperature for 12 hr, during which time a white precipitate formed. Ether (25 ml) was added to the mixture and the precipitate was filtered and washed with cold EtOH and Et_2O. The precipitate was then dissolved in 40 ml of water, and a solution of 0.76 g of $BaCl_2 \cdot 2H_2O$ in 5 ml of water was added. The pH of the solution was adjusted to 8.5 with dilute NH_4OH. Then 30 ml of EtOH was added which precipitated the Ba salt of **15** (1.10 g, 63%).

The filtrate (A) was treated with more EtOH (15 ml), and the precipitated solids were collected (0.15 g). This consisted of a mixture of the nucleotide disulfide (**15**) and trisulfide (**16**) which were separated by preparative tlc on Cellex-PEI anion-exchange cellulose [2 M CH_3COOH–1 M LiCl (1:1)]: R_f 0.74 for **15**, 0.48 for **16**. After elution and evaporation of the eluates *in vacuo* to dryness, the LiCl was extracted from the residues with MeOH. The residues were dissolved in water and treated with 2 equiv of aqueous $BaCl_2$ and with dilute NH_4OH to adjust the pH to 8.5. This precipitated the Ba salts of the disulfide **15** (0.08 g, 5%; total yield of **15**, 68%) and of the trisulfide **16** (0.04 g, 2.3%), respectively.

From the mother liquor (B), by further addition of EtOH, the Ba salt of deoxyuridine 5′-monophosphate (**13**) was isolated (0.09 g, 7%) and identified by comparison of uv spectra and R_f values on tlc [Cellex-PEI, 2 M CH_3COOH–1 M LiCl (1:1)] with those of an authentic sample.

Barium Salt of the Disulfide 15.—The barium salt of **15** was obtained: uv (pH 7.2) λ_{max} 273 mμ (ϵ 15,260) and λ_{min} mμ 247 (ϵ 11,090) [upon addition of DTT,[6] the spectrum changes to that of the thiolate ion, **17**: λ_{max} 330 mμ (ϵ 8060) and λ_{min} 295 mμ (ϵ 5380)]; $[\alpha]^{25}D$ 106.02° (c 0.46, 0.1 N HCl).

Sodium Salt of the Disulfide 15.—This was prepared by the treatment of the Ba salt with Chelex 100 ion-exchange resin (Na^+ form) in water: uv (pH 7.2) λ_{max} 273 mμ (ϵ 16,020) and λ_{min} 247 (ϵ 11,260) [upon addition of DTT[6] (**17**) the spectrum changes: λ_{max} 330 mμ (ϵ 8560) and λ_{min} 293 (ϵ 5390)]; $[\alpha]^{25}D$ +27.54° (c 0.305, H_2O); nmr (D_2O) δ 6.14 (5, J = 6.5 Hz, 1′-CH nucleosidic proton) and 7.57 ppm (s, 6-CH).

Anal. Calcd for $C_{18}H_{20}N_4O_{16}P_2S_2Na_4 \cdot 5H_2O$: C, 25.23; H, 3.53; N, 6.54; S, 7.48; P, 7.23. Found: C, 25.38; H, 3.11; N, 6.10; S, 7.04; P, 6.77.

Free Acid Form of the Disulfide 15.—This was obtained upon treatment of the sodium salt with Dowex 50-WX8 (H^+ form): $[\alpha]^{25}D$ +121.11° (c 0.28, H_2O); nmr (D_2O) δ 6.18 (t, J = 6.4 Hz, 1′-CH) and 7.91 ppm (s, 6-CH).

Barium Salt of the Trisulfide 16.—The barium salt of **16** was obtained: uv (pH 7.2) λ_{max} 277 mμ (ϵ 13,470) and λ_{min} 249 mμ (ϵ 7450) [after reduction with DTT to **17** the spectrum changed: λ_{max} 332 mμ (ϵ 6880) and λ_{min} 295 mμ (ϵ 4010)].

Anal. Calcd for $C_{18}H_{20}N_4O_{16}P_2S_3Ba_2 \cdot 6H_2O$: C, 19.84; H, 2.96; S, 8.83. Found: C, 19.15; H, 2.66; S, 8.90.

Registry No.—**3**, 23735-47-9; **4**, 615-77-0; **11**, 23735-49-1; **12**, 23735-50-4; **14** monosodium salt, 23735-51-5; **15**, 23735-52-6; **15** barium salt, 23735-53-7; **15** sodium salt, 23735-54-8; **16**, 23735-55-9; **16** barium salt, 23735-56-0.

(13) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930).

(14) Y. O. Gabel and L. F. Shpeier, *J. Gen. Chem.* (USSR), **17**, 2277 (1947).

Ω,Ω,Ω-Trifluoroamino Acids[1a]

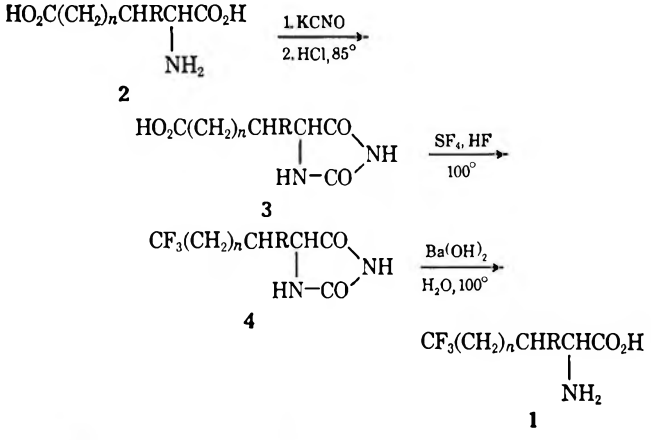
R. M. BABB AND F. W. BOLLINGER[1b]

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

Received October 21, 1969

DL-5,5,5-Trifluoronorvaline and DL-4,4,4-trifluorovaline have been synthesized in three steps from readily available starting materials. In the preparation of these compounds, hydantoin intermediates have been shown to be chemically, but not optically, stable to sulfur tetrafluoride in liquid hydrogen fluoride.

The furtherance of certain laboratory objectives required a supply of DL-5,5,5-trifluoronorvaline (**1**, n = 1, R = H). A search of the literature revealed that this compound had been previously prepared[2] from trifluoroacetaldehyde and ethyl bromoacetate in seven steps and in an overall yield of 6%. For a shorter synthesis involving no shortening or lengthening of the carbon chain, glutamic acid (**2**, n = 1, R = H) appeared to be an ideal starting material. If the α-carboxyl group is protected, the γ-carboxyl group can be treated with sulfur tetrafluoride[3] to yield, after removal of the protecting group, 5,5,5-trifluoronorvaline (**1**, n = 1, R = H). Search for a protective group disclosed[3] esters and to a lesser extent amides. Application of the usual esterification processes to glutamic acid yields γ-hemiesters rather than α-hemiesters. The more circuitous methods by which α-hemiesters of glutamic acid are obtained would greatly decrease the attractiveness of our projected synthesis. A possible way around this difficulty involved use of the hydantoin[4] (**3**, n = 1, R = H), a cyclic imide which incorporated both the α-amino and the proximal carboxyl group. Use of the imide as a protective group would be novel. The projected synthesis is outlined below.



While the hydantoin ring was shown to be chemically stable under the reaction conditions, the product was largely racemized. By independent experiments L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H) has been shown to lose 97% of its optical activity on exposure to anhydrous hydrogen fluoride at 100° for 3 hr and all optical activity on exposure to constant-boiling hydrochloric acid at 108° for 3 hr.

In contrast, Raasch[5] has shown that under similar reaction conditions, noncyclic amino acids retain some of their optical activity. He did not, however, provide an independent measure of or any proof of optical purity. The degree of retention of optical activity in his experiments cannot be stated with assurance, although it would appear to be high. Hydantoins can also racemize in basic media. West[6] has shown that L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), on treatment with strong base, loses optical activity (20% over a period of 6 hr at reflux in 0.5 *N* sodium hydroxide). L(Enriched)-5-(3′,3′,3′-trifluoropropyl)-hydantoin (**4**, n = 1, R = H) was racemized completely on hydrolysis with saturated barium hydroxide at reflux for 30 hr. Hydrolysis so vigorous as to liberate fluoride ion must be avoided. DL-5,5,5-Trifluoronorvaline (**1**, n = 1, R = H) was obtained in three steps in an overall yield of 50%.

Failure to obtain the physical constants reported by Dakin[4] for L-5-hydantoin-β-propionic acid has led to preparation of the compound optically pure and to improvements in the method for making it thus. Since, however, the end product of this work, 5,5,5-trifluoronorvaline, is racemic, there is no requirement for conservation of optical activity in any of the intermediates. Racemization can occur in each of the three steps and there is no preferred step for its occurrence.

To illustrate the versatility of this method, DL-4,4,4-trifluorovaline (**1**, n = 0, R = CH_3) was prepared starting from DL-*threo*-β-methylaspartic acid (**2**, n = 0, R = CH_3). From nuclear magnetic resonance spectra the *threo* configuration was preserved in synthesis of DL-5-hydantoin-α-propionic acid (**3**, n = 0, R = CH_3). In DL-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3) the *threo* to *erythro* ratio was at least 9:1, while in 4,4,4-trifluorovaline (**1**, n = 0, R = CH_3) the ratio had fallen to 3:1; hence epimerization was not serious until the final step. It is not known whether this is the equilibrium ratio. DL-4,4,4-Trifluorovaline (**1**, n = 0, R = CH_3) has been previously prepared[7,8a] by another method. Examination of these preparations by nuclear magnetic resonance shows them to be mixtures of *threo* and *erythro* isomers in the ratio of 2:1.

This consideration also applies to preparations of DL-5,5,5-trifluoroleucine,[8a-f] which are still unknown mixtures of *threo* and *erythro* isomers. Conclusions based on microorganism-feeding experiments, which

(1) (a) A portion of this paper was presented: 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969. (b) To whom inquiries should be addressed.

(2) H. M. Walborsky, M. Baum, and D. F. Loncrini, *J. Amer. Chem. Soc.*, **77**, 3637 (1955).

(3) W. C. Smith, *Angew. Chem. Intern. Ed. Engl.*, **1**, 467 (1962).

(4) H. D. Dakin, *Amer. Chem. J.*, **44**, 48 (1910); *Biochem. J.*, **13**, 406 (1919).

(5) M. S. Raasch, *J. Org. Chem.*, **27**, 1406 (1962).

(6) C. J. West, *J. Biol. Chem.*, **34**, 194 (1918).

(7) D. F. Loncrini and H. M. Walborsky, *J. Med. Chem.*, **7**, 369 (1964).

(8) (a) J. Lazar and W. A. Sheppard, *ibid.*, **11**, 138 (1968); (b) O. M. Rennert and H. S. Anker, *Biochemistry*, **2**, 471 (1963); (c) R. E. Webster and S. R. Gross, *ibid.*, **4**, 2309 (1965); (d) T. Satayanarayana, H. E. Umbarger, and G. Lindegren, *J. Bacteriol.*, **96**, 2018 (1968); (e) E. D. Fenster and H. S. Anker, *Biochemistry*, **8**, 269 (1969); (f) J. M. Calvo, M. Freundlich, and H. E. Umbarger, *J. Bacteriol.*, **97**, 1272 (1969).

employed such unknown mixtures, are not necessarily firm.

Our method promises to be useful in synthesizing other Ω,Ω,Ω-trifluoroamino acids. Aspartic acid (**1**, n = 0, R = H), α-aminoadipic acid (**1**, n = 2, R = H), and levulinic acid are available starting materials.

Experimental Section[9]

L-5-Hydantoin-β-propionic Acid.—By the method of Dakin,[4] L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), mp 179–181° (last traces melting at 184°), $[\alpha]^{22}D$ −66.8 ± 1.0° (*c* 2, H_2O), was obtained in 64.9% yield. This material was later shown to have an optical purity of 93.6% (the remaining 6.4% was racemic). A second crop, mp 155–160°, $[\alpha]^{22}D$ −25 ± 1° (*c* 2, H_2O), amounted to 24.9%. Dakin's material, mp 179–181°, $[\alpha]D$ −50° (*c* 2, H_2O), 85.5% yield, had an optical purity of 70%.

The following modification of Dakin's method yields a product of higher optical purity. To a slurry of 100 g (0.680 mol) of glutamic acid, mp 205° dec, $[\alpha]^{22}D$ 30.9 ± 1.0° (*c* 1, 6 *N* HCl), purity by phase solubility 100.0%, in 340 ml of water at 80° was added with warming and stirring 36.7 ml of 11.7 *N* sodium hydroxide to bring the pH to 6.0 (5.5 would be slightly better). Addition of 68 g (0.839 mol) of potassium cyanate increased the pH to 7.5. The mixture was stirred and maintained at 85° for 1 hr while 16 ml of concentrated hydrochloric acid was added in portions to maintain the pH at 7.0. During this heating the mixture becomes a solution. Concentrated hydrochloric acid was added to pH 3.5, and then an additional 86 ml was added for a total of 179 ml. The mixture was maintained at 85° for 2 hr, allowed to cool to room temperature, and aged for 18 hr. After filtration, washing with three 35-ml portions of cold water, and drying, the product, mp 182–184°, $[\alpha]^{22}D$ −68.2 ± 1.0° (*c* 2, H_2O), optical purity 96%, amounted to 96.4 g (82.3%).

One recrystallization from water gave an optically pure product, mp 184–186°, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), 68.7% recovery, 56.2% yield. A second recrystallization with 92.0% recovery showed no change in physical properties: mp 185° (DTA); equiv wt, 174 (theory 172.15); $\lambda_{max}^{CH_3OH + base}$ 226 mμ (log ε 3.7); purity by phase solubility 99.5 ± 0.5%; ir (Nujol) 3000–3200, 3300 (NH), 1660–1720, and 1740 (sh) cm^{-1} (C=O).

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 42.07; H, 4.62; N, 16.14.

In an autoclave 5.0 g of L-5-hydantoin-β-propionic acid, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), and 10 ml of liquid hydrogen fluoride were maintained at 100° for 3 hr. The mixture was cooled to room temperature, poured into a polyethylene beaker, evaporated in a current of air, and finally dried over solid potassium hydroxide in a plastic desiccator. The recovery of hydantoin, mp 164–167° (lit.[4] mp 167–169°), $[\alpha]^{22}D$ −2.3 ± 1.0° (*c* 2, H_2O), was quantitative and the racemization was 97% complete.

Refluxing 5-hydantoin-β-propionic acid, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), in constant-boiling hydrochloric acid (108°) for 3 hr yielded a product, mp 153–160°, racemic at all wavelengths. One recrystallization from water with 85% recovery yielded racemic material, mp 167–170° (lit.[4] mp 167–169°).

L-5-(3′,3′,3′-Trifluoropropyl)hydantoin and the DL Compound.—To 63.0 g (0.366 mol) of L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), $[\alpha]^{22}D$ −66.8 ± 1.0° (*c* 2, H_2O), was added 50 ml of anhydrous liquid hydrogen fluoride and 119 g (1.1 mol) of sulfur tetrafluoride. The mixture was heated in a bomb for 3 hr at 100°, cooled to room temperature, vented, and emptied into a polyethylene beaker. The mixture was poured with stirring into a slurry of 150 g of sodium carbonate in 1 l. of water. Care was taken to keep the reaction mixture mildly alkaline. The mixture was extracted with 500-ml and 250-ml portions of ethyl acetate, the extract was filtered through Super-Cel to remove a small amount of black solid, and the filtrate was dried over anhydrous magnesium sulfate. Concentration of dryness yielded 63.9 g (89.0%) of crude product, mp 126–130°, $[\alpha]^{25}D$ −2.7 ± 1.0° (*c* 1, CH_3OH), suitable for the next step.

One recrystallization from methanol and one from acetone–benzene yielded L-5-(3′,3′,3′-trifluoropropyl)hydantoin (1.15% based on the crude product) (**4**, n = 1, R = H) as white clusters of needles, mp 138–141°, ir spectrum consistent with proposed structure, $[\alpha]^{23}D$ −25.8 ± 1.0° (*c* 1, CH_3OH). Another recrystallization from acetone–benzene showed no change in physical properties.

Anal. Calcd for $C_6H_7F_3N_2O_2$: C, 36.74; H, 3.60; N, 14.28; F, 29.06. Found: C, 37.65; H, 3.50; N, 14.21; F, 29.3.

In a similar experiment racemic starting material yielded DL-5-(3′,3′,3′-trifluoropropyl)hydantoin as white scales, mp 136–137°, inactive at all wavelengths (*c* 1, CH_3OH).

Anal. Found: C, 36.72; H, 3.72; N, 14.49; F, 29.3.

Walborsky, *et al.*,[2] prepared the racemic compound by another route but did not characterize it other than to hydrolyze it to DL-5,5,5-trifluoronorvaline.

DL-5,5,5-Trifluoronorvaline.—To 325 ml of water were added 16.0 g (0.0817 mol) of DL- and L-5-(3′,3′,3′-trifluoropropyl)-hydantoin, $[\alpha]^{25}D$ −2.7 ± 1.0° (*c* 1, CH_3OH), and 80 g of barium hydroxide octahydrate. The mixture was refluxed under nitrogen for 30 hr. After cooling to 50°, the mixture was filtered through Super-Cel and the cake was washed with hot water. Gaseous carbon dioxide was passed into the filtrate to precipitate barium ion. The warm mixture was filtered through Super-Cel and the filtrate was brought to pH 6 by dropwise addition of 50% sulfuric acid. The mixture was warmed with 1 g of Nuchar C 1000N, filtered, washed, and concentrated *in vacuo* until the mixture began to deposit crystals. This mixture was warmed at atmospheric pressure to dissolve solid product and set aside to cool slowly overnight. After filtration, washing with water, and drying, DL-5,5,5-trifluoronorvaline (**1**, n = 1, R = H), 6.30 g (45.1%), was obtained as white, electrostatic, crystalline scales, mp 270–272° dec, ir and nmr spectra consistent with proposed structure, inactive at all wavelengths (*c* 1, 6 *N* HCl).

Anal. Calcd for $C_5H_8F_3NO_2$: C, 35.09; H, 4.71; N, 8.18; F, 33.3. Found: C, 35.14; H, 4.94; N, 8.13; F, 32.4.

Concentration of the aqueous mother liquors yielded a second crop, 2.45 g (17.5%), mp 271° dec. The isolated yield in two crops was 62.6%. From glutamic acid the overall yield in three steps was 50.0%.

Anal. Found: C, 34.66; H, 4.69; N, 8.06; F, 34.1.

Walborsky, *et al.*,[2] obtained the compound and characterized it by analysis, paper chromatography, and melting point (258° dec). They report 30% yield overall for the conversion of 4,4,4-trifluorobutyraldehyde into DL-5,5,5-trifluoronorvaline *via* the hydantoin.

DL-*threo*-5-Hydantoin-α-propionic Acid.—By the method of Dakin,[4] DL-*threo*-5-hydantoin-α-propionic acid (**3**, n = 0, R = CH_3), mp 206–208°, ir and nmr spectra consistent with proposed structure, was prepared from DL-*threo*-β-methylaspartic acid (**2**, n = 0, R = CH_3), in 60% yield. The ir and nmr spectra of starting material were compared with those of a sample of DL-*erythro*-β-methylaspartic acid.[10]

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28; O, 37.17. Found: C, 41.98; H, 4.56; N, 15.98; O, 37.1.

DL-*threo*-5-(1′,1′,1′-Trifluoro-2′-propyl)hydantoin.—By the method previously described, DL-*threo*-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3), mp 211.5–213°, was obtained in 32% yield. The ir spectrum was consistent with the proposed structure and the nmr spectrum was consistent but suggested at least a 9:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_6H_7F_3N_2O_2$: C, 36.74; H, 3.60; N, 14.28; F, 29.06. Found: C, 37.19; H, 3.56; N, 14.08; F, 26.9.

DL-4,4,4-Trifluorovaline.—To 162 ml of water in a stainless steel flask were added 8.0 g (0.0408 mol) of DL-*threo*-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3) and 40 g of barium hydroxide octahydrate. The mixture was refluxed under nitrogen for 22 hr. Without cooling the mixture was filtered and the cake was washed with hot water. The combined filtrates were titrated to pH 5 with dilute sulfuric acid and filtered through Super-Cel. The filtrate was concentrated at or below room temperature *in vacuo* until the first precipitate appeared. The mixture was chilled overnight in the refrigerator at 5° to yield 0.1 g of DL-N-carbamyl-4,4,4-trifluorovaline, mp 196° dec, ir spectrum consistent with the proposed structure and nmr spectrum consistent but suggesting a 3:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_6H_9F_3N_2O_3$: C, 33.68; H, 4.24; N, 13.08; F, 26.68. Found: C, 33.88; H, 4.12; N, 13.00; F, 25.67.

(9) Melting points were taken with total immersion thermometers and are uncorrected. Rotations were measured on a Zeiss polarimeter, while nmr spectra were obtained on a Varian 60-MHz spectrometer.

(10) Kindly supplied by Professor H. A. Barker.

After removal of the hydantoic acid by-product, the filtrate was concentrated to a slurry, diluted with methanol, and filtered to yield 2.45 g (26.8%) of 4,4,4-trifluorovaline (1, n = 0, R = CH_3), mp 252° dec, ir spectrum consistent with the proposed structure and nmr spectrum consistent but suggesting a 3:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_5H_8F_3NO_2$: C, 35.06; H, 4.70; N, 8.18; F, 33.3. Found: C, 35.02; H, 4.75; N, 7.92; F, 34.4.

A sample of DL-4,4,4-trifluorovaline,[11] mp 248° dec, prepared by Loncrini and Walborsky,[7] was by nmr spectrum a 2:1 mixture of *threo* and *erythro* isomers, respectively. Another sample,[12] mp 239° dec, prepared by Lazar and Sheppard,[8a] was by nmr spectrum the same 2:1 mixture. The above-reported decomposition points were verified in our laboratory. The position of the α-H doublet center is pH dependent, but the relative chemical shift, *threo* to *erythro*, is τ 0.22, while that for the methyl doublet, *threo* to *erythro*, is τ −0.17. The infrared spectra of these two samples, despite the difference in decomposition point, were identical and differed only slightly in relative intensities between 650 and 950 cm^{-1} from that of the 3:1 mixture of *threo* and *erythro* isomers.

(11) Kindly supplied by Dr. D. F. Loncrini. In a personal communication he states that the melting point in ref 8a should be corrected to the one given above.

(12) Kindly supplied by Dr. J. Lazar.

Registry No.—1 (n = 1, R = H), 23809-57-6; 1 (n = 0, R = Me) (*threo*), 23809-58-7; 1 (n = 0, R = Me) (*erythro*), 23796-83-0; 3 (n = 1, R = H), 17027-50-8; 3 (n = 0, R = Me), 23809-60-1; 4 (n = 1, R = H), 23809-61-2; 4 (n = 0, R = Me), 23809-62-3; DL-5-(3′,3′,3′-trifluoropropyl)hydantoin, 23809-63-4; DL-*threo*-N-carbamyl-4,4,4-trifluorovaline, 23809-64-5; DL-*erythro*-N-carbamyl-4,4,4-trifluorovaline, 23809-65-6.

Acknowledgment.—The authors are indebted to Dr. J. M. Chemerda and Dr. J. van de Kamp for encouragement and valued advice, to Mr. R. N. Boos and associates for microanalytical data, and to Mr. R. W. Walker and Dr. B. H. Arison for instrumental assistance.

Synthesis and Application in Peptide Chemistry of Amino Acids Possessing an Optically Active Selenohomocysteine Skeleton[1a-c]

C. S. PANDE, J. RUDICK, AND RODERICH WALTER[1d]

Departments of Surgery and Physiology, Mount Sinai Medical and Graduate Schools, New York, New York 10029, and The Medical Research Center, Brookhaven National Laboratory, Upton, New York 11973

Received October 6, 1969

The general and convenient method developed earlier in these laboratories to replace the O-tosyl moiety by selenium nucleophiles has been extended to O-tosylated homoserine derivatives and has resulted in the preparation of L-selenomethionine (**17**), L-selenoethionine (**20**), Se-benzyl-L-selenohomocysteine (**10**), and L-(+)-selenocystathionine (**23**). The specific optical rotations of **10**, **17**, and **20** were found to be higher than reported earlier for these compounds. The use of the derivatives of the foregoing selenium-containing amino acids in the synthesis of peptides was demonstrated in the case of Se-benzyl-L-selenohomocysteine. During decarbobenzoxylation of N-carbobenzoxy-L-selenomethionine and N-carbobenzoxy-L-selenoethionine with hydrogen bromide, the attack by the benzyl bromide on the selenium, which results in the displacement of the methyl or ethyl group, was prevented by the addition of the highly nucleophilic β-mercaptoethanol.

With the displacement of the O-tosyl moiety by selenium nucleophiles we introduced a general and convenient method for the preparation of selenocysteine and selenocystine derivatives which bear readily and selectively removable protecting groups[2-4] and which therefore fulfill all the prerequisites for incorporation into peptides—even those of more complex structures.[5-7] This method should also provide a versatile pathway for the synthesis of derivatives of selenohomocysteine and of amino acids possessing a selenohomocysteine skeleton as long as appropriately protected O-tosyl homoserine derivatives can be secured.

In our initial experiments we attempted to apply a synthetic route which had been successful for the conversion of L-serine into L-selenocysteine, *i.e.*, the use of O-tosylated N-carbobenzoxy-L-serine esterified with benzhydrol.[2] However, when DL-homoserine was carbobenzoxylated according to Flavin and Slaughter[8] and then allowed to react with diphenyldiazomethane,[9] the sole product was the γ-lactone of DL-N-carbobenzoxyhomoserine.[10] This result was not quite unexpected in view of the extensive lactone formation encountered when amino acids possessing a free γ-hydroxyl function are prepared, derivatized, or employed for peptide synthesis.[8,11-15] In fact, the ready formation of the γ-lactone is the basis for the selective, nonenzymatic cleavage of the peptide chain at amino acid residues which are convertible into γ-hydroxyamino acid resi-

(1) (a) This work was supported by U. S. Public Health Service Grants AM-11580 and AM-10080 and by the U. S. Atomic Energy Commission. One of us (J. R.) was a recipient of a Career Scientist Award from the New York Health Research Council (I-541). (b) Part of this work was presented before The First American Peptide Symposium, Yale University, New Haven, Conn., Aug 1968. (c) The following abbreviations have been used: Z, carbobenzoxy; Tos, *p*-toluenesulfonyl; Bzl, benzyl; DPM, diphenylmethyl; BZLN, *p*-nitrobenzyl; AcOH, acetic acid; DMF, dimethylformamide; TosBZLN, *p*-nitrobenzyl *p*-toluenesulfonate; MeOH, methanol. (d) To whom correspondence should be addressed: Department of Physiology, Mount Sinai School of Medicine of The City University of New York, 10 East 102nd St., New York, N. Y. 10029.

(2) (a) D. Theodoropoulos, I. L. Schwartz, and R. Walter, *Tetrahedron Lett.*, No. 25, 2411 (1967); (b) D. Theodoropoulos, I. L. Schwartz, and R. Walter, *Biochemistry*, **6**, 3927 (1967).

(3) R. Walter in "Peptides; Chemistry and Biochemistry" (Yale University, New Haven, Conn., 1968), B. Weinstein, Ed., Marcel Dekker, Inc., New York, N. Y., 1970, p 467.

(4) J. Roy, W. Gordon, I. L. Schwartz, and R. Walter, *J. Org. Chem.*, **35**, 510 (1970).

(5) R. Walter and V. du Vigneaud, *J. Amer. Chem. Soc.*, **87**, 4192 (1965).

(6) R. Walter and V. du Vigneaud, *ibid.*, **88**, 1331 (1966).

(7) R. Walter and W. Y. Chan, *ibid.*, **89**, 3892 (1967).

(8) M. Flavin and C. Slaughter, *Biochemistry*, **4**, 1370 (1965).

(9) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(10) M. Flavin and C. Slaughter, *J. Biol. Chem.*, **235**, 1103 (1960).

(11) J. S. Morley and J. M. Smith, *J. Chem. Soc.*, 726 (1968).

(12) J. P. Greenstein and M. Winitz in "Chemistry of the Amino Acids," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1961, p 2589.

(13) T. Wieland, *Fortsch. Chem. Org. Natur.*, **25**, 214 (1967).

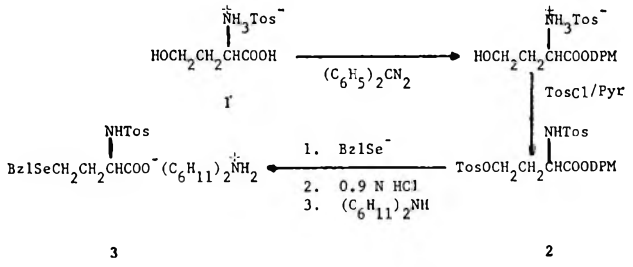
(14) Y. Fujita, J. Kollonitsch, and B. Witkop, *J. Amer. Chem. Soc.*, **87**, 2030 (1965).

(15) E. A. Bell and A. S. L. Tirimanna, *Biochem. J.*, **91**, 356 (1964).

dues, such as those of methionine[16] and aspartic acid,[17] or which already possess a γ-hydroxyl group, such as of γ,δ-dihydroxyleucine.[13] Moreover, this lactone formation has been used for the development of a N-protecting group, the γ-hydroxyisocaproyl residue.[18]

In an attempt to reduce the lactone formation we employed the poorly nucleophilic *p*-toluenesulfonate as the counterion to the NH_3^+ group of homoserine (**1**) (Scheme I). This salt, stable in dimethylformamide

SCHEME I



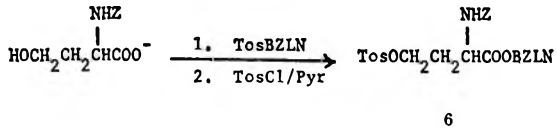
for prolonged periods of time, when treated with diphenyldiazomethane, yielded a mixture of the desired ester as well as lactone and by-products resulting from the decomposition of the diazo compound. The major by-product, as characterized by elemental analysis and ultraviolet absorption spectrum, was tetraphenylethene, which was predicted but not detected earlier.[19] Attempts to separate the ester or to acylate the amino function with carbobenzoxy chloride gave rise to additional lactone formation. However, when homoserine diphenylmethyl ester *p*-toluenesulfonate was treated with *p*-toluenesulfonyl chloride, the crystalline N,O-ditosylhomoserine diphenylmethyl ester (**2**) was secured in low yield. Both optically active and racemic **2** were converted into the corresponding Se-benzylselenohomocysteine derivatives (**3**).

From these preliminary experiments it became apparent that the most advantageous path in obtaining a fully protected O-tosylated homoserine derivative would be *via* the introduction of the amino blocking group in alkaline medium followed by the conversion of the resulting carboxylate into a suitable ester. For this purpose L-homoserine was carbobenzoxylated and the sodium N-carbobenzoxy-L-homoserinate was allowed to react with N-chloromethyl phthalimide,[20] benzyl iodide, 2,4,6-trimethylbenzyl chloride,[21] and diphenylmethyl *p*-toluenesulfonate,[22] respectively; however, in all instances the only product isolated was the α-L-carbobenzoxyaminobutyrolactone.[8] The attempt to substitute the 2,4,6-trimethylbenzyl chloride by the more reactive 2,4,6-trimethylbenzyl *p*-toluenesulfonate failed owing to the polymerization of the tosylate in the course of its preparation, a finding which is in line with the self-alkylation noticed with other tosylates.[23,24]

(16) B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961).
(17) E. Gross, J. L. Morrell, and P. Q. Lee, *Ann. N. Y. Acad. Sci.*, **151**, 556 (1968).
(18) T. Wieland, K. Mannes, and A. Schöpf, *Justus Liebigs Ann. Chem.*, **617**, 152 (1958).
(19) A. A. Aboderin, G. R. Delpierre, and J. S. Fruton, *J. Amer. Chem. Soc.*, **87**, 5469 (1965).
(20) G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. Chim. Pays-Bas*, **82**, 941 (1963).
(21) F. H. C. Stewart, *Aust. J. Chem.*, **19**, 1067 (1966).
(22) A. Ledwith and D. G. Morris, *J. Chem. Soc.*, 508 (1964).
(23) D. Theodoropoulos and J. Tsangaris, *J. Org. Chem.*, **29**, 2272 (1964).

The above findings suggested that lactonization might be controlled by the use of esters, *e.g.*, *p*-nitrobenzyl, which do not readily form an intermediate carbonium ion. Indeed, the results were encouraging when N-carbobenzoxy-L-homoserine was esterified in the form of its sodium salt with *p*-nitrobenzyl tosylate[23] (Scheme II); the N-carbobenzoxy-L-homoserine *p*-ni-

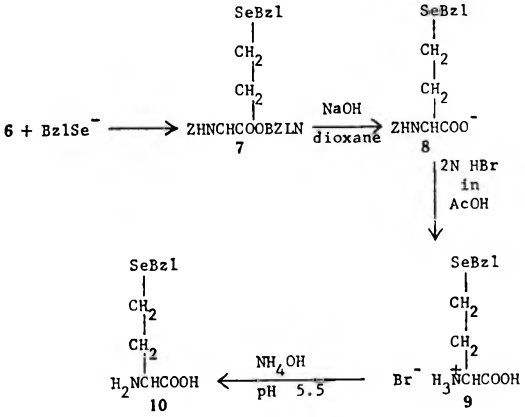
SCHEME II



trobenzyl ester, which readily crystallized and was stable when stored at 4° for a prolonged period of time, was obtained in high yields even in large-scale preparations. Treatment of this ester with tosyl chloride afforded N-carbobenzoxy-O-tosyl-L-homoserine *p*-nitrobenzyl ester (**6**), which proved to be a valuable intermediate for the preparation of optically active amino acids and peptides possessing a selenohomocysteine skeleton.

The nucleophilic displacement of the O-tosyl moiety of **6** by the benzylselenide anion gave the corresponding Se-benzyl derivative **7** (Scheme III). Prior to saponi-

SCHEME III



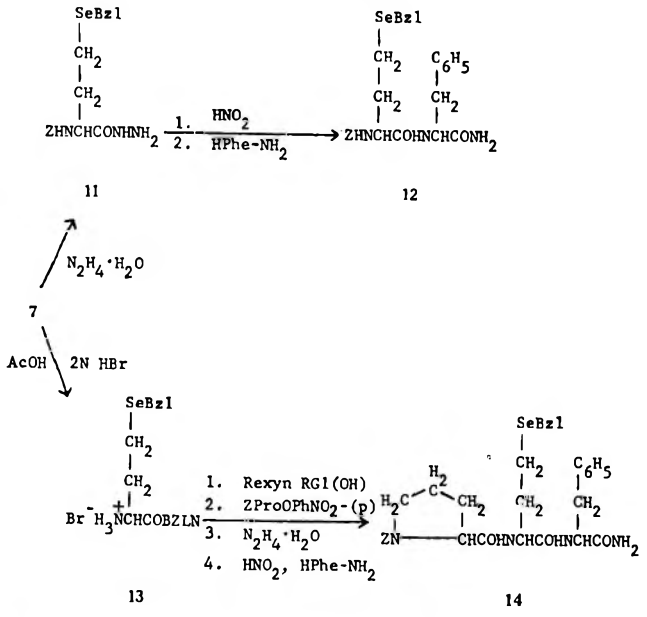
fying **7** we established the reaction conditions to remove the *p*-nitrobenzyl group on the model compound, N-carbobenzoxy-L-alanine *p*-nitrobenzyl ester. The procedure, described by Iselin and Schwyzer,[25] which gave N-carbobenzoxy-L-alanine in high yield and without racemization, proved to be most suitable and was applied to the hydrolysis of **7** to yield N-carbobenzoxy-Se-benzyl-L-selenohomocysteine (**8**). Decarbobenzoxylation of **8** afforded the hydrobromide **9**, which was converted into Se-benzyl-L-selenohomocysteine (**10**). We observed that the specific optical rotation of **10** in hydrochloric acid is extremely temperature dependent and that it has to be read at once; the value of the specific rotation decreases as **10** is allowed to stand in the acidic solution. This may, in part, explain the lower values for the optical rotation reported for this compound by other authors. However, data presented in this paper (*vide infra*) would indicate that **10**, despite

(24) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3443 (1953).
(25) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **45**, 1499 (1962).

the fact that it has previously been prepared by essentially two independent routes,[26,27] was not secured in an optically pure form—because selenomethionine[26-28] and selenoethionine[27] obtained after debenzylation of Se-benzyl-L-selenohomocysteine with sodium in liquid ammonia and subsequent alkylation also exhibited lower values for the optical rotation. In view of our own findings and those of others,[29,30] it is likely that, in addition to the factor of temperature sensitivity, the discrepancies may be attributed to the sodium–liquid ammonia reduction employed in these earlier studies.

It has previously been shown from this laboratory that N-carbobenzoxy-Se-benzyl-L-selenocysteine *p*-nitrobenzyl ester is ideally suited for the attachment of a Se-benzyl-L-selenocysteine residue to either the amino or the carboxyl end of an amino acid or a peptide.[2b] In the present study we explored the possibility of applying these reactions to the selenohomocysteine peptides. Therefore, on the one hand, **7** was hydrazinolyzed to yield **11**, which was then, *via* the azide method, elongated to N-carbobenzoxy-Se-benzyl-L-selenohomocysteinyl-L-phenylalanine amide (**12**) (Scheme IV).

SCHEME IV

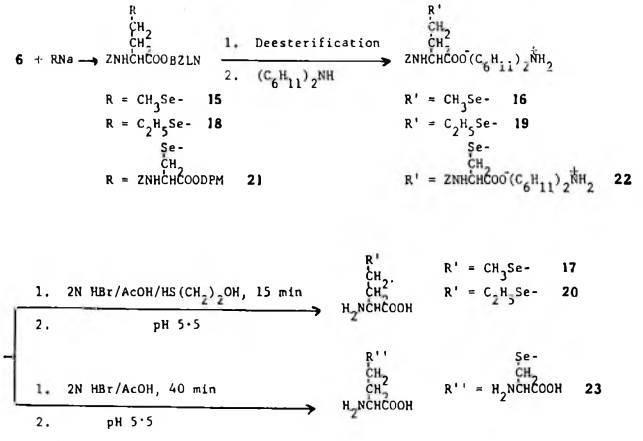


On the other, **7** was decarbobenzoxylated and the methanolic solution of the hydrobromide **13** was passed through a Rexyn RG1(OH) column to give the Se-benzyl-L-selenohomocysteine *p*-nitrobenzyl ester. Only trace amounts of *p*-nitrobenzyl alcohol were liberated during this process. The base was allowed to react with N-carbobenzoxy-L-proline *p*-nitrophenyl ester[31] and the resulting dipeptide ester was converted directly into N-carbobenzoxy-L-prolyl-Se-benzyl-L-selenohomocysteine hydrazide. This hydrazide in turn was converted in excellent yield into the protected tripeptide amide **14** *via* the azide procedure.

(26) F. Pan and H. Tarver, *Arch. Biochem. Biophys.*, **119**, 429 (1967).
(27) H.-D. Jakubke, J. Fischer, K. Jost, and J. Rudinger, *Collect. Czech. Chem. Commun.*, **33**, 3910 (1968).
(28) G. Zdansky, *Ark. Kemi*, **29**, 437 (1968).
(29) W. H. H. Günther and H. G. Mautner, *J. Amer. Chem. Soc.*, **87**, 2708 (1965).
(30) L. B. Agenäs and B. Persson, *Acta Chem. Scand.*, **21**, 835 (1967).
(31) M. Bodansky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 5688 (1959).

Next we investigated the feasibility of transforming N-carbobenzoxy-L-homoserine *p*-nitrobenzyl ester into derivatives of L-selenomethionine, L-selenoethionine, and L-(+)-selenocystathionine. First, we attempted to convert the protected ester with sodium hydrogen selenide into N-carbobenzoxy-L-selenohomocysteine *p*-nitrobenzyl ester according to the procedure introduced in this laboratory by Gordon.[3,4] However, in spite of several experimental modifications, this compound was not secured and *p*-nitrobenzyl alcohol was consistently liberated; apparently the selenol moiety of the initially formed N-carbobenzoxy-L-selenohomocysteine *p*-nitrobenzyl ester attacks the ester bond with the concomitant release of the alcohol. This difficulty was circumvented when the desired selenium nucleophile, *i.e.*, the sodium salt of methylselenol, ethylselenol,[32] or N-carbobenzoxy-L-selenocysteine diphenylmethyl ester,[2b] was allowed to react *in situ* with the ester, yielding the fully protected L-selenomethionine (**15**), L-selenoethionine (**18**), or L-(+)-selenocystathionine (**21**) derivatives, respectively, in good yields (Scheme V).

SCHEME V



In the case of **15** and **18** saponification as detailed for **8** readily yielded the N-protected amino acids, which were characterized as their dicyclohexylammonium salts. Initial attempts to decarbobenzoxylate **16** and **19** by catalytic hydrogenation or treatment with 2 *N* HBr in glacial acetic acid in the absence or presence of methyl ethyl sulfide[33,34] were unsuccessful. While in the former experiment the complete recovery of the starting material indicated that the catalyst had been poisoned, in the latter the sole product isolated was Se-benzyl-L-selenohomocysteine, a finding reminiscent of earlier experiences with N-carbobenzoxy-L-methionine.[35,36] Obviously, the nucleophilicity of methyl ethyl sulfide does not suffice to compete with the unsymmetrical dialkyl selenide for the benzyl bromide which is formed during the decarbobenzoxylation of **16** and **19** with hydrogen bromide. Therefore, in another experiment we introduced a stronger nucleophile, β-mercaptoethanol, into the reaction medium and were

(32) H. Rheinboldt in "Methoden der Organischen Chemie (Houben-Weyl)," E. Müller, Ed., Georg Thieme Velag, Stuttgart, 1955, p 952.
(33) St. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).
(34) F. Chillemi, *Gazz. Chim. Ital.*, **93**, 1079 (1963).
(35) C. A. Dekker and J. S. Fruton, *J. Biol. Chem.*, **173**, 471 (1948).
(36) N. F. Albertson and F. C. McKay, *J. Amer. Chem. Soc.*, **75**, 5323 (1953).

able to secure L-selenomethionine (**17**) and L-selenoethionine (**20**). In fact, from qualitative experiments it emerged that the greater the quantity of added β-mercaptoethanol the higher was the yield of **17** and **20**. The specific optical rotations of L-selenomethionine and L-selenoethionine prepared by other synthetic routes[26-28] are appreciably lower than those reported in this study.

The fully protected L-selenocystathionine derivative (**21**) was deesterified stepwise; the *p*-nitrobenzyl ester was saponified and, without isolation of the intermediate, the diphenylmethyl ester group was cleaved by acidolysis and the resulting acid was then characterized as its di(dicyclohexylammonium) salt (**22**). Decarbobenzoxylation of **22** gave the hydrobromide of L-selenocystathionine, which upon adjustment of the pH to the isoelectric point, afforded the free amino acid **23**. The optical rotation of the product agreed with that reported for synthetic L-selenocystathionine[37] as well as that isolated from the South American nut, *Lecythis ollaria*.[38]

Experimental Section[39]

L-Homoserine *p*-Toluenesulfonate (1a).—*p*-Toluenesulfonic acid monohydrate (4.75 g) was added with stirring to a solution of L-homoserine (3.0 g) in water (12 ml). When the dissolution was complete, the solvent was quickly evaporated under reduced pressure. The resulting syrup was diluted with acetone (400 ml). Crystallization of the product was induced by scratching. After completion of the crystallization the salt was isolated by filtration, washed with acetone, and recrystallized from methanol–ether, yielding 5.6 g (76%), mp 124–125°, $[\alpha]^{23}D$ +6.8° (*c* 2, methanol).

Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.4; H, 5.84; N, 4.80. Found: C, 45.1; H, 5.64; N, 4.65.

DL-Homoserine *p*-toluenesulfonate (1b) was obtained analogously, mp 141°.

Anal. Found: C, 45.3; H, 6.00; N, 4.88.

N,O-Ditosyl-L-homoserine Diphenylmethyl Ester (2a).—To a solution of L-homoserine *p*-toluene sulfonate (7.5 g) in DMF (12 ml) at 50°, diphenyldiazomethane (7.5 g) in DMF (25 ml) was added. The reaction mixture was kept at 50° for 10 min; then the solvent was removed under reduced pressure and the syrup was washed with ether to remove any excess diazomethane, benzhydrol, tetraphenylethene (*vide infra*), and other uncharacterized by-products. The resulting syrup (12 g), dried over P_2O_5 *in vacuo*, failed to crystallize. It was dissolved in dry pyridine (50 ml), the solution was cooled to −10°, and tosyl chloride (15 g) was added. After being stirred at 0° for 4 hr the reaction mixture was poured over crushed ice. The resulting oil was washed with water, dried, and extracted several times with ether. The ether-soluble fraction was applied to a column of silica gel prepared in petroleum ether (bp 90–110°). The product was eluted with ether–petroleum ether (1:1). Upon evaporation of the solvent, the desired product was isolated: yield 3.5 g (17%); mp 132–133°; $[\alpha]^{22}D$ −15.5° (c 1, DMF); silica gel (S_{III}) R_f 0.77.

Anal. Calcd for $C_{31}H_{31}NO_7S_2$: C, 62.7; H, 5.23; N, 2.36. Found: C, 62.8; H, 5.35; N, 2.38.

In a preliminary investigation the DL derivative **2b** was obtained in low yield, mp 118–119°.

Anal. Found: C, 63.1; H, 5.40; N, 2.28.

N-Tosyl-Se-benzyl-L-selenohomocysteine Diphenylmethyl Ester (3a).—Benzylselenol (0.48 g) was dissolved in DMF (2.5 ml), and a 13% NaOH solution (0.8 ml) was added to it. This was quickly followed by the addition of N,O-ditosyl-L-homoserine diphenylmethyl ester (1.5 g) in acetone (10 ml). The mixture was stirred for 5 min, after which it was brought to pH 5 with dilute acetic acid. Subsequently, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate, giving a syrup. The latter was taken up in benzene and chromatographed on a column of silica gel packed in the same solvent. Washing with benzene removed all the dibenzyl diselenide formed from excess benzylselenol during the isolation procedure. The product was eluted with benzene–ethyl acetate (95:5, v/v). Fractions containing the product, as tested by tlc, were combined. After removal of the solvent the resulting oil was crystallized from ether–petroleum ether–cyclohexane: yield 1.3 g (86%); mp 4°; $[\alpha]^{22}D$ +36.0° (*c* 1, chloroform); silica gel (S_{II}) R_f 0.76.

Anal. Calcd for $C_{31}H_{31}NO_4SSe$: C, 62.8; H, 5.24; N, 2.36. Found: C, 63.0; H, 5.36; N, 2.21.

The chromatographically pure, syrupy racemic compound **3b** was prepared similarly in 95% yield.

Anal. Found: C, 62.9; H, 5.31; N, 2.28.

N-Tosyl-Se-benzyl-L-selenohomocysteine Dicyclohexylammonium Salt (4a).—Compound **3a** (0.5 g) was dissolved in dry nitromethane (6 ml) containing 0.9 *N* HCl. After the solution had been left at room temperature for a period of 1 hr, the solvent was removed. The residue was triturated with dilute sodium bicarbonate solution and the insoluble portion was filtered off. From the filtrate the N-protected amino acid was extracted with ethyl acetate after acidification with dilute hydrochloric acid. The ethyl acetate solution was concentrated and the acid was isolated as its dicyclohexylammonium salt (0.4 g, 78%). On recrystallization from methanol–ether the melting point remained unchanged, mp 176–178°, $[\alpha]^{22}D$ +42.4° (*c* 1, methanol).

Anal. Calcd for $C_{30}H_{44}N_2O_4SSe$: C, 59.3; H, 7.25; N, 4.61. Found: C, 59.1; H, 7.07; N, 4.42.

The corresponding data for the racemic derivative **4b** follow: yield 80%, mp 184–186°.

Anal. Found: C, 59.1; H, 7.07; N, 4.42.

In the course of the work-up of the deesterification reaction, **3b**, **N-tosyl-Se-benzyl-DL-selenohomocysteine**, was isolated as a crystalline product, mp 113–115°.

Anal. Calcd for $C_{18}H_{21}NO_4SSe$: C, 50.7; H, 4.93; N, 3.29. Found: C, 51.1; H, 4.86; N, 3.25.

N-Carbobenzoxy-L-homoserine *p*-Nitrobenzyl Ester (5).—L-Homoserine (5 g) and sodium bicarbonate (11.1 g) were dissolved together in water (160 ml), and to the well-stirred solution carbobenzoxy chloride (7.6 ml) was added over a period of 1 hr at room temperature. After stirring for an additional 4 hr the solution was washed repeatedly with ether and the aqueous phase was evaporated to dryness under vacuum. Sodium N-carbobenzoxy-L-homoserinate was extracted from the dry residue with DMF and isolated upon removal of the solvent under vacuum as a hygroscopic powder. This was dissolved in DMF (35 ml) and acetone (70 ml), and after *p*-nitrobenzyl tosylate (15 g) had been added the mixture was gently refluxed over a water bath for 30 min. The fluffy precipitate of sodium tosylate was filtered off and the solution was concentrated under reduced pressure. On diluting the resulting syrup with water an oil separated, which was taken up in ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated. On adding an excess of ether and cooling overnight, crystals of the *p*-nitrobenzyl ester separated and were recrystallized from ethyl acetate–ether: yield 9.6 g (64%); mp 85°; $[\alpha]^{22}D$ −19.8° (*c* 2, methanol); silica gel (S_{III}) R_f 0.21.

Anal. Calcd for $C_{19}H_{20}N_2O_7$: C, 58.8; H, 5.15; N, 7.22. Found: C, 59.01; H, 5.14; N, 7.06.

(37) G. Zdansky, *Ark. Kemi*, **29**, 449 (1968).

(38) F. Kerdel-Vegas, F. Wagner, P. B. Russell, N. H. Grant, H. E. Alburn, D. E. Clark, and J. A. Miller, *Nature*, **205**, 1185 (1965).

(39) All melting points were determined with a Thomas–Hoover capillary melting point apparatus and are corrected. Optical rotations were determined with a Carl Zeiss photoelectric precision polarimeter to ± 0.005°. Elementary analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The hydrogen selenide was purchased from Matheson Coleman and Bell. The following solvent systems were used for thin layer chromatography: benzene–ethyl acetate (1:2, v/v) (S_I); benzene–ethyl acetate (4:1) (S_{II}); benzene–ethyl acetate (2:1) (S_{III}); benzene–ethyl acetate–methanol (5:5:1) (S_{IV}); benzene–ethyl acetate–acetic acid (10:5:1) (S_V); and 1-butanol–water–acetie acid (4:1:1) (S_{VI}). 1-Butanol–water–acetic acid (5:5:1, upper phase) (S_{VII}) was used for paper chromatography. In the case of protected amino acids and peptides, thin layer chromatograms were run on silica gel plates and the plates were visualized by the procedure of Zahn and Rexroth.[40] Free amino acids were chromatographed on cellulose plates or Whatman #1 paper and the chromatograms were developed with ninhydrin reagent. The free amino acids were also tested for purity by chromatography on a Beckman–Spinco Model 120C amino acid analyzer according to the procedure described earlier.[41] The selenium-containing amino acids are stored at 4° and with the exclusion of light.

(40) H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).

(41) R. Walter, D. H. Schlesinger, and I. L. Schwartz, *Anal. Biochem.*, **27**, 231 (1969).

N-Carbobenzoxy-O-tosyl-L-homoserine *p*-Nitrobenzyl Ester (6).—Compound **5** (8 g) was dissolved in dry pyridine (40 ml) at −10°, and tosyl chloride (5.4 g) was added with stirring. The reaction was allowed to continue for 3 hr at −10°, after which the mixture was poured over crushed ice. On cooling a semisolid mass was separated overnight which, after decantation of the supernatant liquid, was dissolved in ethyl acetate. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated. On adding ether and cooling, the product precipitated as crystals in 81% yield. For elemental analysis a sample was recrystallized from ethyl acetate–ether: mp 114–115°; $[\alpha]^{23}D$ −7.8° (c 2, DMF); silica gel (S_{III}) R_f 0.61.

Anal. Calcd for $C_{26}H_{26}N_2O_9S$: C, 57.6; H, 4.80; N, 5.17. Found: C, 57.8; H, 4.87; N, 5.24.

N-Carbobenzoxy-Se-benzyl-L-selenohomocysteine *p*-Nitrobenzyl Ester (7).—To a solution of benzylselenol (2 g) dissolved in DMF (10 ml), water (3 ml) containing NaOH (0.4 g) was added. To this mixture a solution of **6** (5.4 g) dissolved in acetone (40 ml) was quickly added. The product was worked up in the same manner as **3**, yielding 4.5 g (83%). Crystallization from ether–ethanol afforded pure product in fine needles: mp 65–66°; $[\alpha]^{21}D$ −18.4° (c 1, DMF); silica gel (S_{II}) R_f 0.74.

Anal. Calcd for $C_{26}H_{25}N_2O_6Se$: C, 57.7; H, 4.80; N, 5.17. Found: C, 57.9; H, 4.64; N, 4.95.

N-Carbobenzoxy-L-alanine *p*-Nitrobenzyl Ester.—N-Carbobenzoxy-L-alanine (4.46 g) and sodium methoxide (1.08 g) were dissolved in methanol (*ca.* 50 ml) and the solvent was then removed under reduced pressure. The resulting sodium N-carbobenzoxy-L-alaninate was dissolved in DMF–acetone (1:2, 22 ml), and *p*-nitrobenzyl tosylate (6.14 g) was added. The reaction mixture was gently refluxed for 30 min, after which the precipitated sodium tosylate was filtered off and the filtrate was concentrated to a syrup under vacuum. Upon addition of water (200 ml) the syrupy material crystallized readily. The crystals were collected, washed with water, and recrystallized from ethyl acetate–ether–cyclohexane: yield 4.5 g (60%); mp 100–101° (lit.[42] mp 99–100°); $[\alpha]^{22}D$ −12.9° (c 2, DMF); silica gel (S_{II}) R_f 0.66.

N-Carbobenzoxy-L-alanine.—N-Carbobenzoxy-L-alanine *p*-nitrobenzyl ester (1.22 g) was dissolved in dioxane (19 ml) and treated with 0.5 *N* NaOH (9 ml) added over a period of 30 min. Stirring was continued for an additional 15 min, after which the pH of the solution was brought to 7 with 1 *N* HCl. The solvent was removed under reduced pressure and the residue was shaken with ether–water to remove the *p*-nitrobenzyl alcohol. The aqueous phase was separated, washed thrice with ether, acidified to Congo red, and then extracted with ethyl acetate. The ethyl acetate solution was washed with water and dried over sodium sulfate, and the product was subsequently precipitated by the addition of petroleum ether. Recrystallization from ethyl acetate–petroleum ether afforded 0.7 g (97%) of product, mp 85–86°, $[\alpha]^{22}D$ −14.3° (c 2, acetic acid) [*cf.* N-carbobenzoxy-L-alanine used as a starting material in the previous experiment, mp 84–85°, $[\alpha]^{22}D$ −14.2° (c 2, acetic acid)].

N-Carbobenzoxy-Se-benzyl-L-selenohomocysteine (8).—Compound **7** (2 g) was dissolved in dioxane (20 ml) at room temperature and 9 ml of 0.5 *N* aqueous NaOH was added to the solution over a period of 30 min. Stirring was continued for an additional 20 min, after which the pH was lowered to 7 with 1 *N* HCl and the solution was concentrated under reduced pressure. After the dioxane had been removed, the aqueous solution was washed with ethyl acetate. The pH was lowered to 2 and the product was extracted with ethyl acetate. Crystallization from benzene–cyclohexane gave 1.2 g (50%) of the compound: mp 93–94°; $[\alpha]^{22}D$ −22.2° (c 1, DMF); silica gel (S_V) R_f 0.66.

Anal. Calcd for $C_{19}H_{21}NO_4Se$: C, 56.2; H, 5.17; N, 3.45. Found: C, 56.2; H, 5.28; N, 3.52.

Se-Benzyl-L-selenohomocysteine Hydrobromide (9).—Compound **8** (0.5 g) was allowed to react with 2 *N* HBr in glacial acetic acid for 1 hr. On adding a large excess of ether an oil separated which soon crystallized. The crystals were washed with ether by decantation and recrystallized from methanol–ether: yield 0.4 g (92%); mp 152–154°; $[\alpha]^{22}D$ +9.74° (c 1, methanol).

Anal. Calcd for $C_{11}H_{15}NO_2Se \cdot HBr$: C, 37.4; H, 4.53; N, 3.97. Found: C, 37.3; H, 4.64; N, 3.95.

Se-Benzyl-L-selenohomocysteine (10).—The hydrobromide **9** (0.2 g) was suspended in water (30 ml) and the pH was adjusted to 5.5 with ammonium hydroxide. The mixture was thoroughly stirred and left for a few hours at 4°. The crystals which had formed were separated by filtration, washed with a small amount of cold water, and recrystallized from hot water: yield 0.15 g (97%); mp 238–240° dec; $[\alpha]^{21}D$ +23.2° (c 0.5, 2 *N* HCl) [lit.[27] mp 213–214°; $[\alpha]^{22}D$ +19.2° (c 0.51, 2 *N* HCl); $[\alpha]^{27}D$ +15.1° (c 2, 1 *N* HCl)[26]; $[\alpha]^{25}D$ +15.5° (c 1, 1 *N* HCl)];[28] cellulose (S_{VI}) R_f 0.77, paper (S_{VII}) R_f 0.7.

Anal. Calcd for $C_{11}H_{15}NO_2Se$: C, 48.5; H, 5.51; N, 5.15. Found: C, 48.4; H, 4.45; N, 5.15.

N-Carbobenzoxy-Se-benzyl-L-selenohomocysteine Hydrazide (11).—Compound **7** (0.4 g) was dissolved in methanol–DMF (2:1, 1.5 ml). Hydrazine hydrate (0.3 ml) was added and the reaction was allowed to proceed at room temperature for 18 hr. At the end of this period the reaction mixture was diluted with water (100 ml) and the precipitate thus formed was filtered and washed with cold water. The product was recrystallized from methanol–ether: yield 0.25 g (81%); mp 129–130°; $[\alpha]^{23}D$ −6.5° (c 1.1, DMF); silica gel (S_{IV}) R_f 0.45.

Anal. Calcd for $C_{19}H_{23}N_3O_3Se$: C, 54.3; H, 5.48; N, 10.0. Found: C, 54.2; H, 5.55; N, 9.80.

N-Carbobenzoxy-Se-benzyl-L-selenohomocysteinyl-L-phenylalanine Amide (12).—The hydrazide **11** (0.3 g) was dissolved in DMF (5 ml) and the soluion was cooled to −20°. Concentrated HCl (0.8 ml) followed by a precooled solution of sodium nitrite (0.06 g in 1 ml of water) were then added. The reaction was allowed to proceed for 3 min, after which the temperature was lowered to −40°. The solution was neutralized with triethylamine. A precooled solution of L-phenylalanine amide (0.15 g) in DMF (2 ml) was then added. Subsequently, the reaction mixture was allowed to warm from −40 to −5° and was allowed to remain at this temperature for 1 hr. Stirring was continued overnight at 4°. The solvent was then removed under reduced pressure and the resulting residue was washed well with water. After drying, the product was recrystallized from 95% ethanol: yield 0.2 g (51%); mp 174–176°; $[\alpha]^{22}D$ −29.5° (c 2, DMF); silica gel (S_{IV}) R_f 0.57.

Anal. Calcd for $C_{28}H_{31}N_3O_4Se$: C, 60.9; H, 5.62; N, 7.61. Found: C, 60.9; H, 5.71; N, 7.52.

Se-Benzyl-L-selenohomocysteine *p*-Nitrobenzyl Ester Hydrobromide (13).—Compound **7** (1 g) was decarbobenzoxylated with 2 *N* HBr (3 ml) in glacial acetic acid over a period of 1 hr. On adding an excess of ether an oil separated, which crystallized on scratching in the presence of a drop of methanol. Recrystallization from methanol–ether afforded the pure product: yield 0.65 g (72%); mp 116°; $[\alpha]^{22}D$ +10.4° (c 1, methanol).

Anal. Calcd for $C_{18}H_{20}N_2O_4Se \cdot HBr$: C, 44.3; H, 4.30; N, 5.74. Found: C, 44.0; H, 4.31; N, 5.76.

N-Carbobenzoxy-L-prolyl-Se-benzyl-L-selenohomocysteine Hydrazide.—The hydrobromide **13** (1.2 g) dissolved in methanol (20 ml) was passed through a column of Rexyn RG1(OH). On evaporating the solvent 1.0 g of a gummy residue was obtained. It was dissolved in dry methylene chloride (3 ml), and N-carbobenzoxy-L-proline *p*-nitrophenyl (0.92 g) ester was added. The mixture was stirred overnight at room temperature; then the solvent was removed and the resulting residue was chromatographed on a silica gel column packed in benzene. Fractions containing the dipeptide (eluted with benzene containing 20% ethyl acetate) were collected. On removing the solvent 1.4 g (89%) of an oily residue was obtained which resisted crystallization. Therefore the ester was converted into its hydrazide according to the procedure outlined for **11**. The product was recrystallized from methanol–ether: yield 0.9 g (79%); mp 139–140°; $[\alpha]^{22}D$ −37.2° (c 1, DMF); silica gel (S_{IV}) R_f 0.27.

Anal. Calcd for $C_{24}H_{30}N_4O_4Se$: C, 55.8; H, 5.80; N, 10.8. Found: C, 55.8; H, 5.75; N, 10.8.

N-Carbobenzoxy-L-prolyl-Se-benzyl-L-selenohomocysteinyl-L-phenylalanine Amide (14).—The hydrazide above (0.5 g) was converted into the azide and coupled with L-phenylalanine amide under the same experimental conditions as described for the preparation of **12**. After the reaction was completed, the solvent was removed under reduced pressure and the resulting residue was washed thoroughly with water. The product was recrystallized from hot methanol: yield 0.6 g (95%); mp 196–198°; $[\alpha]^{22}D$ −40.4° (c 2, DMF); silica gel (S_{IV}) R_f 0.47.

Anal. Calcd for $C_{33}H_{38}N_4O_5Se$: C, 61.1; H, 5.86; N, 8.63. Found: C, 60.9; H, 5.99; N, 8.56.

(42) V. G. Debabov and V. A. Shibnev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1031 (1962).

N-Carbobenzoxy-L-selenomethionine *p*-Nitrobenzyl Ester (15).—Sodium (0.065 g) was dissolved in ethanol (5 ml) in a three-necked flask equipped with two dropping funnels, a magnetic stirrer, an inlet for passing the gases through the solution, and an outlet connected to a trap containing a 10% solution of NaOH. Hydrogen selenide from a tank mixed with a slow stream of hydrogen was passed under exclusion of air through the solution of sodium ethoxide. When the formation of sodium hydrogen selenide was complete, the excess of hydrogen selenide was swept away with a fast current of hydrogen. The reaction vessel was then placed in an ice bath, the current of hydrogen was slowed down, and a solution of methyl iodide (0.43 g) in DMF (2 ml) was introduced. The reaction was allowed to proceed for 10 min, after which a solution of NaOH (0.104 g) in water (2 ml) was added. This was followed by the addition of **6** (1.084 g) in DMF (3 ml). After standing for 1 hr at room temperature, the mixture was poured into 150 ml of water and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The resulting syrup, which contained dimethyl diselenide as the major impurity, was dissolved in benzene and chromatographed through a column of silica gel packed in benzene. After removal of the solvent from fractions containing the product, it was recrystallized from ether–ethanol: yield 0.6 g (66%); mp 56–57°; $[\alpha]^{22}D$ −18.2° (*c* 1, DMF); silica gel (S_{II}) R_f 0.54.

Anal. Calcd for $C_{20}H_{22}N_2O_6Se$: C, 51.6; H, 4.73; N, 6.02. Found: C, 51.5; H, 4.70; N, 5.93.

N-Carbobenzoxy-L-selenomethionine Dicyclohexylammonium Salt (16).—The ester **15** (0.75 g) was dissolved in dioxane (7 ml), and 0.5 *N* NaOH (3 ml) was added at room temperature over a period of 30 min with stirring. The reaction was allowed to continue for an additional 30 min, at the end of which the starting material had completely disappeared, as revealed by tlc. In a manner analogous to the isolation of **8**, N-carbobenzoxy-L-selenomethionine was obtained as a syrup, converted into its dicyclohexylammonium salt, and recrystallized from methanol–ether: yield 0.8 g (97%); mp 163–164°; $[\alpha]^{22}D$ +12.7° (*c* 1, DMF).

Anal. Calcd for $C_{25}H_{40}N_2O_4Se$: C, 58.7; H, 7.83; N, 5.48. Found: C, 58.8; H, 7.93; N, 5.47.

L-Selenomethionine (17).—The salt **16** (0.3 g) was shaken with 2 *N* H_2SO_4 (10 ml) and ethyl acetate (20 ml), and the organic layer was separated, washed once with 2 *N* H_2SO_4 and twice with water, and dried with anhydrous sodium sulfate. The residue obtained on removing the solvent was dried under vacuum over P_2O_5 overnight. It was then dissolved in dry acetic acid (0.3 ml) and β-mercaptoethanol (0.7 ml). To this mixture, 4 *N* HBr (1 ml) in glacial acetic acid was added. The reaction was allowed to proceed for 15 min, after which dry ether (100 ml) was added. An oil separated, which was washed repeatedly with dry ether and finally dried under vacuum over potassium hydroxide. The dried mass was dissolved in water (5 ml) and the pH was adjusted to 5.5 with ammonium hydroxide. The solution was then concentrated to near dryness and the residue was washed several times with ethanol and recrystallized once from aqueous acetone to give 0.057 g (50%) of the product: mp 266–268° dec; $[\alpha]^{22}D$ +21.6° (*c* 0.5, 2 *N* HCl) [lit.[27] mp 275° dec; $[\alpha]^{22}D$ +17.5° (*c* 0.5, 2 *N* HCl); $[\alpha]^{27}D$ +17.8° (*c* 1, 1 *N* HCl)[26]; $[\alpha]^{25}D$ +18.1° (*c* 1, 1 *N* HCl)[28]]; cellulose (S_{VI}) R_f 0.58, paper (S_{VII}) R_f 0.39.

Anal. Calcd for $C_5H_{11}NO_2Se$: C, 30.6; H, 5.65; N, 7.14. Found: C, 30.5; H, 5.66; N, 6.62.

N-Carbobenzoxy-L-selenoethionine *p*-Nitrobenzyl Ester (18).—The method of synthesis of **18** and purification was identical with that described for **15**. Recrystallization from 95% ethanol afforded 0.8 g (82%) of the product: mp 66°; $[\alpha]^{22}D$ −19.1° (*c* 1, DMF); silica gel (S_{II}) R_f 0.6.

Anal. Calcd for $C_{21}H_{24}N_2O_6Se$: C, 52.6; H, 5.01; N, 5.85. Found: C, 52.7; H, 5.10; N, 5.83.

N-Carbobenzoxy-L-selenoethionine Dicyclohexylammonium Salt (19).—As described for the corresponding selenomethionine derivative, the *p*-nitrobenzyl ester **18** (0.55 g) was deesterified, yielding 0.35 g (89%) of the free acid. The acid was best characterized as its dicyclohexylammonium salt, which on recrysallization from methanol–ether melted at 154–155°, $[\alpha]^{22}D$ +8.2° (*c* 1.5, DMF).

Anal. Calcd for $C_{26}H_{42}N_2O_4Se$: C, 59.4; H, 8.00; N, 5.33. Found: C, 59.3; H, 8.05; N, 5.17.

L-Selenoethionine (20).—The salt **19** (0.3 g) was converted into the free acid and subsequently decarbobenzoxylated in a manner similar to the experimental procedure described for **17**. The product was recrystallized from aqueous acetone, yielding 0.08 g (67%) of compound: mp 253–256° dec; $[\alpha]^{22}D$ +21.5° (*c* 0.5, 2 *N* HCl) [lit.[27] mp 235–250° dec; $[\alpha]^{22}D$ +15.9° (*c* 0.5, *N* HCl)]; cellulose (S_{VI}) R_f 0.71, paper (S_{VII}) R_f 0.49.

Anal. Calcd for $C_6H_{13}NO_2Se$: C, 34.3; H, 6.24; N, 6.67. Found: C, 34.5; H, 6.06; N, 6.42.

N-Carbobenzoxyselenyl(β-diphenylmethoxycarbonyl-β-N′-carbobenzoxy-L-amino)ethyl-L-selenohomocysteine *p*-Nitrobenzyl Ester (21).—Sodium hydrogen selenide was prepared from sodium (0.048 g) in ethanol (5 ml) in an analogous manner as described for the preparation of **15**. Subsequently, N-carbobenzoxy-O-tosyl-L-serine diphenylmethyl ester[2b] (1.118 g) dissolved in DMF (3 ml) was introduced into the reaction vessel. After 1 hr NaOH (0.084 g) dissolved in H_2O (2 ml) was added followed by NaOH (1.084 g) in DMF (3 ml) 5 min later. The reaction flask was stored with exclusion of air and light for 3 days. For the isolation and purification of the product the same method was followed as for **15**. Two recrystallizations from 95% ethanol afforded 0.9 g (53%) of **21**, which changes its crystal contours at 58°, $[\alpha]^{21}D$ −26.3° (*c* 1, DMF), silica gel (S_{II}) R_f 0.5.

Anal. Calcd for $C_{43}H_{41}N_3O_{10}Se$: C, 61.6; H, 4.89; N, 5.01. Found: C, 61.7; H, 4.96; N, 4.89.

N,N′-Dicarbobenzoxy-L-selenocystathionine Di(dicyclohexylammonium) Salt (22).—Compound **21** (0.5 g) was saponified as described for the preparation of **8**. The acid was then converted into the dicyclohexylammonium salt, 0.3 g (56%), which on recrystallization from methanol–ether melted at 202–204°, $[\alpha]^{21}D$ +19.6° (*c* 0.5, DMF).

Anal. Calcd for $C_{47}H_{72}O_8N_4Se$: C, 62.7; H, 8.01; N, 6.23. Found: C, 63.0; H, 8.13; N, 6.34.

L-Selenocystathionine (23).—The salt **22** (0.3 g) was treated with 2 *N* H_2SO_4 and the free acid was obtained in the manner as described for **17**. The free acid was treated with 2 *N* HBr (2 ml) in glacial acetic acid for 40 min, and by diluting the reaction mixture with excess of dry ether, the hyrobromide was obtained as a gummy solid. It was dried under vacuum over KOH. The solid was then dissolved in 3 ml of water and the pH adjusted to 5.5 with ammonium hydroxide. On concentrating and cooling, L-selenocystathionine crystallized as fine needles which were collected by filtration, washed with ethanol, and recrystallized from water: yield 0.06 g (67%); mp 256–258° dec; $[\alpha]^{22}D$ +35.8° (*c* 1, 1 *N* HCl) [lit.[38] $[\alpha]D$ +36.5° (*c* 1, 1 *N* HCl); $[\alpha]^{25}D$ +36.1° (*c* 1, 1 *N* HCl)[37]], cellulose (S_{VI}) 0.07, paper (S_{VII}) 0.05.

Anal. Calcd for $C_7H_{14}N_2O_4Se$: C, 31.2; H, 5.25; N, 10.4. Found: C, 31.2; H, 5.35; N, 10.3.

Registry No.—**1a,** 23809-71-4; **1b,** 23809-72-5; **2a,** 23796-86-3; **2b,** 23809-73-6; **3a,** 23809-74-7; **3b,** 23809-75-8; **4a,** 23809-76-9; **4b,** 23796-87-4; **5,** 23809-78-1; **6,** 23809-79-2; **7,** 23809-80-5; **8,** 23809-82-7; **9,** 23809-83-8; **10,** 19635-25-7; **11,** 23809-85-0; **12,** 23796-88-5; **13,** 23809-86-1; **14,** 23809-88-3; **15,** 23796-89-6; **16,** 23809-89-4; **17,** 3211-76-5; **18,** 23796-90-9; **19,** 23809-91-8; **20,** 20999-05-7; **21,** 23809-93-0; **22,** 23809-94-1; **23,** 23809-95-2; N-tosyl-Se-benzyl-DL-selenohomocysteine, 23809-77-0; N-carbobenzoxy-L-alanine, 1142-20-7; N-carbobenzoxy-L-prolyl-Se-benzyl-L-selenohomocysteine hydrazide, 23809-87-2.

Acknowledgments.—Dr. S. Hsieh was involved in the exploratory experiments of this work and the authors thank him for his contribution. They are also grateful for the technical assistance rendered by Mrs. Bella White and Mr. Duke Kasprisin.

The Crystal and Molecular Structure of Propane-1,3-diol Cyclic Phosphate ($C_3H_7PO_4$)

MAZHAR-UL-HAQUE, CHARLES N. CAUGHLAN, AND W. L. MOATS

Department of Chemistry, Montana State University, Bozeman, Montana 59715

Received June 30, 1969

The structure of propane-1,3-diol cyclic phosphate ($C_3H_7PO_4$) has been solved by X-ray diffraction study. Crystals are orthorhombic, space group $P2_12_12_1$, $a = 5.98$, $b = 7.92$, $c = 12.47$ Å; four molecules per unit cell; $d_{obsd} = 1.4$ g/cc; $d_{calcd} = 1.551$ g/cc. Intensity data were collected visually from Weissenberg photographs. The structure was solved from the Patterson map and several subsequent Fourier maps. Refinement by least squares has proceeded to an R factor of 10.8 for 374 observed reflections, refining positional and anisotropic thermal parameters. The bond angles around phosphorus are nearly tetrahedral, ranging from 104.5 to 116.6°. The acyclic oxygen atoms of one molecule are hydrogen bonded to the other molecules related by a twofold screw axis, forming helical chains up the a axis. The O···O distance for this hydrogen bond is 2.44 Å, which is a very short hydrogen bond. The P=O and the P—OH bonds are nearly the same, 1.51 and 1.55 Å. The other P–O distances are 1.56 and 1.58 Å. The rest of the bond distances and angles are quite normal. The average standard deviations are 0.03 Å for bond distances and 0.9° for bond angles.

Cyclic organic phosphates have attracted much attention, particularly the relationship between the rates of hydrolysis and structure. Five-membered cyclic organic phosphates have been shown to hydrolyze at rates 10^6 to 10^8 times faster than noncyclic phosphates.[1-3] Reasons for this have been considered to be (1) ring strain and (2) ease of formation of the pentavalent intermediate due to the fact that the ring bond angles at phosphorus are near 90°.[4-8] Thus the thermodynamic stability of the five-membered cyclic phosphate is low, and there is a low activation energy between the five-membered cyclic phosphate and the trigonal bipyramid intermediate. To test some of the structural aspects presumed to account for the rapid hydrolysis of the five-membered cyclic phosphates, we have studied the structure of some six-membered cyclic phosphates, since six-membered cyclic phosphates are known to have hydrolysis rates essentially the same as their noncyclic analogs. We are here reporting the crystal and molecular structure of one of these.

Experimental Section

Propane-1,3-diol cyclic phosphate was prepared according to the method described by Khorana, *et al.*[9] Purification and crystallization were accomplished from tetrahydrofuran by addition of ether and cooling. From the crystals formed, several were obtained which were satisfactory for collection of X-ray data. It was necessary to enclose the crystals of capillaries during collection of the intensity data. The density was measured by flotation in a mixture of CCl_4 and benzene. The crystals were soluble in this mixture and only an approximate value for the density was obtained.

The crystal chosen for collection of intensity data was approximately 0.3 mm in diameter and about 1 mm long, somewhat cylindrically shaped, but quite irregular. The crystal was enclosed in a Lindemann glass capillary; Weissenberg and precession photographs were taken with Cu Kα radiation to determine the space group and lattice parameters (Table I). The crystal was found to be orthorhombic. Systematic absences occurred for $h00$, $0k0$, and $00l$ reflections, when h, k, and $l \neq 2n$, respectively, which indicates space group $P2_12_12_1$.

TABLE I

a, Å	5.98 ± 0.01
b, Å	7.92 ± 0.01
c, Å	12.47 ± 0.01
Space group	$P2_12_12_1$
Molecules per unit cell	4
Measured d, g cm^{-3}	1.40
Calculated d, g cm^{-3}	1.55
Observed reflections	374
$F(000)$	288
Linear absorption coefficient for Cu Kα radiation, cm^{-1}	36.0

Multiple film Weissenberg photographs were taken using Cu Kα radiation. The intensities were measured visually by comparing them with a standard intensity strip. The films were originally indexed on a diagonal axis and an appropriate transformation was applied to give indices in the orthorhombic cell. Lorentz and polarization corrections were applied using data reductions program for the IBM 1620 computer.[10] This gave a preliminary scale factor and an overall temperature factor. No absorption corrections or corrections for extinction were made, since these did not appear necessary considering the size and shape of the crystals.

For structure factor calculations, form factors were used from the literature;[11] anomalous terms of the form factors were not included.

Results and Discussion

Structure Determination.—Solution of the structure was accomplished by location of the phosphorus positions from the Harker section of the Patterson map, and subsequent Fourier syntheses from phases based on this partial structure. From the first Fourier, after location of the correct phosphorus positions,[12] three oxygen were found and the rest of the structure was found with two more three-dimensional Fourier maps. The R factor at this stage was 25%, and refinement was started.

(1) J. Kumamoto and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2515 (1955).

(2) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956).

(3) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, *Chem. Ind.* (London), 929 (1959).

(4) P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).

(5) M. Ponar, E. R. Kaiser, and F. H. Westheimer, *ibid.*, **85**, 602 (1963).

(6) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1774 (1963).

(7) A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

(8) D. H. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

(9) H. G. Khorana, G. M. Tener, R. S. Wright, and J. F. Moffat, *ibid.*, **79**, 430 (1957).

(10) All programs used except the least-squares refinement were from Montana State University's crystallographic Program Library written for the IBM 1620 Model II by C. N. Caughlan, C. T. Li, G. W. Svetich, K. D. Watenpaugh, and R. D. Witters.

(11) "International Tables for Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1962, Table 3.3 1A, p 202.

(12) Several false starts were made on the structure solution. The difficulty was location of the correct phosphorus–phosphorus vectors in the Patterson. Once the correct phosphorus position was found the solution and refinement proceeded smoothly.

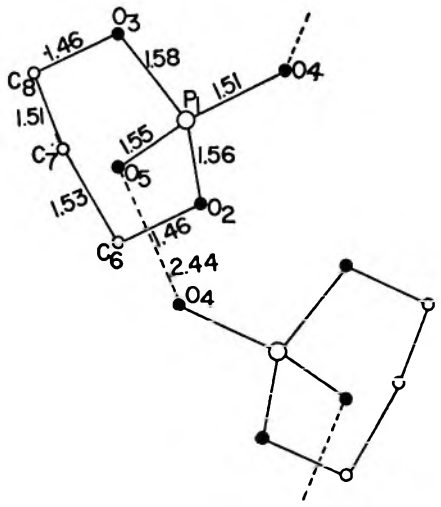


Figure 1.—Part of [010] projection of the structure of propane-1,3-diol cyclic phosphate and bond distances; the standard deviations are 0.02–0.05 Å.

Five cycles of refinement using Ahmed's[13] block-diagonal least-squares program, refining the atomic positions and individual temperature factors, reduced the R factor to 16.0%. The final nine cycles of refinement, refining positional parameters and individual anisotropic thermal parameters, reduced the R factor to 10.8%. A Hughes weighting scheme was used in the refinement.[14]

The final atomic positions with their standard deviations are given in Table II. The listing of anisotropic thermal parameters, the principal axis of thermal vibration, and the final set of observed and calculated structure factors have been deposited with the American Documentation Institute.[15]

TABLE II
ATOMIC PARAMETERS AND THEIR STANDARD DEVIATIONS

Atom	x	y	z
P(1)	0.2019 (8)[a]	0.0610 (5)	−0.0479 (3)
O(2)	0.3822 (20)	−0.0795 (14)	−0.0316 (8)
O(3)	0.0161 (17)	−0.0250 (16)	−0.1194 (9)
O(4)	0.1046 (24)	0.1130 (20)	0.0593 (8)
O(5)	0.3001 (22)	0.2043 (16)	−0.1188 (9)
C(6)	0.4671 (29)	−0.1756 (32)	−0.1224 (14)
C(7)	0.2617 (31)	−0.2503 (21)	−0.1774 (18)
C(8)	0.0924 (31)	−0.1197 (31)	−0.2125 (15)

[a] The number in parentheses is the standard deviation and refers to the least significant digits.

Table III gives the bond angles, with their standard deviation. Figure 1 shows a part of the [010] projection of the structure, giving an indication of the hydrogen-bonding arrangement and the interatomic distances.

Several interesting and significant features are apparent from the figures and tables. The P–O distances differ only slightly, the two esterified oxygens being 1.56 and 1.58 Å from the phosphorus atom, while the shorter P–O distances are 1.51 and 1.55 Å. It is assumed that O(5) is the –OH oxygen, while P–O(4) is the phosphoryl bond, although its identity has nearly disappeared. The relatively long P–O(4) distance is probably due to the very strong hydrogen bond, which has significantly lengthened this distance. The distance between O(4) and O(5)′ is only 2.44 Å, which is a very short hydrogen-bonded distance. The molecules form a helical chain up the a axis through these hydrogen bonds. The sum of the P–O bond distances is 6.20 Å. This compares with 6.14 Å in dibenzyl phosphate,[16] 6.20 Å in L-α-glycerylphosphoxycholin,[17] 6.25 Å in barium diethyl phosphate.[18] Most organic phosphate esters have the sum of P–O distances between 6.13 and 6.23 Å.

The C–O and the C–C distances are normal. The O–P–O angles are nearly tetrahedral and the P–O–C angles are about 120°, which is considered normal for such esterified oxygens.[19]

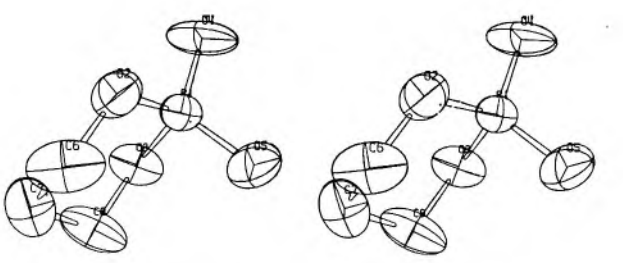


Figure 2.—The structure of the propane-1,3-diol cyclic phosphate molecule showing the chair form. P(1) is 0.17 Å below plane; O(2) and O(3) are 0.2 Å above plane; C(6) and C(8) are 0.24 and 0.25 Å below plane; C(7) is 0.25 Å above best least-squares plane formed by P(1)–O(2)–O(3)—C(6)–C(7)–C(8). The numbers for figures and on tables are consecutive and not consistent with the chemical nomenclature of propane-1,3-diol cyclic phosphate. This diagram was drawn using computer program OR TEP, written by Carrol K. Johnson of Oak Ridge National Laboratory, and adapted for computation at University of Washington.

TABLE III
BOND ANGLES AND THEIR STANDARD DEVIATIONS

Atoms	Angle, degree
O(2)–P(1)–O(3)	104.6 (5)[a]
O(2)–P(1)–O(4)	110.1 (5)
O(2)–P(1)–O(5)	109.5 (6)
O(3)–P(1)–O(4)	110.2 (6)
O(3)–P(1)–O(5)	105.1 (7)
O(4)–P(1)–O(5)	116.6 (7)
P(1)–O(2)–C(6)	120.8 (9)
P(1)–O(3)–C(8)	116.9 (11)
O(2)–C(6)–C(7)	105.8 (14)
C(6)–C(7)–C(8)	113.8 (14)
C(7)–C(8)–O(3)	109.4 (16)

[a] The number in parentheses is the standard deviation and refers to the least significant digits.

Figure 2 shows that the ring is in the chair form. The dihedral angle between the best least-squares plane through O(2), O(3), C(6), and C(8) and the plane defined by P(1), O(2), and O(3) is 40.4°. The corresponding dihedral angle with the plane of C(6), C(7), and C(8) is 54.2°.

(13) F. R. Ahmed, Structure Factor and Block-Diagonal Least-Squares Program, Division of Pure Physics, National Research Council, Ottawa, Ontario, Canada. This was adapted for use on the SDS Sigma 7 computer by Eric Enwall and David Smith.

(14) E. W. Hughes, *J. Amer. Chem. Soc.*, **63**, 1737 (1941).

(15) Document NAPS-00897 from ASIS National Auxiliary Publications Service, % CCM Information Corp., 909 3rd Ave., New York, N. Y., 10022. A copy may be secured by citing the document number and by remitting $1.00 for microfilm or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to CCMI-NAPS.

(16) J. D. Dunitz and J. S. Rollet, *Acta Cryst.*, **9**, 327 (1956).

(17) S. Abrahamasson and I. Pascher, *ibid.*, **21**, 79 (1966).

(18) Y. Kyogogu and Y. Iitaka, *ibid.*, **21**, 79 (1966).

(19) M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *J. Amer. Chem. Soc.*, **88** 1503 (1966); D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan, and C. P. Smith, *ibid.*, **89**, 6503 (1967); C. N. Caughlan and M. Ul-Haque, *Inorg. Chem.*, **6**, 1998 (1967).

Table IV gives the dihedral angles of the O–P–O planes and also the angle the O(4)–P–O(5) plane makes with the best least-squares plane of the ring.

TABLE IV
DIHEDRAL ANGLE BETWEEN PLANES IN PROPANE-1,3-DIOL CYCLIC PHOSPHATE

Plane	Angle, degree
[O(4)–P(1)–O(5)] and [O(2)–P(1)–O(3)]	91.7
[O(4)–P(1)–O(5)] and [O(5)–P(1)–O(3)]	122.4
[O(4)–P(1)–O(5)] and [O(4)–P(1)–O(2)]	54.5
[O(3)–P(1)–O(5)] and [O(2)–P(1)–O(4)]	90.1
[O(2)–P(1)–O(5)] and [O(3)–P(1)–O(4)]	88.5
[O[4]–P(1)–O(5)] and [P(1)–O(2)–C(6)–C(7)–C(8)–O(3)]	92.3

Thus we have found that this six-membered cyclic phosphate has essentially no ring strain and has normal tetrahedral bond angles around the phosphorus. These structural features should contribute to the stability of this molecule and give it a normally high activation energy for the formation of the five coordinated intermediate, thus accounting for the relatively slow rate of hydrolysis compared with five-membered cyclic phosphates.

Registry No.—Propane-1,3-diol cyclic phosphate, 13507-10-3.

Acknowledgment.—One of us (W. L. M.) wishes to acknowledge a NASA fellowship during the time this research was carried out. We also wish to acknowledge a grant from NIH, GM 08395-07, which has made this research possible and a grant from Montana State University for computer use in the calculations. We wish to thank Dr. K. D. Watenpaugh of the University of Washington who assisted in computer drawing of Figure 2.

Structure and Absolute Configuration of Pulchellin. Crystal and Molecular Structure of 3-Bromoanhydrodehydrodihydropulchellin[1,2]

K. AOTA,[3] C. N. CAUGHLAN,[4] MERLE T. EMERSON,[3] WERNER HERZ,[3,5] S. INAYAMA,[3] AND MAZHAR-UL-HAQUE[4]

Departments of Chemistry, The Florida State University, Tallahassee, Florida 32306, and Montana State University, Bozeman, Montana 59715

Received July 15, 1969

The structure and relative configuration of the sesquiterpene lactone pulchellin was established partially by X-ray crystallographic analysis of 3-bromoanhydrodehydrodihydropulchellin (**4**), in which the asymmetric centers at C-2 and C-4 have been destroyed and the center at C-1 has been epimerized. Compound **4** crystallizes in an orthorhombic space group $P2_12_12_1$ with lattice parameters $a = 8.368$, $b = 14.342$, and $c = 25.161$ Å. There are eight molecules in the unit cell and two molecules in the asymmetric unit. Bromine positions were located from a three-dimensional Patterson function. The first three-dimensional Fourier electron density map was calculated. The rest of the structure was found from four additional three-dimensional Fourier maps, and the structure was refined by anisotropic full-matrix least-squares refinement to a final R of 6.6%. The complete stereochemistry and absolute configuration of pulchellin was established by correlation with aromaticin and is in agreement with the hypothesis of a biogenetic pathway involving the guaianolide gaillardin.

Pulchellin, the main sesquiterpene lactone found in coastal races of *Gaillardia pulchella* Foug., has been formulated as **1**,[6] the absolute configuration at C-2 and C-4 being based on applications of the Hudson–Klyne rule[6] and the Horeau method.[7] In this communication we present chemical and crystallographic evidence for its complete structure **2a**.

Efforts at identification of some of the other asymmetric centers by chemical methods having proved unavailing, we decided to attack the problem by X-ray crystallography. However, attempts to prepare esters of pulchellin or dihydropulchellin containing heavy atoms consistently resulted in compounds which were unsuitable for this purpose. Hence we decided to use a bromo derivative **4**,[8] available (see Experimental Section) from dihydroanhydrodehydrodihydropulchellin (**3**),[6] even though the centers at C-1 and C-3 were no longer present and the center at C-1 might have suffered epimerization as a consequence of the introduction of a carbonyl group at C-2.

Crystal Data.—3-Bromoanhydrodehydrodihydropulchellin (**4**), $C_{15}H_{19}O_3Br$, mol wt 326.9, was orthorhombic with lattice parameters $a = 8.368 \pm 0.005$, $b = 14.342 \pm 0.006$, and $c = 25.161 \pm 0.006$ Å. The systematic absences were confined to $h00$, $0k0$, and $00l$ for h, k, and $l/2n$; the space group was therefore $P2_12_12_1$: $V = 3020$ Å^3, $d_m = 1.432$ g cm^{-3}, $Z = 8$, $d_c = 1.437$ g cm^{-3}. The linear absorption coefficient for Cu Kα radiation was $\mu = 40.8$ cm^{-1}. The total number of electrons in the unit cell was $F(000) = 1344$.

Determination of the Structure.—Diffractometer data were collected on a crystal of dimensions 0.10 × 0.12 × 1.2 mm. The crystal was mounted with the a axis parallel to the ϕ axis of the goniostat. Inten-

(1) Constituents of *Gaillardia* Species. X. Previous paper: H. Yoshioka, T. J. Mabry, N. Dennis, and W. Herz, *J. Org. Chem.*, **35**, 627 (1970).

(2) Supported in part by grants from the U. S. Public Health Service (GM-05814 and GM-12408).

(3) Florida State University.

(4) Montana State University.

(5) To whom correspondence should be addressed.

(6) W. Herz, K. Ueda, and S. Inayama, *Tetrahedron*, **19**, 483 (1963). Assignment of the secondary methyl group to C-10 rather than C-6 was based on biogenetic grounds. Since the publication of this paper, the absolute configuration of the C-7 side chain and the C-10 methyl group in a number of related compounds from *Helenium* and *Gaillardia* species has been shown to be β and α, respectively. It was plausible to assume that this would also be true for pulchellin.

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

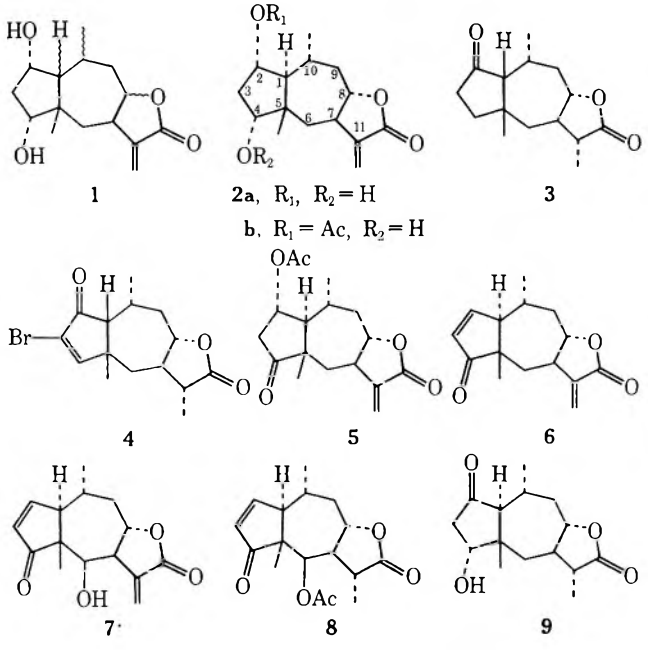
(8) Configurations of compounds, although unknown at the time, are depicted in the light of our final knowledge.

TABLE I

ATOMIC COORDINATES AND THEIR STANDARD DEVIATIONS

	Molecule 1			Molecule 2		
Atom	x	y	z	x	y	z
Br	0.0718(2)[a]	0.0941(1)	0.8496(1)	0.0911(3)	0.4463(1)	0.1381(1)
C(1)	0.2206(17)	0.1022(10)	0.0089(5)	0.0178(14)	0.6102(11)	0.2762(4)
C(2)	0.2405(18)	0.1326(9)	0.9495(5)	−0.0323(16)	0.5662(8)	0.2209(5)
C(3)	0.1219(18)	0.0729(11)	0.9226(5)	0.1076(18)	0.5185(9)	0.2008(5)
C(4)	0.0512(18)	0.0101(11)	0.9535(6)	0.2398(19)	0.5256(11)	0.2305(5)
C(5)	0.1309(19)	0.0099(11)	0.0082(5)	0.2027(15)	0.5926(9)	0.2774(4)
C(6)	0.2282(15)	0.9209(11)	0.0140(5)	0.3095(17)	0.6814(10)	0.2700(5)
C(7)	0.3866(17)	0.9244(11)	0.9828(5)	0.2549(16)	0.7462(8)	0.2247(4)
C(8)	0.5245(15)	0.9663(11)	0.0159(5)	0.1257(14)	0.8129(8)	0.2419(5)
C(9)	0.5274(15)	0.0693(11)	0.0154(6)	−0.0397(14)	0.7772(8)	0.2445(4)
C(10)	0.3750(19)	0.1124(11)	0.0418(5)	−0.0524(14)	0.7041(8)	0.2888(5)
C(11)	0.4593(16)	0.8253(9)	0.9688(5)	0.3863(16)	0.8109(9)	0.2052(5)
C(12)	0.3866(23)	0.7774(13)	0.9200(5)	0.5056(21)	0.7657(13)	0.1624(6)
C(13)	0.6397(21)	0.8580(16)	0.9668(7)	0.2829(20)	0.8873(9)	0.1821(4)
C(14)	0.4092(25)	0.2174(11)	0.0554(6)	−0.2318(19)	0.6895(12)	0.3064(6)
C(15)	0.0004(18)	0.0105(13)	0.0522(6)	0.2549(16)	0.5470(10)	0.3294(4)
O(1)	0.3191(12)	0.1923(7)	0.9312(4)	−0.1569(11)	0.5773(7)	0.1995(4)
O(2)	0.7393(17)	0.8103(10)	0.9396(6)	0.3250(12)	0.9497(6)	0.1501(4)
O(3)	0.6664(11)	0.9357(8)	0.9914(4)	0.1360(10)	0.8877(5)	0.2011(3)

[a] The number in parentheses is the standard deviation and refers to the least significant digit.



sities of all reflections with $2\theta \leq 130°$ were measured on a GE XRD-5 diffractometer with a single-crystal orientor using a scintillation counter as detector. Nickel-filtered copper radiation was used (λ = 1.5418 Å). Intensities were measured using the θ–2θ scan technique counting the background for 50 sec on each side of the peak and scanning over the reflection for 100 sec. In this way 2485 reflections were scanned; only 2376 reflections were visible above the background. Lorentz and polarization corrections were applied using an IBM 1620 data reduction program.[9] This also provided a Wilson plot for the preliminary scale and temperature factors. No absorption corrections were applied. Form factors to calculate the structure factors were used from the literature.[10]

A three-dimensional Patterson map was calculated. Bromine positions were found from the Harker section. The first partial three-dimensional Fourier synthesis phased on the bromine positions gave a number of peaks, but only 10 atomic positions which made some chemical sense were chosen. Four subsequent three-dimensional Fourier maps revealed the structure of both molecules in the asymmetric unit. At this point R was 28.2%. Bond distances and angles were satisfactory and it was decided to proceed with the refinement.

Three cycles of refinement using Busing, Martin, and Levy's full matrix least-squares program[11] and refining only the atomic positions reduced R to 20.5%. Four cycles, refining both the atom positions and the isotropic temperature factors, reduced R to 11.4%. Three additional cycles, refining atomic positions and anisotropic thermal parameters, reduced the R to 6.6%, weighting each reflection equally.

Results and Discussion of the Structure of 4.— Final atomic positions for both molecules in the asymmetric unit with their standard deviations are given in Table I. Tables of anisotropic thermal parameters, intermolecular distances below 4.0 Å, and observed and calculated structure factors, and a figure of 1 (100) projection of the structure showing the molecules in the unit cell have been deposited with the National Auxiliary Publications Service.[12] Interatomic distances and bond angles for the two molecules are shown in Figures 1 and 2. The stereoscopic diagrams down the c^* axis of both molecules are shown in Figure 3.

Both independent molecules have the same relative stereochemistry, the cyclopentanone ring being *cis* fused to the seven-numbered ring and the methyl group at C-10 being *trans* to H-1. The lactone junction

(9) All programs except the least-squares refinement program were from the Montana State University Library for Crystallographic Computing for the IBM 1620, written by C. T. Li, G. Svetieh, C. H. Caughlan, R. D. Witters, and K. D. Watenpaugh.

(10) "International Tables for Crystallography," Kynoch Press, Birmingham, England, 1962, Vol. III, Table 3.31A, p 202.

(11) W. R. Busing, K. D. Martin, and H. A. Levy, Least Squares Program, U. S. Atomic Energy Commission Publication No. ORNL-TM-305, 1962.

(12) Document NAPS-00761 from ASIS National Auxiliary Publications Service, % CCM Information Sciences, Inc., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and by remitting $1.00 for microfiche or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to CCMI-NAPS.

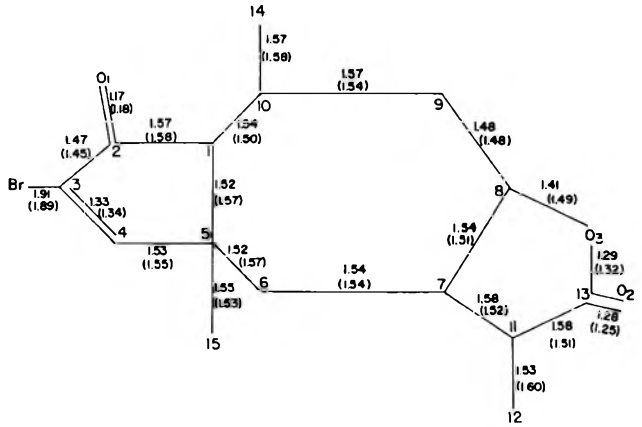


Figure 1.—Interatomic distances of 3-bromoanhydrodehydrodihydropulchellin; distances in parentheses belong to molecule 2. Standard deviations in the bond distances are 0.01–0.02 Å.

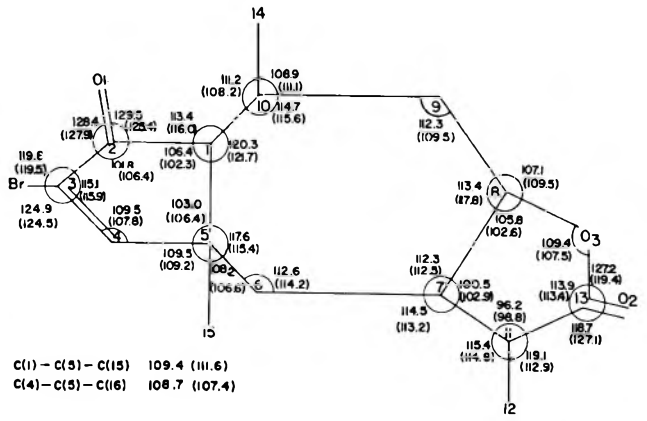


Figure 2.—Bond angles of 3-bromoanhydrodehydrodihydropulchellin; angles in parentheses belong to molecule 2. Standard deviations in the bond angles are 0.9–1.7°.

is *trans*, with the C-7 side chain *trans* to C-10 methyl and the C-11 methyl group *cis* to H-7. The conformation of the seven-membered ring is that of a somewhat deformed chair. Bond distances and angles are quite normal except for a few minor deviations and are consistent in both independent molecules. The average carbon–carbon distance is 1.54 Å. The short C-2–C-3 distance indicates conjugation. Examination of the values indicates agreement with bond distances and angles observed in bromohelenalin[13] and bromomexicanin E.[14] It should be noted that considerable anisotropy exists in the thermal motions of most of the atoms of both molecules of **4**.

Relative and Absolute Configuration of Pulchellin.—Although it seemed probable, on biogenetic grounds, that 3-bromoanhydrodehydrodihydropulchellin should be represented by **4** rather than by the mirror image, the results of the X-ray analysis of **4** required verification of this hypothesis and, as was pointed out previously, left uncertain the relative configuration of pulchellin at C-1. Simultaneously, therefore, with progress on the structure determination of **4**, we continued efforts to correlate pulchellin with other pseudoguaianolides of established structure and were eventually successful in determining the complete stereochemistry of pulchellin. After considerable experimentation, acetylation of pulchellin under controlled conditions finally furnished, in addition to the previously known diacetylpulchellin (**2c**),[6] a monoacetate in 75% yield. The nmr spectrum of the monoacetate revealed that during the acetylation the C-2 hydrogen signal found in pulchellin at 4.33 ppm had suffered an appreciable paramagnetic shift to 5.08 ppm while the higher field doublet at 3.71 ppm associated with H-4[15] had essentially remained unchanged. Hence the monoacetate was formulated as **2b**.

Oxidation of **2b** with chromic oxide–pyridine complex led to a ketoacetate **5** whose ir spectrum (band at 1749 cm^{-1}) showed the presence of a cyclopentenone. An attempt at pyrolysis of this substance resulted merely in recovery of starting material, but facile elimination of the acetoxy group occurred on exposure to pyridine. The product was an α,β-unsaturated ketone identical in all respects with aromaticin (**6**), a substance previously isolated from *Helenium aromaticum* (Hook) Bailey[16] and a North Carolina collection of *H. amarum* Raf.[17] Since the relative and absolute configuration of aromaticin has been established[16] by correlation with mexicanin I (**7**)[18] which in turn has been related to isotenulin (**8**),[19] the absolute configuration of pulchellin at C-1, C-5, C-7, C-8, and C-10 is as represented in **2a** and identical with the absolute configuration at these centers of other pseudoguaianolides isolated from *Helenium* and *Gaillardia* species. The absolute configuration of the C-2 hydroxyl group has been established[7] as α by use of Horeau's method which, because the two hydroxyl groups are *cis*, automatically fixes the configuration at C-4 as well.

It is not possible to say definitely whether isomerization at the C-1 position from the *trans*-bicyclo[5.3.0]decane system present in pulchellin to the more stable[20] *cis*-bicyclo[5.3.0]decane ring fusion present in **4** occurred during the conversion of ketol **9** to **3** or during the bromination of **3**. The ORD curve of **3** displays a negative Cotton effect comparable in sign and amplitude with that of 5α,14β-androstan-15-ones,[21] which suggests that **3** is *cis* fused, but the flexibility of the seven-membered ring renders extrapolation from generalizations strictly applicable only to rigid systems somewhat questionable. Model considerations and application of the octant rule suggest that, if the

(13) 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).

(14) Mazhar-ul-Haque and C. N. Caughlan, *ibid.*, 355 (1967).

(15) For reasons which are not immediately apparent, one of the H-3,H-4 coupling constants is generally 0 in pulchellin and its derivatives although the expected multiplicity is restored in the nmr spectra of compounds in which the cyclopentane ring is deformed by lactone ring formation.[6]

(16) J. Romo, P. Joseph-Nathan, and F. Diaz A., *Tetrahedron*, **20**, 79 (1964). We are grateful to Dr. J. Romo and Dr. A. Romo de Vivar for an authentic specimen of aromaticin.

(17) R. A. Lucas, S. Rovinski, R. J. Kiesel, L. Dorfman, and H. B. MacPhillamy, *J. Org. Chem.*, **29**, 1549 (1964).

(18) E. Dominguez and J. Romo, *Tetrahedron*, **19**, 1415 (1963).

(19) W. Herz, W. A. Rhodes, 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, *Tetrahedron*, **19**, 1359 (1963).

(20) W. Herz, M. V. Lakshmikantham, and R. N. Mirrington, *ibid.*, **22**, 1709 (1966); A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan, and W. Herz, *ibid.*, **22**, 13279 (1966).

(21) C. Djerassi, G. Von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, **87**, 817 (1965); A. R. Van Horn and C. Djerassi, *ibid.*, **89**, 651 (1967).

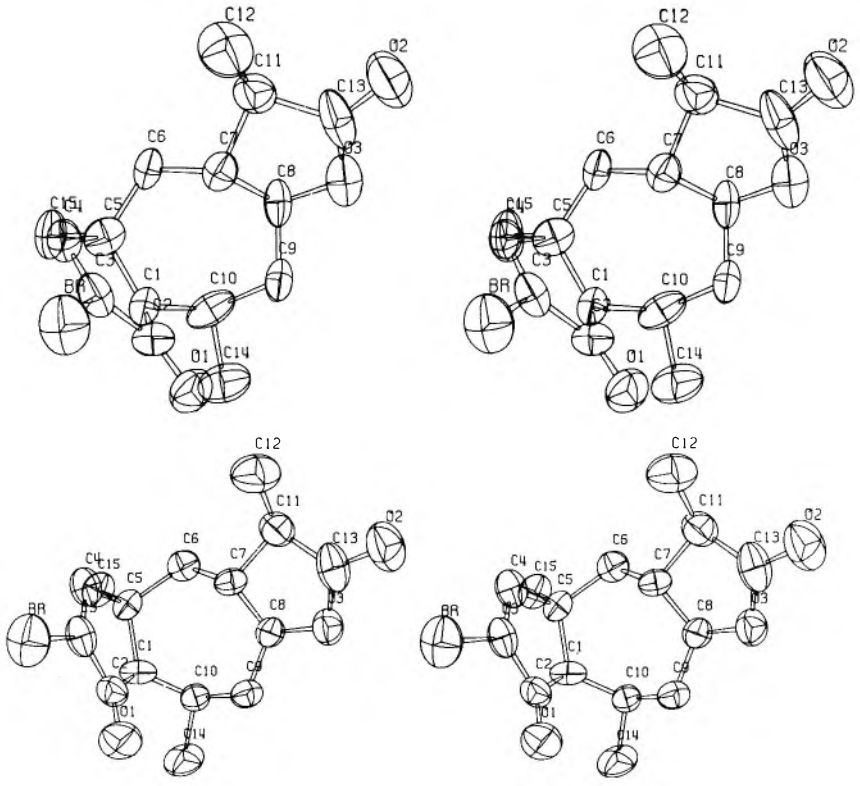
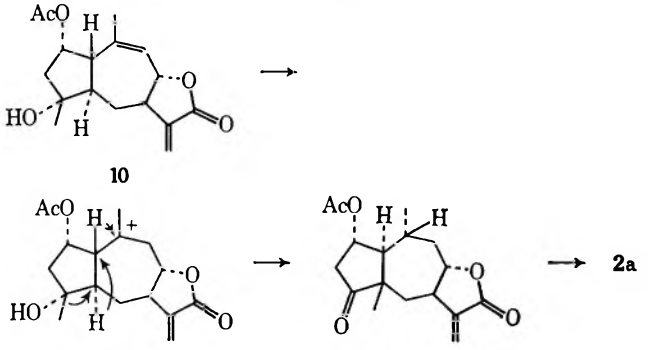


Figure 3.—Stereoscopic diagrams of the structure of 3-bromoanhydrodehydrodihydropulchellin down the c^* axis of both molecules. The diagrams were drawn using computer program ORTEP written by Carrol K. Johnson of Oak Ridge National Laboratory and adapted for computation at the University of Washington.

conformation of **3** in solution approximates that of crystalline **4**, the ring junction of **3** should be *cis*.[22]

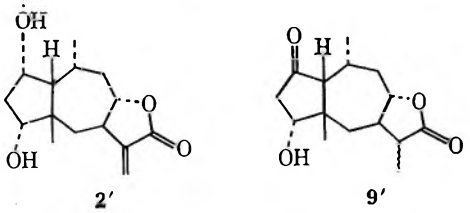
It has been demonstrated recently that the guaianolide gaillardin[24] from a Live Oak County, Texas, collection of *G. pulchella*[25] possesses the relative and absolute configuration shown in **10**. The relationship of **10** to the stereochemistry now established for pulchellin is striking. In fact the series of concerted or sequential 1,2 shifts of stereoelectronically optimally disposed *trans*-oriented groups adumbrated in Scheme I, followed by a reduction step, transforms the guaianolide gaillardin directly into the pseudoguaianolide pulchellin. It seems entirely plausible that Scheme I is paralleled by an enzyme-mediated process,

SCHEME I



a hypothesis which should be verifiable by administering suitably labeled gaillardin to plants of the coastal race of *G. pulchella*.

(22) It might be argued that the conversion of pulchellin into **4** *via* dehydrodihydropulchellin (**9**) and **3** need not be attended by epimerization at C-1, and that pulchellin and dehydropulchellin might be represented by the *cis*-fused formulas **2′** and **9′**. This is contraindicated by the strongly positive Cotton effect of dehydrodihydropulchellin which is indicative of a *trans*-A/B-ring fusion.[21,23] Moreover, formulation of pulchellin as **2′** would require that conversion into aromaticin involve epimerization of a *cis*-fused C-1 epimer of aromaticin to the generally less stable[20] *trans*-bicyclo-[5.3.0]-2-en-1-one system found in **6** which seems highly unlikely.



2′ **9′**

(23) J. F. Biellmann and G. Ourisson, *Bull. Soc. Chim. Fr.*, 331 (1962).

(24) S. M. Kupchan, J. M. Cassady, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **88**, 5292 (1966); T. A. Dullforce, G. A. Sim, D. N. J. White, J. E. Kelsey, and S. M. Kupchan, *Tetrahedron Lett.*, 973 (1969).

(25) This is an area from which a cytologically distinct race of *G. pulchella* has been reported (private communication from Dr. W. P. Stoutamire).

Experimental Section[26]

Purification of Pulchellin.—Crude crystalline pulchellin, isolated as described earlier[6] from the coastal race of *Gaillardia pulchella* Foug., after initial chromatography over alumina contained appreciable amounts of an impurity, as revealed by the nmr spectrum. Further purification was achieved as follows. A solution of 3.3 g of crude pulchellin in 20 ml of chloroform was chromatographed over 100 g of silic acid (Mallinckrodt, 100 mesh), 80-ml fractions being collected. Fractions 1–6 ($CHCl_3$) eluted nothing; fractions 7–20 ($CHCl_3$) eluted 1.92 g of pulchellin (nmr spectrum, tlc) recrystallization of which from ethyl acetate

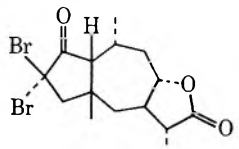
(26) Melting points are uncorrected. Rotations were run in chloroform, ultraviolet spectra in 95% ethanol, and infrared spectra in chloroform. Nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million, line separations in hertz. Signals are denoted in the usual manner: d, doublet; t, triplet; c, complex signal whose center is given; m, multiplet. Singlets are unmarked. Analyses were by Dr. F. Pascher, Bonn, Germany.

furnished pure material, mp 165–168°. Successive elution with $CHCl_3$ (fractions 21–27) and $CHCl_3$–MeOH (10:1) gave 0.62 g of a mixture containing pulchellin and an isomeric substance (nmr spectrum). Further elution with $CHCl_3$–MeOH (fractions 29–30) afforded 0.56 g of the isomer which melted at 166–167° after recrystallization from acetone. The structure of this substance is being investigated.[26a] Later fractions contained nothing.

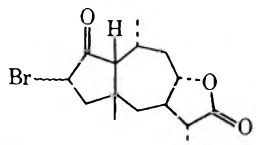
3-Bromoanhydrodehydrodihydropulchellin (4).—To a solution of 0.68 g of **3**[6] in 30 ml of acetic acid containing 3 drops of acetic acid saturated with hydrogen bromide was added dropwise with stirring at 0° a solution of 0.8 g (100% excess of 2 molar equiv) of bromine in 10 ml of acetic acid. Stirring was continued for an additional hour. The mixture was poured on ice, neutralized with solid sodium bicarbonate, and extracted with ether. The ether extracts were washed, dried, and concentrated *in vacuo* to a small volume after addition of 25 ml of 2,6-lutidine. The residue was refluxed at 160–170° for 30 min, cooled, diluted with ether, and filtered to remove a precipitate of lutidine hydrobromide. The solid was washed with ether and the combined filtrate and washings were poured onto ice–hydrochloric acid. The ether layer was washed, dried, passed through a small column of acid-washed alumina, and evaporated *in vacuo*. The residue, 0.25 g, mp 138–142° (33%), was recrystallized from ether to give crystals of **4**, suitable for analysis, which had mp 144–146°; ir (CCl_4) 1785 (γ-lactone), 1735 (α-bromocyclopentanone), 1590 (conjugated double bond); λ_{max} 242 nm(ϵ 8150); $[\alpha]^{20}D$ +34.5° (*c* 1.00, acetone); nmr 7.32 (H-4), 3.84 (td, 11, 5, H-8), 1.41 (d, 7, C-10 methyl), 1.33 (C-5 methyl), 1.10 (d, 7, C-11 methyl).

Anal. Calcd for $C_{15}H_{19}O_3Br$: C, 55.03; H, 5.86; O, 14.68; Br, 24.43. Found: C, 54.90; H, 5.70; O, 14.98; Br, 25.11.

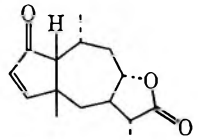
In another run the ether extract obtained after addition of 2 molar equiv of bromine to **3** was worked up without an attempt at dehydrohalogenation. This resulted in the isolation of a gummy dibromo derivative **11** [ir bands at 1780 (γ-lactone) and 1743 cm^{-1} (cyclopentanone)] which had no strong or absorption. Dehydrobromination resulted in formation of **4**; hence the bromine atoms were attached to C-3. Bromination of **3** by the method above, using 1 molar equiv of bromine, gave a gummy monobromo derivative **12** (ir 1780 and 1745 cm^{-1}) which was converted into the dibromide on further treatment with bromine. Heating the gummy monobromo derivative on the steam bath for 10 min or refluxing with 2,6-lutidine for 15 min furnished anhydrodehydrodiphydropulchellin (**13**), mp 118–121°, identical in all respects with authentic material.[5] Attempts to convert **13** into a bromo derivative by bromination-dehydrobromination in the manner described for helenalin[27] or ambrosin[28] failed.



11



12



13

2-Acetylpulchellin (**2b**).—A solution of 1.60 g of pulchellin in 3 ml of dry pyridine was allowed to stand with 1 ml of acetic anhydride at room temperature for 30 min, after which time starting material had disappeared [tlc, silica gel, benzene–ether (1:1)]. The product was isolated in the usual manner and was chromatographed over silica gel. Benzene–$CHCl_3$ (10:1) eluted 0.62 g of diacetylpulchellin (**2c**) which had mp 124–125° after recrystallization from ether–petroleum ether and was identical with authentic **2c** in all respects. Benzene–$CHCl_3$ (2:1, 1:1) eluted 1.35 g of a solid (**2b**) which was recrystallized from ether: mp 143–144°; ir bands at 3620 and 3480 (hydroxyl), 1768 and 1678 (unsaturated γ-lactone), and 1730 and 1272 cm^{-1} (acetate); nmr signals 6.27 (d, 3.5) and 5.60 (d, 2.8) (exocyclic methylene), 5.80 (c, H-2), 4.27 (c, H-8), 3.78 (d, 5.0, H-4), 2.08 (acetate), 105 (d, 6.0, C-10 methyl), and 0.93 ppm (C-5 methyl).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84; O, 25.95. Found: C, 66.10; H, 7.85; O, 26.03.

Dehydro-2-acetylpulchellin (**5**).—A solution of 0.465 g of **2b** in 2 ml of dry pyridine was added to 0.35 g of chromic acid in 1 ml of dry pyridine and set aside for 2 days. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated and the gummy residue, 0.46 g, was chromatographed over 20 g of silica gel. Benzene eluted 0.117 g of **5** which was recrystallized from ethyl acetate: mp 156–157°; ir bands 1770, 1749, 1718, 1675, and 1255 cm^{-1}, nmr signals 6.26 (d, 3.5) and 5.60 (d, 2.8) (exocyclic methylene), 5.55 (td, 7, 1.5, H-2), 4.25 (c, H-8), 2.10 (acetate), 1.17 (d, 6.0), C-10 methyl), and 1.19 ppm (C-5 methyl). It was not analyzed but used in subsequent experiments. Benzene–$CHCl_3$ (10:1) eluted 0.27 g of unoxidized **2b**. Attempted pyrolysis of 40 mg of **5** at 210–230° in a nitrogen atmosphere resulted in recovery of 36 mg of starting material.

Aromaticin (**6**). **A**.—A solution of 0.32 g of **2b** in 2 ml of dry pyridine was added to 0.425 g of chromic acid in 2 ml of dry pyridine and set aside at room temperature for 6 days. The mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed, dried, and evaporated. The crystalline residue, 0.28 g, was recrystallized from acetone and gave 0.12 g of aromaticin: mp 233–234°; ir bands at 1772, 1719, 1678, and 1593 cm^{-1}; nmr signals at 7.60 (dd, 6.5, 2.0, H-2), 6.10 (dd, 6.5, 3.0, H-3), 6.13 (d, 3.2) and 5.48 (d, 3.2) (exocyclic methylene), 4.49 (c, H-8), 125 (d, 6.0, C-10 methyl), and 1.19 ppm (C-5 methyl), identical in all respects with an authentic sample.

B.—A solution of 32 mg of **5** in 1 ml of dry pyridine was heated on the water bath for 5 hr, cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated. The crystalline residue of crude aromaticin, 27 mg, was recrystallized from acetone, mp 233–234°, identical in all respects with an authentic sample.

ORD Curve of 3.—The following data (*c* 0.007, in CH_3OH) were obtained: $[\alpha]_{600}$ −47°, $[\alpha]_{320}$ −2720°, $[\alpha]_{312}$ −2710°, $[\alpha]_{308}$ −2810°, $[\alpha]_{302}$ 0°, $[\alpha]_{280}$ +2830°, $[\alpha]_{274}$ +2310° (last reading).

ORD Curve of 9.—The following data (*c* 0.07, in CH_3OH) were obtained: $[\alpha]_{600}$ +71°, $[\alpha]_{320}$ +2170°, $[\alpha]_{302}$ 0°, $[\alpha]_{280}$ −2080°, $[\alpha]_{270}$ −472° (last reading).

Registry No.—**2a**, 6754-35-4; **2b**, 23667-91-6; **2c**, 23754-36-1; **3**, 23667-92-7; **4**, 23667-93-8; **5**, 23667-94-9; **6**, 5945-42-6; **9**, 23667-96-1.

Acknowledgment.—We wish to acknowledge a grant from the Montana State University Computing Center without which it would not have been possible to perform the calculations. We also thank Dr. K. D. Watenpaugh of the University of Washington who assisted with the computer diagram of Figure 3.

(26a) NOTE ADDED IN PROOF.—This lactone is identical with neopulchellin: M. Yanagita, S. Inayama, and T. Kawamota, *Tetrahedron Lett.*, 131 (1970).

(27) R. G. Adams and W. Herz, *J. Amer. Chem. Soc.*, **71**, 2546 (1949).

(28) H. Abu-Shady and T. D. Soine, *J. Amer. Pharm. Assoc.*, **42**, 387 (1953); **43**, 365 (1954).

Structure Elucidation of Sesquiterpene Dilactones from *Mikania Scandens* (L.) Willd.[1]

WERNER HERZ, P. S. SUBRAMANIAM, P. S. SANTHANAM, K. AOTA, AND ALLEN L. HALL

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received August 29, 1969

Six new sesquiterpene dilactones—mikanolide, dihydromikanolide, scandenolide, dihydroscandenolide, deoxymikanolide, and miscandenin—have been isolated from above-ground parts of *Mikania scandens* (L.) Willd. The first five are germacranediolides whose structure and stereochemistry were determined by a combination of chemical methods and nmr techniques and by correlation of deoxymikanolide with the germacranediolide isabelin. Miscandenin is an elemanediolide containing a dihydrooxepine ring, whose formation can be rationalized as involving the Cope rearrangement of a 1,10-deoxymikanolide precursor.

Extracts of many members of the large genus *Mikania* (family *Compositae*, tribe *Eupatorieae* Cass., subtribe *Ageratinae* Less.) which is abundantly represented in the western hemisphere, are used as folk medicine within their respective ranges. Since we suspected, on phylogenetic grounds, the presence of sesquiterpene lactones, we undertook an examination of accessible *Mikania* species. In the present paper we report the isolation and structure determination of six lactones from *Mikania scandens* (L.) Willd. (climbing hempvine).[2,3] Five of these belong to the class of novel sesquiterpenoid dilactones of the germacrane type some of which are reported to exhibit tumor-inhibitory activity.[8,9] The sixth represents an interesting and hitherto undescribed variant resulting from a germacradiene–elemadiene interconversion.

Table I lists these dilactones in the order of their elution. Isolation was effected by a combination of chromatography over silicic acid and fractional crystallization. Relative yields of mikanolide and dihydromikanolide, which invariably were the major constituents, varied depending on the date and location of collection. Scandenolide was next in abundance while the remaining three were present in minor amounts only. In fact, miscandenin and desoxymikanolide appeared to be absent from some collections (see Experimental Section).

TABLE I

CONSTITUENTS OF *Mikania scandens* (L.) WILLD.

Compd	Molecular formula	Mp, °C	$[\alpha]_D$, degree
Miscandenin	$C_{15}H_{14}O_5$	232–235	−181.4
Mikanolide	$C_{15}H_{14}O_6$	226–228	+53.4
Dihydromikanolide	$C_{15}H_{16}O_6$	241–244	+91.1
Desoxymikanolide	$C_{15}H_{16}O_5$	198–200	+98.9
Scandenolide	$C_{17}H_{18}O_7$	230–234	+62.0
Dihydroscandenolide	$C_{17}H_{20}O_7$	278–280	+83.3

Mikanolide and Dihydromikanolide.—The presence of partial structure A, encountered in many sesquiterpene lactones of *Compositae*, in mikanolide (**1**) was suggested by the uv [λ_{max} 206 nm (ϵ 16700)] and ir spectrum (bands at 1767, 1752, and 1661 cm^{-1}). This was established by ozonolysis which liberated formaldehyde and by the nmr spectrum (Table II) which exhibited the diagnostic[10] H_a and H_b doublets at 6.20 and 5.92 (J = 3.5 Hz) and a complex multiplet (H_d) at 4.72 ppm.[11] Double-resonance experiments at 90 and 100 MHz (Table III and Experimental Section) involving H_a, H_b, H_c, and H_d confirmed the presence of A.

Partial hydrogenation of **1** (Pd–$CaCO_3$) resulted in the formation of a dihydro derivative **2**, ir bands at 1760 (double intensity) and 1650 cm^{-1}, which was identical with dihydromikanolide isolated from the plant. In the nmr spectrum of **2**, the H_a and H_b doublets of **1** were replaced by a methyl doublet at 1.28 ppm, reflecting the change brought about by reduction of A. Total reduction of **1** led to tetrahydromikanolide (**3**) which had ir bands at 1800 and 1755 cm^{-1} and no uv absorption.

The presence of a second α,β-unsaturated lactone group in **1** was surmised from the ir spectra of **1**, **2**, and **3** which exhibited two strong bands in the γ-lactone region and the uv spectrum of **2** which, despite saturation of chromophore A, displayed strong absorption at 217 nm (ϵ 8800).[12]

That partial structure B represented this second chromophore was indicated by the nmr spectra of **1** and **2** which displayed a narrow doublet at 7.56 (J = 1.7 Hz, H_e, 7.43 in **2**) absent in **3** and a narrowly split multiplet at 5.42 (H_f, 5.28 in **2**) which in **3** had moved upfield to

(1) Supported in part by a grant from the U. S. Public Health Service (GM-05814).

(2) Part of this material has been published in preliminary form: W. Herz, P. S. Santhanam, P. S. Subramaniam, and J. J. Schmid, *Tetrahedron Lett.*, 3111 (1967).

(3) The *Mikania scandens* aggregate of North American and pantropical distribution has been treated by Robinson.[4] The work described in the present paper deals with the constituents of *M. scandens* (L.) Willd. *sensu strictiori*, found in wet thickets and swamps, chiefly near the coast, of the southeastern United States. Since our original publication,[2] mikanolide and dihydromikanolide have also been isolated[5] from *M. cordata* (Burm. f.) Robinson, an Afro-Malaysian member of the complex and from *M. batatifolia* DC,[6] a segregate found in Cuba and the Florida Keys. Work on other *Mikania* species is in progress. Mikanolide has also been isolated from *Gaillardia fastigiata* Greene (tribe *Helenieae* Benth. and Hook.).[7]

(4) B. L. Robinson, *Contrib. Gray Herbarium Harv. Univ.*, **104**, 55 (1934).

(5) A. K. Kiang, K. Y. Sim, and S. W. Yoong, *Phytochem.*, **7**, 1035 (1968).

(6) W. Herz, P. S. Santhanam, H. Wagner, R. Höer, L. Hörhammer, and L. Farkas, *Tetrahedron Lett.*, 3419 (1969).

(7) W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid, and R. N. Mirrington, *Tetrahedron*, **22**, 1907 (1966).

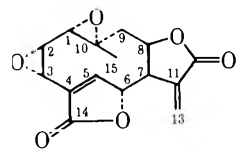
(8) S. M. Kupchan, Y. Aynehchi, M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **88**, 3674 (1966); S. M. Kupchan, Y. Aynehchi, J. M. Cassady, H. K. Schnoes, and A. L. Burlingame, *J. Org. Chem.*, **34**, 3867 (1969).

(9) H. Yoshioka, T. J. Mabry, and H. E. Miller, *Chem. Commun.*, 1679 (1968); H. Yoshioka and T. J. Mabry, *Tetrahedron* **25**, 4767 (1967).

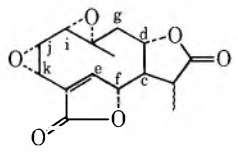
(10) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem Soc.*, **84**, 2601 (1962).

(11) Measured in DMSO-d_6, unless otherwise specified, on a Varian A-60 nmr spectrometer.

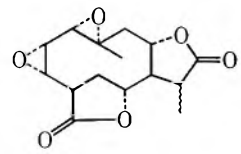
(12) *Cf.* the uv maxima of dihydroelephantolide [λ_{max} 211 nm (ϵ 8700)] and dihydroelephantol [λ_{max} 211 nm (ϵ 9600)]. Subtraction of the uv spectrum of **2** from the uv spectrum of **1** gave a difference curve with λ_{max} 205 nm (ϵ 8800) and 225 (4400).



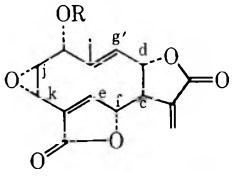
1



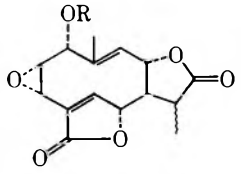
2



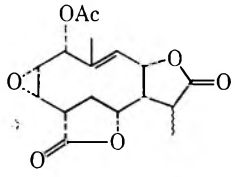
3



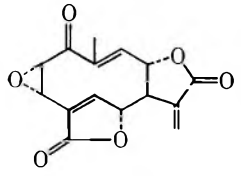
4a, R = Ac
b, R = H



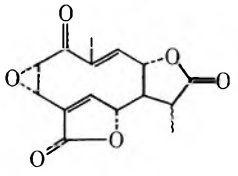
5a, R = Ac
b, R = H



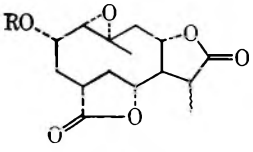
6



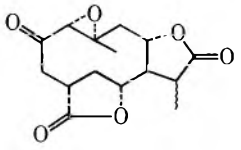
7



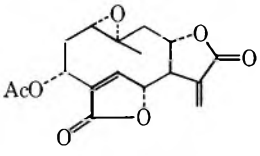
8



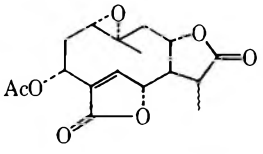
9a, R = Ac
b, R = H



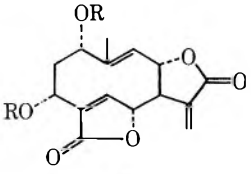
11



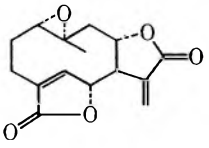
12



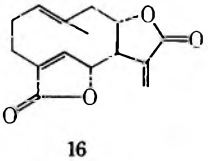
13



14a, R = H
b, R = Ac



15

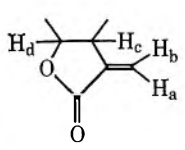


16

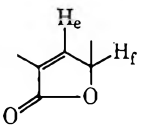
4.68 ppm and merged with the signal of H_d.[13] This was again confirmed by double-resonance experiments (*vide infra*).

(13) *Cf.* the corresponding resonances in the nmr spectra of elephantopin and its derivatives,[8] ovatodiolide,[14] linderalactone, and neolinderane.[15]

(14) H. Immer, J. Polonsky, R. Toubiana, and H. D. An, *Tetrahedron*, **21**, 2117 (1965).



A



B

The evidence presented so far accounted for four of the six oxygen atoms present in **1**. The absence of hydroxyl groups revealed by the ir and nmr spectra and the absence of ketone groups indicated by negative chemical tests and the CD curve (no Cotton effect in the 290-nm region) suggested that the remaining two oxygen atoms might be ethereal. This conclusion was strongly reinforced by the presence in the nmr spectrum of **1** of a one-proton signal at 3.96 (broadened doublet, $J_1 = 3.5$, $J_2 = 1.1$ Hz) and a complex two-proton signal at 3.36 ppm.[16] On this basis **1**, because of the presence of only one quaternary methyl group (singlet at 1.01 ppm),[17] had to possess a single ten-membered carbocyclic ring.

The presence of three protons assignable to carbon atoms bearing two ethereal oxygens prompted us to postulate the carbon atom carrying the quaternary methyl group as the fourth point of attachment of the two ether bridges, as indicated in partial structure C. Confirmative evidence came from the following transformation of mikanolide. Treatment of **1** with excess acetic anhydride in the presence of *p*-toluenesulfonic acid under reflux gave in moderate yield an olefinic acetate **4a**. In the nmr spectrum of this substance, the quaternary methyl of **1** was replaced by a vinyl methyl at 1.72 (J = 0.7 Hz), the methylene multiplet of **1** (H_{g_1} and H_{g_2} of C) was replaced by a new vinyl proton at 5.32 (broad doublet, $H_{g'}$ of D, A part of AB system with weak allylic coupling to H_h and strong coupling—10.2 Hz—to H_d), H_d had experienced a slight downfield shift and simplification to a triplet at 4.82 (B of AB system, J = 10.2 Hz), and H_i, formerly in the 3.36 cluster of **1**, had moved downfield to 5.52 ppm (doublet, J = 4.7 Hz). These spectral changes were interpretable on the basis of the transformation C to D.[18]

In agreement with partial structure D, acid hydrolysis of **4a** afforded the allylic alcohol **4b** which had the requisite spectral properties (Table II and Experimental Section).[20] In fact mikanolide itself was converted in good yield into **4b** on treatment with methanol–hydrochloric acid. Compounds **5a**, **5b**, and **6** with the expected properties were similarly formed from **2** and

(15) B. S. Joshi, V. N. Khamat, and T. R. Govindachari, *ibid.*, **23**, 261, 267 (1967).

(16) Integration in this region was deceptive in DMSO-d_6 solution because of the superposition of the water signal. The nmr spectrum in pyridine-d_5 indicated the presence of three protons near 3.4 ppm. That one of these had to be assigned to H_6 was established by spin decoupling. The remaining two protons and the proton responsible for the signal at 3.96 ppm were therefore identified with hydrogen on carbon carrying ether oxygen.

(17) This methyl group was apparently shielded in **1** and **2** by the double bond of partial structure B because it displayed the customary chemical shift of CH_3CO at 1.35 ppm in the nmr spectrum of **3**. The only other resonance not yet mentioned, in the nmr spectrum of **1** was a complex two-proton multiplet in the methylene region (2.03 ppm).

(18) It is of interest that the reagent combination used in this experiment did not effect cyclization to a eudesmane derivative as observed, for example, in the pyrethrosin series.[19]

(19) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 150 (1957); D. H. R. Barton, O. C. Böckman, and P. de Mayo, *ibid.*, 2263 (1960); S. Iriuchijima and S. Tamura, *Tetrahedron Lett.*, 1965 (1967).

(20) That no rearrangement had taken place under these conditions was shown by reacetylation of **4b** to **4a**.

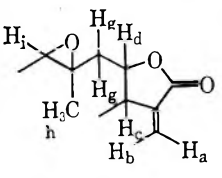
TABLE II

NMR SPECTRA OF CONSTITUENTS OF *Mikania scandens* AND DERIVATIVES[a]

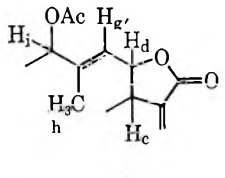
Compd	H-1	H-2	H-3	H-5	H-6	H-8	H-9	H-13	C-10 Me	C-11 Me	Misc
1	3.36 (c)	3.36 (c)	3.96 (dbr, 3.5)	7.56 (d, 1.7)	5.42 (nm)	4.72 (c)	2.03 (c)	6.20 (d, 3.5) 5.92 (d, 3.5)	1.01		
2	3.30 (c)	3.30 (c)	3.95 (dbr, 3.5)	7.52 (d, 2.0)	5.36 (nm)	4.56 (c)	2.0 (c)		0.98	1.28 (d, 6.5)	
3	3.9 (c)	3.9 (c)	3.9 (c)		4.68 (c)	4.68 (c)			1.35	1.17 (d, 6.5)	
4a	5.22 (d, 4.7)	3.62 (t, 4.7)	3.90 (nm)	7.72 (t, 1.5)	5.78 (nm)	4.88 (t, 10.2)	5.32 (dbr, 10.2)	6.15 (d, 3.2) 5.95 (d, 3.2)	1.72 (d, 0.7)		2.10[b]
4b	4.29 (br)[c]	3.42 (t, 4.7)	3.75 (nm)	7.50 (t, 1.5)	5.64 (nm)	4.83 (t, 10.2)	5.14 (dbr 10.2)	6.09 (d, 3.2) 5.95 (d, 3.2)	1.70 (d, 0.7)		5.52 (d, 3.5)[d]
5a	5.30 (d, 4.7)	3.67 (t, 4.7)	3.87 (nm)	7.78 (t, 1.5)	5.50 (nm)	4.87 (t, 10.2)	5.12 (dbr, 10.2)		1.73 (d, 0.7)	1.24 (d, 6.5)	2.13[b]
5b	4.30 (br)[b]	3.41 (t, 4.7)	3.87 (nm)	7.78 (t, 1.5)	5.50 (nm)	4.87 (t, 10.2)	5.12 (dbr, 10.2)		1.73 (d, 0.7)	1.23 (d, 6.5)	5.75 (br)[d]
7		4.40 (d, 4.7)	4.16 (nm)	7.37 (t, 1.5)	5.81 (nm)	4.71 (t, 10.2)	5.61 (dbr, 10.2)	6.31 (d, 3.2) 6.01 (d, 3.2)	2.08 (d, 1.1)		
8		4.48 (d, 4.7)	4.25 (nm)	7.58 (t, 1.5)	5.50 (nm)	4.62 (t, 10.2)	5.56 (dbr, 10.2)		2.0 (d, 1.1)	1.22 (d, 6.5)	
9a	3.5 (d, 10)	4.72 (c)			4.72 (c)	4.72 (c)			1.33	1.15 (d, 6.5)	1.99[b]
9b	3.15 (d, 10)	3.5 (c)[e]			4.75 (c)	4.75 (c)			1.30	1.15 (d, 6.5)	4.92 (d)[d]
11[f]	4.26				4.8 (c)	4.8 (c)			1.15	1.20 (d, 6.5)	
12	2.95 (dd, 12.0, 2.5)		5.55 (m)	7.83 (br)	5.55 (m)	4.7 (m)		6.18 (d, 3) 6.00 (d, 3)	1.09		3.5,[g] 2.12[b]
13	3.0 (dd)		5.5 (m)	7.82 (t, 1)	5.5 (m)	4.5 (m)			1.50	1.25 (d, 7)	2.12[b]
14a	4.5 (c)	~2.6[h] ~2	4.5 (c)	7.42 (t, 1)	5.66 (m)	5.0 (m)	5.0 (m)	6.08 (d, 3) 5.89 (d, 3)	1.60 (br)		3.4 (m)[g] 5.43 (d, 4)[d] 4.74 (d, 4)[d]
14b	5.5 (c)	~2.6[h] ~2	5.3 (c)	7.8 (t, 1)	5.78 (m)	5.05 (t, 10)	5.50 (dbr, 10)	6.08 (d, 3) 5.90 (d, 3)	1.65 (br)		3.4 (m)[g] 2.12,[b] 1.98[b]
15	2.85 (dd, 12, 2.5)	1.8 (m)		7.70 (t, 1)	5.42 (br)	4.7 (m)		6.18 (d, 3) 5.99 (d, 3)	1.10		3.45 (m)[g]
17	4.84 (d, 8.5)	6.23 (d, 8.5)	7.24 (d, 3.5)	3.5 (dd, 7, 3.5)	4.98 (dd, 10, 7)	4.18 (td, 11, 3.5)	1.9 (c)	5.98 (d, 3.5) 5.65 (d, 3.5)	1.26		2.84 (c)[g]
18	1.9 (c)	4.2 (m)	7.42 (d, 3.5)	3.5 (dd, 10, 3.5)	4.82 (dd, 10, 7)	4.2 (t, 11, 3.5)	1.9 (c)		1.18	1.15 (d, 7)	2.75 (m)[i]

[a] Spectra were run in DMSO-d_6 solution on a Varian A-60 nmr spectrometer using tetramethylsilane as internal standard.[6] Superimposed signals were frequently separated in pyridine-d_5 solution; such spectra are given in the Experimental Section. Chemical shifts are quoted in parts per million, signals being denoted in the usual way: d, doublet; dbr, broadened doublet; t, triplet; q, quartet; nm, narrow multiplet; c, complex signal whose center is given. Singlets are unmarked. Figures in parentheses are line separations in hertz. H-9 in 1 and 2 integrated for two protons, methyl signals for three protons, other signals had one-proton intensities. [b] Acetate. [c] Sharpens to doublet on addition of D_2O. [d] Hydroxyl proton, disappears on addition of D_2O. [e] Narrows on addition of D_2O. [f] Narrows on addition of D_2O. [f] Run at 100°. [g] H-7. [h] Partially obscured by DMSO signal. [i] H-11.

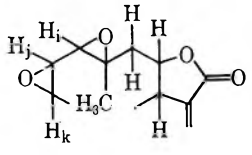
3. The incorporation of partial structure A into C and D as illustrated was further demonstrated by spin-decoupling experiments involving H_a, H_b, H_c, H_d, H_g and $H_{g'}$, H_h, and H_i of **4a** detailed in Table III.



C



D



E

Inspection of the nmr spectra of **4a**, **4b**, **5a**, and **5b** suggested, and the data of Table III confirmed, that H_i was the X component of an ABX system where H_A (*e.g.*, in **4a**) was at 3.62 and H_B at 3.90 (J_{AX} = J_{AB} = 4.7 Hz, J_{BX} = 0 Hz) and where H_B in turn was weakly coupled to H_e and H_f of partial structure B ($J_{H_BH_e}$ = 1.5, $J_{H_BH_f}$ = 1.1 Hz). Hence partial struc-

TABLE III

DOUBLE IRRADIATION OF **4a**[a]

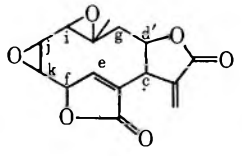
Signal irradd	Signal obsd	Change obsd	Inference
6.16 (H_a)	3.38 (m, H_c)	Sharpened	
5.95 (H_b)	3.38 (m, H_c)	Sharpened	
3.38 (m, H_c)	6.16 (d, H_a)	Collapsed to s	$J_{a,c}$ = 3.2
	5.95 (d, H_b)	Collapsed to s	$J_{b,c}$ = 3.2
	5.80 (nm, H_f)	Affected	
	4.92 (t, H_d)	Collapsed to d	$J_{c,d}$ = 10
4.92 (H_d)	5.35 (dbr, $H_{g'}$)	Collapsed to br?[b]	
	3.38 3(m, H_c)	Simplified	
5.35 ($H_{g'}$)	4.92 (t, H_d)	Collapsed to d	$J_{d,g'}$ = 9.8
	1.72 (d, H_h)	Collapsed to s	$J_{g',h}$ = 1
5.27 (H_i)	3.63 (t, H_j)	Collapsed to d	$J_{i,j}$ = 5.1
3.63 (H_j)	5.27 (dbr, H_i)	Collapsed to br[c]	$J_{i,j}$ = 5.1
	3.91 (dt, H_k)	Collapsed to nm	
3.91 (H_k)	7.77 (t, H_e)	Collapsed to d	$J_{e,k}$ ~ 1
	5.80 (nm, H_f)	Simplifies	
	3.63 (t, H_j)	Collapsed to d	$J_{j,k}$ = 4.2
5.80 (H_f)	7.77 (t, H_e)	Collapsed to d	$J_{e,f}$ = 1.6
	3.91 (dt, H_k)	Collapsed to dd	
7.77 (t, H_e)	3.91 (t, H_h)	Collapsed to dd	$J_{f,k}$ = 1.2
	5.80 (nm, H_f)	Somewhat resolved[d]	

[a] Run on Bruker 90-MHz spectrometer in DMSO-d_6 solution. Limits of error 0.1 Hz. [b] Difficult to determine owing to proximity irradiation frequency to signal observed. [c] Broadening due to allylic coupling to $H_{g'}$ (J < 0.5 Hz). [d] Line broadening due to coupling to H_c ($J_{c,f}$ ~ 0.5 Hz).

ture C could be expanded to E where $H_A = H_i$ and $H_B = H_k$.

In accordance with partial structures D and E, manganese dioxide oxidation of **4b** gave an α,β-unsaturated ketone **7** which had λ_{max} (after subtraction of the chromophore present in **1**) 250 and 310 nm (ϵ 3080 and 200)[21] and ir bands at 1778, 1768, 1700, 1675 (weak), and 1645 cm^{-1} characteristic of the two α,β-unsaturated lactones and a transoid conjugated ketone. In the nmr spectrum of **7** the signals of $H_{g'}$ and H_j had experienced the expected paramagnetic shift, now appearing at 5.61 and 4.40 ppm, respectively, and the resonance of H_j had collapsed to a doublet as required by E. The ketone **8**, λ_{max} (after subtraction of the chromophore of **2**) 255 and 318 nm (ϵ 1200 and 150) and ir bands at 1780, 1747, 1698, 1660, and 1635 cm^{-1}, with the expected nmr signals (Table II), was similarly formed from **5b**.

Partial formulas B and E together accounted for all atoms and functional groups of mikanolide and could be combined in two ways. The first of these possibilities, **1**, possesses the regular isoprenoid skeleton, but its adoption requires the assumption (see Table III) that, in the derivative **4a**, H-6 (H_f) and H-7 (H_c), although vicinal, are not coupled. The observed coupling between H_k and H_e would then be allylic and the coupling between H_k and H_f homoallylic. The second possibility, F, is biogenetically quite implausible but would explain the lack of coupling in **4a** between H_c and H_f. On the other hand it provides no simple rationale for the observed coupling between H_e and H_k.[23]

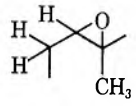


F

A clear decision in favor of **1** and against F was made possible by the observation that hydrogenation of mikanolide or dihydromikanolide to **3** was accompanied by formation of an alcohol **9b** obviously generated by hydrogenolysis of an allylic carbon–oxygen bond.[24,26] Acetylation produced the acetate **9a**; spectral changes accompanying this transformation (Table II and Experimental Section) were consonant with the proposed formulas.[27] Furthermore, oxidation of **9b** with Jones reagent furnished a saturated ketone **11**, λ_{max} 285 nm (ϵ 68) and ir bands at 1780, 1770, and 1715 cm^{-1}, whose H-1 resonance had experienced the expected paramagnetic shift to 4.25 ppm and had collapsed to a singlet as required by the assigned structure. These transformations were not explicable in terms of F, but provided positive proof for formulation of mikanolide as **1** (devoid of stereochemistry).

Scandenolide and Dihydroscandenolide.—Ultraviolet [λ_{max} 209 nm (ϵ 15,250)], infrared (1770, 1747, and 1657 cm^{-1}), and nmr spectrum (Table II) indicated the presence of partial structures A and B in scandenolide (**12**). This was established in the now familiar manner by decoupling the resonances of H-13a and H-13b (H_a and H_b) at 6.18 and 6.00, H-7 (H_c) at 3.5, and H-8 (H_d) at 4.7 ppm on the one hand and H-5 (H_e) at 7.83 and H-6 (H_f) at 5.55 ppm on the other. That the relationship of scandenolide and dihydroscandenolide resembled that of **1** and **2** was evident from the spectra and was confirmed by partial hydrogenation of **12** to **13**. That **12** and **13** were acetates was suggested by the analysis and the ir spectrum which contained an additional band at 1739 cm^{-1} and was confirmed by the nmr spectrum which exhibited an acetate singlet at 2.12 ppm.

The nmr spectrum of scandenolide lacked the signals of H_j and H_k in partial structure E of mikanolide. Instead of the three-proton multiplet near 3.4 ppm (H_c, H_j, and H_k) there was the typical one-proton multiplet of H_c (H-7) at 3.5 ppm, a distinct one-proton doublet of doublets at 2.96 ppm attributable perhaps to epoxidic hydrogen in partial structure G, and a new signal at 5.55 ppm provisionally assigned to hydrogen under the acetate function. Because of the presence of high field multiplets which corresponded to two methylene or methinyl protons, it was logical to assign



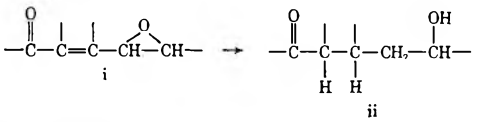
G

(21) Compare with the uv spectra of similarly constituted heliangine derivatives.[22] The low intensity may be attributed to steric deformation of the chromophore.

(22) S. Iriuchijima, S. Kuyama, N. Takahashi, and S. Tamura, *Agr. Biol. Chem.* (Tokyo), **30**, 511, 1152 (1966); H. Morimoto, Y. Sanno, and H. Oshio, *Tetrahedron*, **22**, 3173 (1966); M. Nishikawa, K. Kamiya, A. Takabatake, and H. Oshio, *ibid.*, **22**, 3601 (1966).

(23) Spin-decoupling experiments on mikanolide at 100 MHz, described in the Experimental Section, permitted clarification of all coupling constants and demonstrated the existence of vicinal coupling (J = 4.2 Hz) between H-6 and H-7 in mikanolide. However, at this stage this information could not be used to distinguish between formulas **1** and F because the superposition of the H-1, H-2, and H-7 resonances at 100 MHz did not allow us to assign the 4.2-Hz coupling specifically to the influence of H-1, H-2, or H-7.

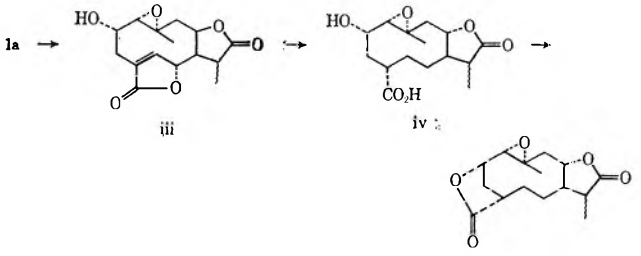
(24) Because of this the hydrogen uptake was always more than 2 molar equiv. Compare with the hydrogenolysis of magnamycin[25] in which i is converted into ii.



i ii

(25) R. B. Woodward, *Festschr. Arthur Stoll*, 524 (1957); *Angew. Chem.*, **69**, 50 (1957).

(26) A third minor product formed during the hydrogenation of **1** or **2** had infrared bands at 1770 and 1760 cm^{-1} and an R_f value very similar to that of **3**. The analytical data and nmr signals (see Experimental Section) indicated that it possessed structure **10** which could arise from further hydrogenolysis of an intermediate iii on the route to **9b** *via* iv. Relative yields of **3**, **9b**, and **10** in a typical run were *ca.* 5:1.5:0.5.



iii iv 10

(27) In the DMSO spectrum of **9b**, the signal of H-1 could not be discerned clearly as it was partially obscured by the DMSO–H_2O and other signals. However in pyridine solution it was clearly visible as a doublet at 3.7 ppm (10 Hz) and H-2 appeared at 4.29 ppm (shifted to 5.45 ppm—apparent octet—in the acetate **9a**).

to scandenolide formula **12** in which the 2,3-epoxide function of mikanolide was opened toward C-3. This was established in the following manner.

On treatment with 4% methanolic hydrochloric acid, scandenolide underwent a transformation parallelling the conversion of mikanolide into **4b**. The only additional feature in the product **14a** which requires mention at this stage was the simultaneous hydrolysis of the acetate function evident from the analysis and the nmr spectrum. Attempts at selective removal of one of the two hydroxyl groups, whose α protons were superimposed at 4.5 ppm, to effect a possible correlation with deoxymikanolide (*vide infra*) were not successful. However, the beautifully distinct 90-MHz nmr spectrum[28] of the diacetate **14b** permitted delineation and combination of all structural features (Table IV).

Irradiation at the frequencies of H-13a and H-13b identified the signal of H-7. Conversely, irradiation at the frequency of H-7 collapsed not only the signals of the exocyclic methylene group, but identified the neighboring protons H-6 and H-8. Which of the affected signals corresponded to H-8 became clear on irradiating at a frequency corresponding to the signal of H-9 (broadened doublet at 5.26 ppm). This collapsed the narrowly split (allylic coupling) C-10 methyl resonance and simplified the broadened triplet at 4.98 (H-8), but did not affect the narrowly split multiplet of H-6 at 5.46 ppm. H-6 was not only coupled vicinally to H-7 and H-5, but also (homoallylically, just as in **4a**) to a multiplet at 5.60 ppm which corresponded to hydrogen under the acetate group originally present in scandenolide. This hydrogen was coupled allylically, as in **4a**, to H-5 and vicinally to two geminally coupled protons of a methylene group whose signals were at 2.71 and 2.05 ppm. Each of these two high-field protons was in turn coupled to hydrogen under the acetate function introduced during the conversion of **12** into **14b** which must therefore be attached to C-1. This completed the structure proof of **14b** and therefore **12**.

Deoxymikanolide.—This minor lactone of *M. scandens* was intermediate in polarity between mikanolide and scandenolide. That it should possess structure **15** (devoid of stereochemistry) was apparent when its nmr spectrum (Table II) was compared with that of scandenolide. The spectrum was superimposed on that of **12** except for the absence of the signal of the acetate methyl and the proton under it. This was compensated for by a two-proton increase in the methylene region.

The appearance of a communication dealing with the structure of the germacranolide isabelin (**16**)[29] suggested the possibility of establishing a correlation of isabelin with deoxymikanolide. Indeed, peracid oxidation of isabelin[30] afforded in excellent yield a substance which was identical in all respects with deoxymikanolide, thus confirming its structure. Because isabelin has been related to cnicin of established relative and absolute configuration, the stereochemistry of deoxymikanolide at C-6, C-7, and C-8 was thereby settled. Furthermore inspection of an isabelin model indicated that reagent attack should occur preferentially from the α side. This would lead to the configuration at C-1 and C-10 depicted in **15**. In this orientation the C-10 methyl group is somewhat shielded by the 4,5 double bond as required by the nmr spectrum (Table III see also footnote 17). Additional evidence for this assignment will be cited in the sequel.

Stereochemistry of Mikanolide and Scandenolide.—A number of attempts were made to interrelate mikanolide and scandenolide with deoxymikanolide by removal of oxygen functions at C-2 and C-3. These were unsuccessful. Nevertheless, leaving aside biogenetic considerations, the pronounced similarity in chemical shifts and coupling constants evident from Table II and from the spin-decoupling experiments left practically no doubt that mikanolide, scandenolide, and deoxymikanolide possessed the same stereochemistry at C-1, C-6, C-7, C-8, and C-10. This was supported by the following observations.

Irradiation at the frequency corresponding to H-9 produced a 10% enhancement in the integrated intensity of the C-10 methyl signal of **4a** and an 11% enhancement in the integrated intensity of the C-10 methyl signal of **14b**.[31] The existence of an appreciable NOE showed that the newly introduced double bond was therefore *cis*, as indicated in the formulas. If **4b** and **14a** are formed from mikanolide and scandenolide by concerted reactions as seems likely because of the absence of $\Delta^{10,15}$ isomers, the required antiparallel orientation for the C-10 oxygen and C-9 hydrogen bonds which are broken in the elimination process leading to a *cis*-$\Delta^{9,10}$ olefin necessitates that mikanolide and scandenolide be formulated as 1,10-α-epoxides. As in the case of deoxymikanolide, the α configuration of the 1,10-epoxide should result in deshielding of the C-10 methyl group by the 4,5 double bond as was actually observed (Table II).[17]

An additional consequence of the α configuration of the 1,10-oxirane ring and a lactone stereochemistry corresponding to that of deoxymikanolide is the pronounced proximity of H-1, H-5, and H-8 apparent from the models of mikanolide (Figure 1) and **4a** (Figure 2) which should be reflected in relatively strong NOE's. Indeed, irradiation at the frequency of H-5 produced, for **4a**, a 26% enhancement in the in-

(28) Measured on a Bruker 90-MHz nmr spectrometer purchased with the aid of a grant from the National Science Foundation for which we express our thanks.

(29) In ref 9, the planar formulas of isabelin which is a mixture of two conformers and those of its derivatives are drawn so as to show a *cis* relationship between H-1 and the C-10 methyl group. The spatial formulas are drawn so as to show a *trans* relationship between H-1 and C-10 methyl. The latter appears to be correct. In our hands, irradiation[28] at either of the frequencies of H-1 collapsed the signals of the vinyl methyl group corresponding to the appropriate conformer, but produced no enhancement whatsoever in the integrated intensity of the C-10 methyl resonance.

The absence of a nuclear Overhauser effect indicates that H-1 and the C-10 methyl group of isabelin are *trans*, as shown in formula **16**. On the other hand irradiation at the two frequencies corresponding to H-8 of isabelin produced a 16% enhancement in the integrated intensity of the H-5 signals, as required by the formula which brings H-5 and H-8 into close proximity. Neither of the C-10 methyl signals was a simple doublet as reported.[9] The upfield signal appeared as a triplet, possibly due to the presence of homoallylic coupling ($J_{1,15} = J_{2a(?),15} = 0.65$ Hz), the lower methyl as a broadened doublet ($J_{1,15} = 1.2$, $J_{2a(?),15} < 0.5$ Hz).

(30) We are grateful to Dr. H. Yoshioka and Professor T. J. Mabry for a generous sample of this compound.

(31) An 11% increase in the intensity of the 1-acetate methyl signal of **14b** was also noted, but there was no effect on the intensity of the acetate methyl of **4a**. This is probably due to the greater conformational rigidity imposed on **4a** by the presence of the epoxide ring which results in somewhat different conformations for **4a** and **14a** also evident from the difference in the homoallylic coupling constants $J_{3,5}$ and the difference in the NOE's involving H-5 and H-8 (*vide infra*). This appears to produce preferred orientations for the acetate methyl closer to H-9 in **14b** than in **4a**.

TABLE IV

DOUBLE IRRADIATION OF **14b**[a]

Signal irradd	Signal obsd	Change obsd	Inference[b]
1.79 (C-10 Me)	5.26 (dbr, H-9)	Sharpens to d (10.6)	$J_{8,9}$ = 10.6 $J_{9,15}$ = 1.0
5.26 (H-9)	1.79 (d, C-10 Me)	Collapsed to s	
	4.98 (tbr, H-8)	Perturbed	
4.98 (H-8)	4.26 (dbr, H-9)	Collapsed to br	$J_{8,9}$ = 10.6
	3.28 (dtd, H-7)	Collapsed to td (3.5, 1.5)	
3.28 (H-7)	6.34 (dd, H-13a)	Collapsed to d (0.6)	$J_{7,13a}$ = 3.6
	5.70 (dd, H-13b)	Collapsed to d (0.6)	$J_{7,13b}$ = 3.2
	5.46 (ddd, H-6)	Collapsed to dd	
	4.98 (tbr, H-8)	Collapsed to dbr	
6.34 (H-13a)	5.70 (dd, H-13b)	Collapsed to d (3.2)	$J_{13a,13b}$ = 0.6
	3.28 (dtd, H-7)	Collapsed to ddd (9.6, 3.2, 1.2)	
5.70 (H-13b)	6.34 (H-13a)	Collapsed to d (3.6)	
	3.28 (dtd, H-7)	Collapsed to ddd (9.6, 3.6, 1.2)	
5.46 (H-6)	7.36 (dd, H-5)	Collapsed to d (1.6)	$J_{3,5}$ = 1.6 (allylic)
	5.75 (m, H-3)	Affected	
	3.28 (dtd, H-7)	Collapsed to dt (1.2, 3.5)	$J_{7,8}$ = 9.6
7.36 (H-5)	5.46 (ddd, H-6)	Collapsed to dd (2.7, 1.2)	$J_{6,7}$ = 1.2 $J_{3,6}$ = 2.7 H-3 signal is at 5.75
5.75 (H-3)	7.36 (dd, H-5)	Collapsed to d (1.4)	$J_{5,6}$ = 1.4
	5.46 (ddd, H-6)	Affected	
	2.71 (ddd, H-2a)	Collapsed to dd (15.5, 9.6)	$J_{2a,3}$ = 3.5[d]
	2.06 (ddbr, H-2b)[c]	Collapsed to dbr (15.5)	$J_{2b,3}$ = 3.1
2.71 (H-2a)	5.75 (m, H-3)	Affected	$J_{2a,2b}$ = 15.5[d]
	5.60 (dbr, H-1)	Collapsed to br[e]	$J_{1,2a}$ = 9.6[d]
5.60 (H-1)	2.71 (ddd, H-2a)	Collapsed to dd (15.5, 3.5)	$J_{1,2b}$ < 1.0
	2.05 (ddbr, H-2b)[c]	Affected	

[a] Run on Bruker 90-MHz nmr spectrometer in $CDCl_3$. [b] Limit of error 0.1 Hz. [c] Partially hidden under acetate signal. INDOR experiment using H-2b to monitor the sweep showed H-2b to be ddbr. [d] Values taken directly from a 4-Hz/cm scan without confirmation by spin decoupling. [e] Broadening due to $J_{1,9} \sim 0.5$ Hz and to a small coupling with H-8.

tegrated intensity of H-8, a 13% increase in the intensity of H-1,[32] and a 19% increase in the intensity of the vicinal H-6. Hence H-1, H-6, and H-8 were *cis* to each other and β.

The α orientation of the 2,3-oxirane ring of mikanolide and of the 3-acetoxy function of scandenolide postulated in the formulas is based on the magnitude of the observed coupling constants and on the impossibility of constructing a Dreiding model of mikanolide which includes both α-1,10 and β-2,3-oxirane rings. The α- and quasiaxial nature of the C-3 carbon oxygen bond is further supported by the facile hydrogenolysis of **1** or **2** to **3**.[33a] Hydrogenation of the 4,5 double bond of **1** and **12** should proceed from the convex or β face and produce the α attachment of the carbonyl group at C-4 depicted in the formulas of the reduction products. Further work is in progress to verify these conclusions.

(32) (a) Owing to overlap of H-1 and H-9 signals in the nmr spectrum of **4a**, H-1 and H-9 had to be integrated together. The 13% figure assumes that there was no significant enhancement in the intensity of the H-9 resonance on irradiation of H-5. This could be demonstrated for **14b**. In the latter, the conformational difference referred to earlier[31] appeared to be responsible for the observation that irradiation at the frequency of H-5 produced a 12% increase in the integrated intensity of the combined H-1 and H-3 signals,[32b] but only relatively small enhancements (approximately 6% each) in the intensities of H-8 and H-6. However, the *cis* orientation of H-1 and H-8 in **14b** (and therefore in **12**) was conclusively demonstrated by irradiation at the frequency of H-1 which produced a 35% increase in the integrated intensity of the H-8 signal. (b) Based on the assumption that the H-13b signal which overlaps H-1 nd H-3 was not enhanced significantly.

(33) (a) Hydrogenolysis of allylic-type carbon–oxygen bonds proceeds when the bond is quasiaxial.[33b] (b) T. B. H. McMurry and R. C. Mollan, *J. Chem. Soc.*, 1619 (1969); A. Giger, M. Fetizon, J. Henniker, and L. Jaque, *Compt. Rend.*, **251**, 2194 (1960).

Miscandenin.—Although paucity of this substance, the least polar of the *M. scandens* constituents, precluded extensive chemical studies, evidence, based mainly on physical measurements, was acquired which supported its formulation as the interesting structure **17**.

At the outset the spectral data disclosed that miscandenin was structurally different from the mikanolide group of lactones. Thus the infrared spectrum, in addition to displaying the usual intense bands at 1770 and 1760 cm^{-1} characteristic of the dilactone functions of A and B, also displayed equally intense bands at 1680 and 1658 cm^{-1} which were too strong to be attributed to ordinary double bonds. Their position and intensity was, however, consistent with the presence of two enol ether functions as in **17**.[34–36] Furthermore the uv spectrum exhibited not only high intensity end absorption at 203 nm (ϵ 11900) due to an α,β-unsaturated lactone chromophore, but also a lower intensity maximum at 263 nm (ϵ 5640).

The nmr spectrum (Table II) of miscandenin was in complete accord with its formulation as **17** exclusive of stereochemistry. The assignments were confirmed

(34) The absence of one or more α,β-unsaturated ketone function implicit in this assumption was based on the uv spectrum (*vide infra*) and the ORD curve which showed no Cotton effect in the 290-nm region.

(35) See, for example, F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953), for a discussion of ir spectra of representative compounds containing simple enol ethers and the grouping ROOC=CO–.

(36) The band at 1658 cm^{-1} was stronger than the band at 1680 cm^{-1}, probably owing to the superposition of the enol ether band on the absorption of the exocyclic double bond conjugated with the lactone function.

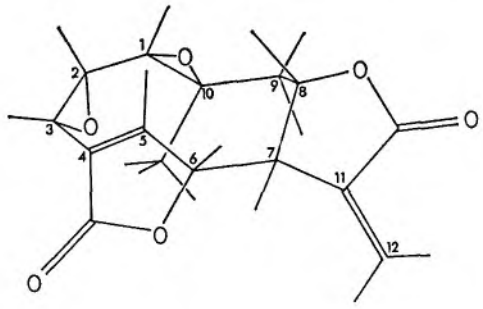
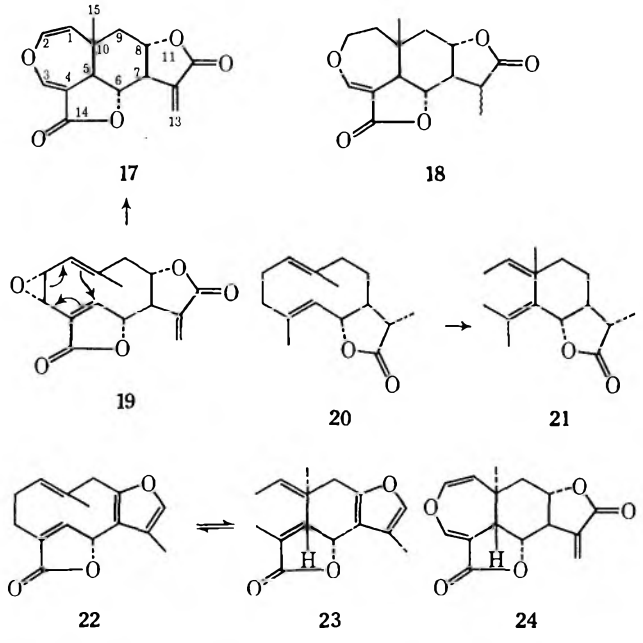


Figure 1.—Model of mikanolide.

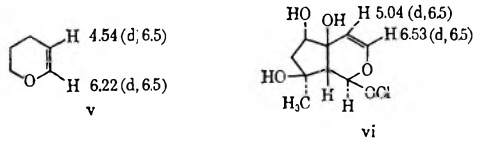
by double-resonance experiments. Chemical shifts of H-2 and H-1 were in good agreement with chemical shifts of α and β protons in enol ethers, the 8.5-Hz coupling constant being in excellent accord with a seven-numbered cyclic enol ether group,[37] but inconsistent with their incorporation into a smaller ring.[38] H-3 was shown to be allylically coupled to H-5 (J = 3.5 Hz) and H-6 was vicinally coupled to H-5 (J = 7 Hz) and H-7 (J = 10 Hz). As usual the latter[41] was allylically coupled to H_{13a} and H_{13b} (J = 3.5 Hz) and vicinally coupled to H-8 (J = 11 Hz). In turn H-8 was coupled to a two-proton multiplet centered at 1.9 (H-9, $J_{8,9a}$ = 3.5, $J_{8,9b}$ = 11 Hz).[42]



17 18 19 20 21 22 23 24

(37) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Amer. Chem. Soc.*, **90**, 2980 (1968).

(38) For example in 2,3-dihydropyran (v)[39] and harpagide (vi)[40] the coupling constant is 6.5 Hz.



v vi

(39) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1965, Spectrum No. 111.

(40) H. Lichti and A. von Warburg, *Helv. Chim. Acta*, **49**, 1552 (1966); M. L. Scarpati and M. Guiso, *Tetrahedron*, **23**, 4709 (1967).

(41) At 220 MHz, the H-7 multiplet was clearly resolved into a triplet of triplets, with the larger couplings ($J_{6,7}$ and $J_{7,8}$) of approximately 10.5 and the smaller couplings ($J_{7,13}$) of 3–3.5 Hz.

(42) At 220 MHz the H-9 multiplet was resolved into the AB part of an ABX system where A (H-9a) was at 2.11 (dd, 11.5, 3), B (H-9b) was at 1.80 (t, 11.5), and X was obviously H-8. We are grateful to Mr. R. S. Sudol and Dr. D. W. Ovenall, Plastics Department, E. I. du Pont de Nemours and Co., Inc., for determining the spectrum.

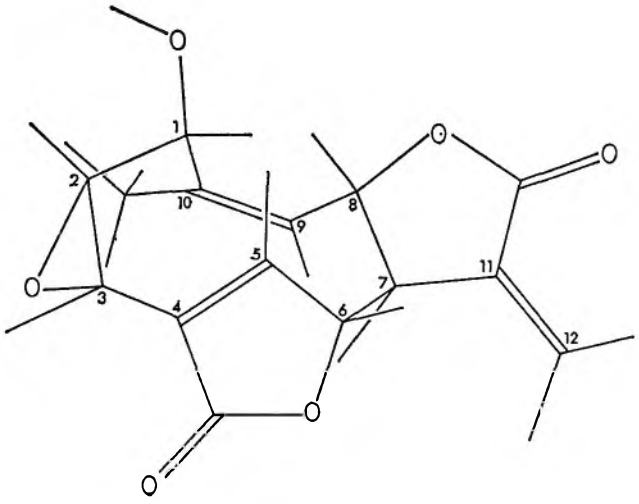
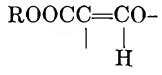


Figure 2.—Model of **4b**.

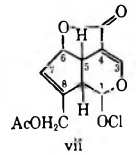
Hydrogenation of miscandenin resulted in the uptake of only 2 molar equiv of hydrogen and the formation of a tetrahydro derivative **18** whose infrared spectrum had retained one of the two intense enol ether bands. In the ultraviolet spectrum, the high intensity end absorption of **17** had disappeared and the long-wavelength band had experienced a hypsochromic shift to 248 nm (ϵ 7990). The nmr spectrum of **18** (Table II) reflected the changes which would be expected on reduction of partial structure A. Furthermore, the AB system of **17** representing H-1 and H-2 had disappeared, but the signal of the vinyl proton at lowest field (H-3) remained and the chemical shifts of H-5 and H-6 were not affected. Thus the nmr spectrum of the reduction product was in good agreement with its formulation as **18**.[43]

That the reduction of miscandenin stopped at the tetrahydro stage was not surprising in view of the observation that the grouping



is resistant to hydrogenation.[45] The absence of hydrogenolysis, in contrast to our experience with mikanolide (*vide supra*), further supports formula **17** for miscandenin which contains no allylic carbon–oxygen bond subject to hydrogenolysis. It is also eminently plausible on biogenetic grounds since it can be rationalized as arising from a hypothetical precursor, 1,10-deoxymikanolide (**19**), by a Cope rearrangement similar to the dihydrocostunolide–saussurea lactone

(43) Comparison of the nmr spectrum of **18** with that of asperuloside (vii),[44] which has H-3 at 7.20 (n d), H-5 at 3.48 (td), and H-6 at 5.49 (d, coupled here to H-5), is instructive.



vii

(44) L. H. Briggs, B. F. Cain, D. W. LeQuesne, and J. N. Shoolery, *Tetrahedron Lett.*, 69 (1963).

(45) See, for example, O. Halpern and H. Schmid, *Helv. Chim. Acta*, **41**, 1109 (1958).

(20 → 21)[46] and linderalactone–isolinderalactone (22 ⇄ 23) interconversions[47] which yield lactones belonging to the elemane class of sesquiterpenes.[50] The present situation is, however, slightly unusual in that the postulated Cope rearrangement would also involve a divinyloxirane–4,5-dihydrooxepine transformation of the type observed in the synthesis of 4,5-dihydrooxepine from *cis*-1,2-divinylethylene oxide.[51]

If, in analogy with the stereochemistry deduced for isabelin,[29] we assume a *trans*-$\Delta^{1(10)}$ bond for the hypothetical precursor **19**, orbital symmetry rules[52] require formation of a *trans*-A/B-fused elemadiene system, either C-10 methyl β, H-5 α, or the reverse.[53] If one makes the further highly plausible assumption that the stereochemistry of **19**, and therefore that of miscandenin, at C-6 and C-8 is identical with that of **1**, **12**, **15**, and **16**, construction of the almost impossibly strained model of **24** with C-10 methyl α, H-5 β, and ring B in a somewhat deformed chair leads to an implausible C-7 axial side chain and dihedral angles of approximately 30° for H-5,H-6 and 80° for H-6,H-7. This is incompatible with the observed coupling constants (7 and 10.5 Hz).[56] On the other hand, in the still strained model of **17**, with ring B in a chair, the all-*trans* relationship of H-5, H-6, and H-7 leads to dihedral angles of approximately 165° which harmonize with the H-5,H-6 and H-6,H-7 coupling constants.

Although all previously cited evidence fits in well with structure **17** for miscandenin, the ultraviolet maximum at 263 nm appears to be somewhat anomalous. The bathochromic shift of 15 nm relative to tetrahydromiscandenin is possibly due to an interaction, enforced by the presence of two fused rings, between the two enol ether double bonds, one of which is conjugated.[57] The ultraviolet maximum of tetrahydromiscandenin at 248 nm is also found at somewhat longer wavelength than that of model compounds possessing basically the same chromophore, though in the model compounds a carbalkoxy group has replaced the lactone ring or the stereochemistry differs.[59] This could account for the bathochromic shift.

Experimental Section[62]

Isolation of Lactones from *Mikania Scandens* (L.) Willd.—The results of two typical large-scale extractions are described. Miscandenin could not be isolated from every collection.

A.—Above-ground material, dry wt 39 lb, collected by R. Lazor and J. Lazor in Sept 1967 in Wakulla County, Fla., along the Wakulla River 5 miles south of the upper bridge at the Wakulla Springs Wildlife Sanctuary, Wakulla County, Fla. (voucher 818-R1 on deposit in the Florida State University herbarium) was extracted with chloroform and worked up in the usual fashion.[63] The crude semisolid gum on being triturated with 300 ml of benzene–chloroform (1:1) deposited 5.2 g of solid which was a mixture of mikanolide (30%), dihydromikanolide (60%), and scandenolide (10%). The filtrate was concentrated to give 89 g of gum which was dissolved in the minimum of benzene–chloroform (1:1) and absorbed on 1.2 kg of silicic acid (Mallinckrodt, 100 mesh) packed in benzene. The column was eluted in the sequence shown below, 1:1 fractions being collected. In each case the solvents were evaporated and the residue was recrystallized from chloroform (or acetone)–ether–petroleum ether and monitored by tlc and nmr. The results are reported in Table V.

TABLE V[a]

Fractions	Eluent	Constituents	Wt, g
1–8	Benzene		
9–20	Benzene–chloroform (4:1)	Gummy (several spots)	
21–32	Benzene–chloroform (3:2)	Gummy (several spots)	
33–40	Benzene–chloroform (3:1)	MK	0.8
41–43	Benzene–chloroform (3:1)	MK + 10% DHMK	1.2
44–45	Benzene–chloroform (3:1)	MK + DHMK (1:1)	0.5
46–48	Benzene–chloroform (3:1)	DHMK + 10% MK	0.9
49–51	Benzene–chloroform (3:1)	DHMK	0.45
52–54	Benzene–chloroform (3:1)	DHMK (60%) + SC (40%)	0.35
55	Benzene–chloroform (3:1)	SC + DHSC (1:1)	0.3
Later	More polar	Noncrystallizable gums	

[a] The following abbreviations are used: MK, mikanolide; DHMK, dihydromikanolide; SC, scandenolide; DHSC, dihydroscandenolide.

(46) A. S. Rao, A. Paul, D. Sadgopal, and S. C. Bhattacharya, *Tetrahedron*, **13**, 318 (1961). The depicted *trans* stereochemistry of the $\Delta^{1(10)}$ bond of dihydrocostunolide is based on the conclusions of M. Suchy, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **31**, 2899 (1966).

(47) K. Takeda, H. Minato, and M. Ishikawa, *J. Chem. Soc.*, 4578 (1964); K. Takeda, I. Horibe, and H. Minato, *Chem. Commun.*, 378 (1968). *trans* stereochemistry of the $\Delta^{1(10)}$ bond of **22** was based on the failure to observe an NOE in the H-1 resonance on irradiation at the frequency of the C-10 methyl group[48] and on the facility with which isomerization to **23** occurred.[48] However, sericenin in which the double bond appears to be *cis* undergoes facile isomerization to isosericenin.[49]

(48) K. Takeda, I. Horibe, M. Teraoka, and H. Minato, *ibid.*, 637, 940 (1968).

(49) N. Hayashi, S. Hayashi, and T. Matsuura, *Tetrahedron Lett.*, 4957 (1968).

(50) W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.*, **21**, 331 (1967).

(51) R. A. Braun, *J. Org. Chem.*, **28**, 1383 (1963); E. L. Stogryn, M. H. Gianni, and A. J. Passanante, *ibid.*, **29**, 1275 (1964). See also E. Vogel and H. Günther, *Angew. Chem.*, **79**, 429 (1967).

(52) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **89**, 4389 (1965).

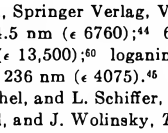
(53) Although isomerization of germacranolides has so far led to isolation of only one of the two possible *trans*-fused elemanolides,[46,47,54] recent work indicates that the germacradiene–elemadiene rearrangement may, in certain cases, lead to both *trans*-fused elemadienes.[55]

(54) N. H. Fischer, T. J. Mabry, and H. B. Kagan, *Tetrahedron*, **24**, 4091 (1968).

(55) K. Morikawa and Y. Hirose, *Tetrahedron Lett.*, 2899 (1968); 869 (1969).

(56) With ring B in a deformed, but nevertheless apparently quite unfavorable boat conformation, the dihedral angles are much more satisfactory (~10 and 180°).

(57) The anomalous maximum near 213 nm in the spectra of germacrone, dihydrocostunolide, and similar compounds has been assigned to interaction between the endocyclic double bonds in the germacra-1,5-diene system.[58] In the present case, models suggest that the presence of the rigid endocyclic γ-lactone system and the (probable) *trans* fusion of ring B may impose geometrical restrictions on the relative orientation of the double bonds not present in 4,5-dihydrooxepin[51] which exhibits no uv absorption >200 nm. The alternative formulation x for miscandenin would account for the uv maximum more conventionally and also for the decoupling data, but is excluded on the basis of the AB system present in the nmr spectrum, the ir spectrum, the reduction experiments, and the properties of tetrahydromiscandenin.



x

(58) F. Sorm in "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zechmeister, Ed., Springer Verlag, Vienna, 1961, p 1.

(59) *Cf.* asperuloside, 234.5 nm (ε 6760);[44] 6-isopropyl-3-carbomethoxy-5,6-dihydropyran, 240 nm (ε 13,500);[60] loganin, 236 nm (ε 10,900);[61] and tetrahydrodeoxyplumieride, 236 nm (ε 4075).[45]

(60) F. Korte, K. H. Büchel, and L. Schiffer, *Chem. Ber.*, **91**, 759 (1958).

(61) K. Seth, E. Ramstad, and J. Wolinsky, *Tetrahedron Lett.*, 394 (1961).

(62) Melting points are uncorrected; rotations were run in dioxane; ultraviolet spectra were run in 95% ethanol on a Cary Model 14 recording spectrophotometer unless otherwise stated; and infrared spectra were run as Nujol mulls on Perkin-Elmer 257 or 521 recording spectrophotometers. Tlc chromatograms were carried out on microslides coated with silica gel G, using chloroform–ethyl acetate–methanol (5:1:0.2) for development. Spots were detected by spraying with concentrated sulfuric acid followed by heating. Petroleum ether was low boiling (30–60°). Analyses were performed by Dr. F. Pascher, Bonn, Germany.

(63) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

TABLE VI[a]

Fractions	Eluent	Constituents	Wt, g
1-10	Benzene		
11-22	Benzene-chloroform (4:1)	Gum	
23-39	Benzene-chloroform (3:1)	Gum	
40-43	Benzene-chloroform (3:2)	MSC	0.5
44	Benzene-chloroform (3:2)	MSC + MK (7:3)	0.05
45-55	Benzene-chloroform (3:2)	MK	3.5
56	Benzene-chloroform (3:2)	MK + DHMK (7:3)	0.4
57-59	Benzene-chloroform (3:2)	MK + DHMK (1:1)	1.0
60	Benzene-chloroform (3:2)	MK + DHMK (3:7)	0.4
61	Benzene-chloroform (3:2)	DHMK	0.38
62	Benzene-chloroform (3:2)	DHMK + DOMK (4:1)	0.3
63	Benzene-chloroform (3:2)	DHMK + DOMK (1:1)	0.25
64-68[b]	Benzene-chloroform (3:2)	DOMK + SC (1:1)	1.1
		DHMK (trace)	
69-70	Benzene-chloroform (3:2)	DOMK + 10% SC	0.9
71	Benzene-chloroform (3:2)	DOMK + SC (6:4)	0.32
72	Benzene-chloroform (3:2)	DOMK + SC (1:1)	0.3
73	Benzene-chloroform (3:2)	DOMK + SC (1:2)	0.3
74	Benzene-chloroform (3:2)	SC + 10% DOMK	0.25
75-86	Benzene-chloroform (3:2)	SC	2.3
87-88	Benzene-chloroform (3:2)	SC + 10% DHSC	0.25
89-91	Benzene-chloroform (3:2)	SC + DHSC (7:3)	0.1
92-93	Benzene-chloroform (3:2)	SC + DHSC (1:1)	0.1
94	Benzene-chloroform (3:2)	SC + DHSC (1:4)	0.05
95-97	Benzene-chloroform (2:3)		
98-102	Benzene-chloroform (2:3)	DHSC	0.4
103-110	Benzene-chloroform (2:3)		
Later	More polar	Noncrystallizable gums	

[a] MK, mikanolide; DHMK, dihydromikanolide; MSC, miscandenin; DOMK, deoxymikanolide; SC, scandenolide; DHSC, dihydroscandenolide. [b] Erratic elution pattern.

B.—Dry plant material, 45 lb, collected by R. Lazor, J. Lazor, and K. Blum in Sept 1967 at the Ocklocknee River and U. S. 90 west of Tallahassee, Leon County, Fla. (voucher 821-R1 on deposit in the Florida State University herbarium) was extracted in the usual manner. The crude semisolid material furnished 7.5 g of a mixture of mikanolide (30%), dihydromikanolide (60%), and scandenolide (10%) on trituration with 200 ml of warm benzene. The filtrate gave 102 g of gum which was chromatographed as described in part A. The results are given in Table VI.

Miscandenin.—Recrystallization of fractions 40–43 in B from methylene chloride–ether or acetone–hexane afforded colorless needles: mp* 232–235°;[64] $[\alpha]^{24}D$ −181.4° (*c* 1.02, $CHCl_3$); λ_{max} 203 nm (ϵ 11,910) and 263 (5640); ir 1770, 1760, 1682, and 1658 cm^{-1}; mol wt (mass spectrum) 274.

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15; O, 29.16. Found: C, 66.05; H, 5.03; O, 29.32.

Mikanolide.—Recrystallization of fractions 33–40 in A and 45–55 in B from acetone–hexane gave colorless rhombs: mp* 226–228°; $[\alpha]^{24}D$ +53.4° (c 1.12); λ_{max} 206 nm (ϵ 16,700); ir (KBr) 1767, 1752, 1666, and 1630 (sh) cm^{-1}; mol wt (mass spectrum) 200. Acetylation of mikanolide with acetic anhydride–pyridine resulted in recovery of starting material.

Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86; O, 33.07. Found: C, 61.90; H, 5.37; O, 32.78.

Dihydromikanolide.—Recrystallization of fractions 49–51 in A and 61 in B from acetone–hexane afforded colorless prisms: mp 240–244° (complete liquefaction with gas evolution at 250–254°); $[\alpha]^{24}D$ +91.1° (*c* 0.47); ir (KBr) 1760 (double intensity) and 1650 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.53; H, 5.58. Found: C, 61.77; H, 5.54.

Deoxymikanolide.—Repeated recrystallization of fractions 69–70 in B from acetone–hexane and acetone–diisopropyl ether afforded colorless plates and prisms: mp 198–200°; $[\alpha]^{26}D$ +98.9° (*c* 1.63); λ_{max} 211 nm (ϵ 12,880); ir bands at 1764, 1752, 1662, and 1654 cm^{-1}; mol wt (mass spectrum) 276.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 65.22; H, 5.80; O, 28.98. Found: C, 65.17; H, 5.72; O, 29.17.

Scandenolide.—A single recrystallization of fractions 75–86 in B from acetone–isopropyl ether gave colorless needles: mp* 230–234°; $[\alpha]^{25}D$ +62.0° (*c* 1.11); λ_{max} 209 nm (ϵ 15,250), ir 1770, 1747, 1739, and 1657; mol wt (mass spectrum) 334 (weak), 294 (molecular ion − ketene).

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.08; H, 5.39; O, 33.54. Found: C, 61.15; H, 5.49; O, 33.40.

Dihydroscandenolide.—A single recrystallization of fractions 98–110 in B from acetone–hexane gave colorless prisms: mp 278–280° dec; $[\alpha]^{25}D$ +83.3° (*c* 0.54); λ_{max} 210 nm (ϵ 8680); ir 1778, 1742, and 1660 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.95; O, 33.34. Found: C, 60.80; H, 5.94; O, 33.36.

Separation of Mixed Fractions.—Mixtures in which one component was predominant, *e.g.*, fractions 41–43 and 46–48 in A, or 69–70, 74, and 87–88 in B, could be purified by repeated recrystallization. Mixtures in which the components were represented equally or nearly so were amenable to separation by a triangular recrystallization scheme from acetone–hexane. For example, fractions 44–45 and 55 in A, and 57–59, 63, and 71 were separated in this manner, the more sparingly soluble components (dihydromikanolide or dihydroscandenolide) being obtainable in almost pure form in the crop IC or ID stage.[65] The second component frequently could be obtained in pure form as crop IIC or IID. Three-component fractions could not be separated in this way and attempts to separate them by chromatography (column and preparative tlc) were unsuccessful.

Double Irradiation Studies on Mikanolide and Scandenolide.—The experiments on mikanolide, for which we are indebted to Mr. R. S. Sudol and Dr. D. W. Ovenall, were carried out on a Varian HA-100 nmr spectrometer in DMSO-d_6 solution. First, H-7 was located among the three-proton cluster of peaks centered around 3.4 ppm. Thus irradiation of either of the doublets at 6.20 and 5.29 ppm (H-13a and H-13b) effected simplification of this region. Conversely, irradiation at 3.4 ppm collapsed the doublets into singlets and also collapsed the 4.72 ppm multiplet (H-8, this

(64) Melting points which are starred were not sharp. The reported temperatures indicate the range in which the compound lost its crystallive form and collapsed to a glass when introduced at 200°. Complete liquefaction was not observed below 300°.

(65) R. S. Tipson in "Technique of Organic Chemistry," Vol. 3, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1950, p 424.

was resolved into an octet at 100 MHz) into a quartet (10.5, 5.0) by removing an 8.5-Hz ($J_{7,8}$) coupling. Conversely, the 3.4-ppm multiplet was simplified by irradiation at 4.72.

The observation that H-8 was an octet required that it be flanked by a methylene group. This was proved as follows. Irradiation at 4.72 ppm (H-8) also collapsed two split doublets (H-9a and 9b, not resolved at 60 MHz) at 2.18 (10.5, 12.5) and 1.85 ppm (12.5, 5.0) into a pair of doublets separated by 12.5 Hz each. Irradiation at 2.0 ppm (center of H-9) caused collapse of the H-6 octet to a doublet (8.5). Hence $J_{8,9a} = 10.5$, $J_{8,9b} = 5.0$, $J_{9a,9b} = |12.5|$ Hz. With all couplings of H-9a and H-9b accounted for, the fourth bond of C-9 must be linked to a quaternary center as in C.

The environment of H-5 and H-6 was next clarified. Irradiation of the narrowly split doublet (1.7) of H-5 at 7.56 ppm converted the multiplet of H-6 at 5.42 ppm (apparent quintet) into a doublet of doublets (4.2, 1.1). Conversely, irradiation of H-6 collapsed H-5, removed the smaller coupling from the doublet of doublets of H-3 at 3.96 ppm (3.5, 1.1), and simplified the 3.4-ppm multiplet containing H-7 and two other protons now identifiable as H-1 and H-2. The converse was also true. Thus irradiation at 3.96 ppm perturbed the signal of H-6 and irradiation at 3.4 ppm collapsed H-6 into a narrow doublet of doublets whose lines were separated by 1.7 ($J_{5,6}$) and 1.1 Hz ($J_{3,6}$). Hence $J_{6,7}$ was 4.2 Hz.

Irradiation of the signal of H-3 perturbed the H-6 multiplet and affected the signals in the 3.4-ppm region, therefore known to contain H-2. Conversely, irradiation at 3.4 ppm removed the larger coupling (3.5 Hz) from the signal of H-3. Hence $J_{2,3}$ was 3.5 Hz.[66]

Decoupling experiments on scandenolide were carried out at 90 MHz in DMSO-d_6 solution. The following coupling constants were observed: $J_{1,2a} = 11.7$, $J_{1,2b} = 2$, $J_{2a,2b} = |14.5|$, $J_{2a,3} = 3.6$, $J_{3,5} < 0.5$, $J_{6,7} \sim 1$, $J_{7,8} = 3$, $J_{7,13a} = 3.5$, $J_{7,13b} = 3$, $J_{8,9a} = 4.7$, $J_{8,9b} = 8.9$ Hz. Owing to signal overlap it was not possible to determine $J_{2b,3}$, $J_{3,6}$ (less than 1 Hz), and $J_{5,6}$ (less than 1 Hz).

Ozonolysis of Mikanolide.—A solution of 100 mg of **1** in 15 ml of acetic acid was ozonized for 30 min at 0°, diluted with water, and steam distilled into an ice-cooled aqueous solution of dimedone. On standing 20 mg of the dimedone derivative of formaldehyde precipitated, mp and mmp 181–183°.

Hydrogenation of Mikanolide. A.—A solution of 145 mg of **1** in 40 ml of ethyl acetate was hydrogenated in the presence of 125 mg of 5% Pd–$CaCO_3$ at atmospheric pressure. The initially rapid uptake of hydrogen ceased after the consumption of 1 molar equiv. The solution was filtered and evaporated. The residue (single spot on tlc) was recrystallized from acetone–hexane, yield 120 mg of dihydromikanolide identical in all respects with material isolated from the plant.

B.—A solution of 145 mg of **1** in 40 ml of ethyl acetate was hydrogenated in the presence of 145 mg of 10% Pd–C catalyst at atmospheric pressure. Hydrogen uptake ceased after the absorption of *ca.* 2.5 molar equiv. The solution was filtered and evaporated. The residue (three spots on tlc) from two such runs was taken up in the minimum amount of chloroform and absorbed on 60 g of silicic acid set in benzene–chloroform (1:1). Elution with chloroform (10-ml fractions) gave the following results: fractions 1–6 (after elution started), 42 mg of tetrahydromikanolide (**3**); fraction 7, 18 mg of **3** and **10** (9:1); fraction 8, 6 mg of **3** and **10** (1:1); fraction 9, 4 mg of **3** and **10**; fraction 10–14, 16 mg of **10**; fractions 15–18, nothing; fractions 19–23 [chloroform–methanol (49:1)], 56 mg of **9b**.

Recrystallization of fractions 1–6 from acetone–hexane or ethyl acetate–petroleum ether furnished tetrahydromikanolide: mp 225–228°; $[\alpha]^{24}D$ +77.4° (*c* 0.8, $CHCl_3$); no uv absorption; ir (KBr) 1800 and 1755 cm^{-1}; nmr (pyridine-d_5) 4.88 (c, 2p, H-6 and H-8), 3.9 (c, 2p) and 3.2 (t, 1p) (H-1, H-2, and H-3), 1.55 (3p, C-10 methyl), and 1.3 ppm (dc, 7, C-11 methyl).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17; O, 32.62. Found: C, 61.36; H, 6.32; O, 32.39.

Recrystallization of fractions 10–14 from ethyl acetate–hexane gave colorless needles of **10**: mp 220–224°, mmp 200–205° with **3**; $[\alpha]^{24}D$ +56.7° (*c* 1.0); no uv absorption; ir 1770 and 1760 cm^{-1}; nmr signals (pyridine-d_5) 4.78 (c, 2p, H-2 and H-8), 3.0–3.4 (c, 3p, H-1 and two other protons), 1.57 (3p, C-10 methyl), and 1.3 ppm (dc, 7, C-11 methyl).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.28; H, 7.23; O, 28.56.

Recrystallization of fractions 19–23 from acetone–hexane or ethyl acetate afforded **9b**: mp 243–245°; $[\alpha]^{24}D$ +58.5° (*c* 1.17); no uv absorption; ir 3468 and 1768 cm^{-1}; nmr (first figure refers to pyridine-d_5, second to $CDCl_3$) 3.43, 3.0 (sext) (H-2), 4.85, 4.66 (c, 2p) (H-6 and H-8), 3.73, 3.25 (d) (H-1), 2.05, 1.98 (3p, acetate), 1.72, 1.52 (3p, C-10 methyl), and 1.20 (d), 1.3 ppm (dc, 3p) (C-11 methyl).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80; O, 32.40. Found: C, 60.99; H, 6.74; O, 32.42.

Hydrogenation of Dihydromikanolide.—A solution of 292 mg of dihydromikanolide in 100 ml of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 292 mg of 10% Pd–C. The initially rapid hydrogen uptake amounting to *ca.* 1 molar equiv during the first 0.5 hour was followed by slow uptake of *ca.* 0.7 molar equiv over several hours, after which consumption of hydrogen ceased. The product was worked up in the usual way: yield of **3**, 142 mg; yield of **10**, 28 mg; and yield of **9b**, 74 mg.

Acetylation of 80 mg of **9b** with acetic anhydride–pyridine and purification of the crude product by chromatography over 2 g of silicic acid (solvent and eluent chloroform) followed by recrystallization from ethyl acetate–petroleum ether afforded 58 mg of **9a**: mp 218–220°; $[\alpha]^{24}D$ +61.0° (*c* 1.0); nmr signals (pyridine-d_5) 4.88 (c, H-6 and H-8), 4.39 (sext, H-2), 3.7 (d, 3.5, H-1), 1.98 (acetate), 1.72 (C-10 methyl), and 1.20 ppm (d, 7, C-11 methyl).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.64; H, 6.55; O, 33.10. Found: C, 60.46; H, 6.51; O, 32.94.

Rearrangement of Mikanolide to 4a and 4b.—A mixture of 0.4 g of mikanolide, 10 ml of acetic anhydride, and 0.2 g of *p*-toluenesulfonic acid was refluxed for 1 hr, taken to dryness *in vacuo*, diluted with ice water, and extracted with chloroform. Chromatography of the residue from the chloroform extract over 27 g of silicic acid (solvent and eluent chloroform) followed by recrystallization of the pure fractions from acetone–isopropyl ether afforded 256 mg of **4a**: mp 258–260°; $[\alpha]^{24}D$ −15.0° (*c* 0.94, $CHCl_3$); λ_{max} 206 nm (ϵ 19,600); ir bands at 1778, 1752, 1742, 1674, and 1661 cm^{-1}; nmr signals (pyridine-d_5) 7.8 (t, 1.5, H-5), 6.29 (d) and 5.82 (d) (3.2, exocyclic methylene), 5.72 (m, H-1 and H-5), 5.48 (dbr, 10, H-9), 5.23 (t, 10, H-8), 4.17 (m, H-3), 3.75 (t, 5, H-2), 1.96 (acetate), and 1.80 ppm (br, C-10 methyl). The same product was obtained in low yield on refluxing mikanolide with acetic acid.

Anal. Calcd for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85; O, 33.70. Found: C, 61.53; H, 4.71; O, 33.93.

Hydrolysis of 106 mg of 4a with 6 ml of a solution of 1.3 ml of concentrated HCl and 11 ml of methanol for 1 hr on the steam bath, evaporation to dryness repeatedly with methanol to remove hydrogen chloride vapors, and recrystallization of the residue from acetone–hexane afforded 82 mg of **4b**: mp 260–262°; $[\alpha]^{24}D$ +35.34° (*c* 0.96); λ_{max} 204 nm (ϵ 18,200); ir bands at 3560, 3460, 1760 (double intensity), 1670, and 1655 cm^{-1}; nmr signals (pyridine-d_5) at 7.6 (t, 1.5, H-5), 6.32 (d) and 5.82 (d) (3.2, exocyclic methylene), 5.77 (m, H-6), 5.37 (dbr, 10, H-9), 5.28 (t, 10, H-8), 4.88 (d, 5, H-1), 4.12 (m, H-3), 3.78 (t, 5, H-2), 3.5 (c, H-7), and 1.80 ppm (br, C-10 methyl).

Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86; O, 33.07. Found: C, 62.38; H, 4.93; O, 32.72.

This substance was obtained more directly by hydrolysis of 120 mg of mikanolide with methanolic HCl in the manner described above. The yield was 78 mg. Reacetylation of 40 mg of **4b** with pyridine–acetic anhyride in the usual manner afforded 32 mg of **4a**.

Rearrangement of Dihydromikanolide to 5a and 5b.—Refluxing 300 mg of dihydromikanolide with acetic anhydride–*p*-toluenesulfonic acid in the manner described in the previous section and recrystallization of the product from acetone–isopropyl ether gave 186 mg of **5a**: mp 250–252°; λ_{max} 202 nm (ϵ 8600); ir bands at 1778, 1742 (double intensity), and 1660 cm^{-1}; nmr signals (pyridine-d_5) at 7.8 (t, 1.5, H-5), 5.65 (d, 5, H-1), 5.6 (m, H-6), 5.35 (dbr, 10, H-9), 5.2 (t, 10, H-8), 4.17 (m, H-3), 3.73 (t, 3, H-2), 2.75 (c, H-7 and H-11), 2.0 (acetate), 1.80 (br, C-10 methyl), and 1.35 ppm (d, C-11 methyl). The same product was obtained in lower yield by refluxing dihydromikanolide with acetic acid.

(66) The following points emerge from a comparison of the nmr spectra of **1** and **4a**. (1) While vicinal coupling exists between H-6 and H-7 in **1**, it is apparently absent in **4a**. (2) Whereas **4a** displays allylic coupling between H-3 and H-5 (J = 1.5 Hz), **1** does not. (3) Both **1** and **4a** exhibit homoallylic coupling between H-3 and H-6.

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43; O, 33.50. Found: C, 60.93; H, 5.78; O, 33.32.

Hydrolysis of 140 mg of **5a** with methanolic HCl as described for **4a** afforded 116 mg of **5b**: mp 281–283° after recrystallization from acetone–hexane; $[\alpha]^{24}D$ +18.7° (c 1.15); λ_{max} 203 nm (ε 8500); ir bands at 3520, 1782, 1750, and 1660 cm^{-1}; nmr signals (pyridine-d_5), at 7.65 (t, 1.5, H-5), 5.5 (m, H-6), 5.2 (H-8 and H-9), 4.85 (d, 5, H-1), 4.1 (m, H-3), 3.73 (t, 3, H-2), 2.7 (H-7 and H-11), 2.0 (br, C-10 methyl), and 1.33 ppm (d, 6.5, C-11 methyl). The same compound was obtained in 86-mg yield by refluxing 120 mg of dihydromikanolide with methanolic HCl.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52; O, 32.85. Found: C, 61.73; H, 5.64; O, 32.68.

Catalytic hydrogenation of 318 mg of **4a** in 13 ml of ethyl acetate with Pd-$CaCO_3$ yielded 230 mg of **5a**.

Rearrangement of Tetrahydromikanolide to 6.—A mixture of 200 mg of tetrahydromikanolide, 100 mg of *p*-toluenesulfonic acid, and 6 ml of acetic anhydride was refluxed for 1 hr. Work-up in the usual manner followed by recrystallization from ethyl acetate afforded 98 mg of **6**: mp 265–267°; $[\alpha]^{24}D$ −67.4° (*c* 0.85); ir bands at 1770 (double intensity) and 1732 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; O, 33.30. Found: C, 61.11; H, 6.29; O, 32.72.

Oxidation of 4b.—A mixture of 100 mg of **4b** and 1.2 g of active maganese dioxide[67] was refluxed in 60 ml of dry benzene for 28 hr, filtered, and evaporated. The crystalline residue (tlc showed a single spot and 10% of starting material) was recrystallized three times from acetone–isopropyl ether and afforded 39 mg of **7** which did not melt below 320° and decomposed at 330–335°. It had $[\alpha]^{24}D$ −120° (*c*, 0.5); λ_{max} 206 and 318 nm (ε 17,350 and 200), λ_{max} (after subtraction of mikanolide chromophore) 250 and 318 nm (ε 3100 and 200); ir bands at 1778, 1768, 1700, 1675 (weak), and 1645 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20; O, 33.30. Found: C, 62.63; H, 4.32; O, 32.99.

Oxidation of 5b.—Oxidation of 100 mg of **5b** with 1.0 g of active manganese dioxide in 50 ml of chloroform at room temperature for 36 hr and work-up in the manner described in the previous paragraph gave, after two recrystallizations from acetone, 56 mg of **8**: mp 315–318° dec; $[\alpha]^{24}D$ −92.9° (*c* 0.55); λ_{max} 206 and 318 nm (ε 9670 and 150), λ_{max} (after subtracting the chromophore of dihydromikanolide) 255 qnd 318 nm (ε 1200 and 150); ir bands at 1780, 1747, 1698, 1660, and 1635 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86; O, 33.07. Found: C, 62.23; H, 4.83; O, 32.85.

Oxidation of 9a.—To an ice-cold stirred solution of 125 mg of **9a** in 10 ml of reagent grade acetone was added dropwise 0.4 ml of Jones reagent. The reaction mixture was stirred at ice temperature for 10 min and at room temperature for 20 min. Excess oxidant was destroyed by addition of a few drops of methanol. The mixture was diluted with ice water and the precipitate was filtered, washed, dried, and recrystallized from acetone. This afforded 68 mg of ketone **11**: mp 305–30°; λ_{max} 203 nm (ε 1275) and 285 nm (ε 68); ir bands at 1780, 1770, and 1715 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17; O, 32.62. Found: C, 60.87; H, 6.24; O, 32.65.

An attempt to reduce **11** with chromous chloride in acetone–acetic acid solution resulted in recovery of starting material.

Hydrogenation of Scandenolide. A.—Hydrogenation of 100 mg of **12** with Pd-$CaCO_3$ catalyst in ethyl acetate in the manner described for mikanolide afforded after recrystallization 73 mg of **13** identical in all respects with material isolated from the plant.

B.—Hydrogenation of 130 mg of **12** with 80 mg of 10% Pd–C in 20 ml of ethyl acetate stopped after consumption of approximately 2 molar equiv of hydrogen (6 hr). Work-up in the usual manner afforded 128 mg of tetrahydroscandenolide (one spot on tlc) which was recrystallized from acetone and had mp 231–233°; $[\alpha]^{24}D$ +50.4° (*c* 0.64, dioxane); nmr peaks (DMSO-d_6) at 2.12 (acetate), 1.28 (C-10 methyl), and 1.16 ppm (C-11 methyl). The other signals could not be distinguished clearly.

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.64; H, 6.55; O, 33.10. Found: C, 60.52; H, 6.62; O, 33.28.

Rearrangement of Scandenolide to 14a.—A solution of 120 mg of scandenolide in 6 ml of methanolic hydrochloric acid (prepared from 5.4 ml of methanol and 0.6 ml of HCl) was refluxed for 1 hr and taken to dryness repeatedly after addition of methanol to remove HCl. The solid residue (single spot on tlc) was recrystallized from acetone and afforded 86 mg of the diol **14a**: mp 312–315°; ir bands (Nujol) at 3500, 1742 (double intensity), 1670, and 1652 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.65; H, 5.48; O, 32.88. Found: C, 61.82; H, 5.45; O, 32.92.

Acetylation of 100 mg of **14a** with 2 ml of pyridine and 2 ml of acetic anhydride at 80° for 2 hr yielded, after recrystallization from ethyl acetate–petroleum ether, colorless needles of the diacetate **14b**, mp 204–206°.

Anal. Calcd for $C_{19}H_{20}O_8$: C, 60.64; H, 5.36; O, 34.01. Found: C, 60.71; H, 5.34; O, 34.08.

Preparation of Deoxymikanolide from Isabelin.—A solution of 95 mg of isabelin (**16**)[30] in 4 ml of chloroform was left with 62 mg of *m*-chloroperbenzoic acid in 2 ml of chloroform at room temperature for 2.5 hr. After the mixture was washed with saturated sodium bicarbonate solution and water, the organic layer was evaporated at reduced pressure to give 123 mg of solid which on recrystallization from acetone–hexane gave deoxymikanolide, mp 198–199.5°, identical in all respects with material isolated from the plant.

Tetrahydromiscandenin (18).—A solution of 100 mg of miscandenin in 25 ml of ethyl acetate was reduced at atmospheric pressure in the presence of 10% Pd–C. Two molar equivalents of hydrogen were rapidly absorbed during the first 25 min, after which hydrogen uptake ceased. After the usual work-up the solid residue (single spot on tlc) was recrystallized from ethyl acetate–petroleum ether. The product, 68 mg, had mp 188–190°, λ_{max} 248 nm (ε 8000), ir bands (Nujol) at 1755 and 1668 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52; O, 28.75. Found: C, 64.35; H, 6.74; O, 29.04.

NOE Experiments.—These were carried out on a 90-Mc Bruker nmr spectrometer on degassed samples in $CHCl_3$–DMSO solution.

4a.—Reference: irradiation 240 Hz upfield from $CHCl_3$ signal, integrated intensity of C-10 methyl 95 ± 1 (average of three integrations), acetate 104 ± 2 (3, reference), ratio 0.91. Irradiation 257.4 Hz upfield (H-9), intergrated intensity of C-10 methyl 95 ± 1 (3), acetate 94 ± 2 (3, reference), ratio 1.01, hence 11% enhancement. Reference: irradiation 49.9 Hz from $CHCl_3$, integrated intensities H-6 73, H-8 84, H-1 + H-9 149, H-13a 69, H-13b 64 (average of five integrations). Irradiation 42.3 Hz upfield (H-5), integrated intensities (average of five integrations), H-6 61 (20% enhancement), H-8 67 (26%), H-1 + H-9 140 (13%), H-13a 66 (4%), H-13b 68 (−6%). H-2 and H-3 were also irradiated and an attempt was made to observe NOE's on H-1, H-5, H-6, H-8, H-9, and H-13, but all enhancements were less than 10%.

12.—Reference: irradiation 36.5 Hz downfield from $CHCl_3$ signal, integrated intensities (average of four integrations) H-1 74, H-3 + H-6 97, H-8 61, H-13 98. Irradiation 27.2 Hz downfield (H-5), integrated intensities (average of four), H-1 71 (−4%), H-3 + H-6 98 (1%), H-8 63 (5%), H-13 96 (−2%). Reference: irradiation 369.6 Hz upfield, integrated intensities (average of five) H-13 130, C-10 methyl 245. Irradiation 493.5 Hz upfield (H-1), integrated intensites (five), H-5 56, H-13 142. Irradiation 402.8 Hz upfield (H-8), integrated intensities (five), H-5 65 (16% enhancement), H-13 148 (4%).

14b.—Reference: irradiation 530 Hz downfield from TMS signal, integrated intensities (six), H-8 37, H-9 41. Irradiation 504.5 Hz downfield (H-1), integrated intensities (six) H-8 50 (34% enhancement), H-9 38 (−8%). Reference: irradiation 675.8 Hz downfield from TMS signal, integrated intensities (four), H-1, H-3 and H-13b 111, H-2 34, H-6 37, H-9 38. Irradiation 661.9 Hz downfield (H-5), integrated intensities (four), H-1, H-3 and H-13b 117 (6% total enhancement, 12% if limited to H-1 and H-3), H-2 37 (9%), H-6 39 (5%), H-7 31 (3%), H-8 37 (6%), H-9 38 (3%). Reference: irradiation 540.2 Hz downfield from TMS, integrated intensities (five), C-1 acetate 54, C-3 acetate 75, C-15 methyl 51. Irradiation 468.2 Hz downfield from TMS, integrated intensities (five), C-1 acetate 70 (11% enhancement), C-3 acetate 72 (−4%), C-15 methyl 56 (10%).

Isabelin (16).—Reference: irradiation 369.6 Hz downfield from TMS, integrated intensities (five), H-13 130, C-10 methyl 245. Irradiation 439.5 Hz fownfield (H-1), integrated intensities (five), H-13 141 (8.5% enhancement), C-10 methyl 247 (0.8%). Reference: irradiation 340.4 Hz downfield from TMS, integrated intensities (five), H-5 56, H-13 142. Irradiation 402.8 Hz down-

(67) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

field, integrated intensities (five), H-5 65 (16% enhancement), H-13 148 (4%).

Registry No.—**1**, 23753-56-2; **2**, 23758-04-5; **3**, 17940-97-5; **4a**, 23758-06-7; **4b**, 23758-07-8; **5a**, 23758-08-9; **5b**, 23758-09-0; **6**, 23758-10-3; **7**, 23758-11-4; **8**, 23758-12-5; **9a**, 23829-41-6; **9b**, 23829-42-7; **10**, 23758-13-6; **11**, 23758-14-7; **12**, 23758-16-9; **13**, 23758-17-0; **14a**, 23758-18-1; **14b**, 23758-19-2; **15**, 23753-57-3; **17**, 23758-20-5; **18**, 23758-21-6; tetrahydroscandenolide, 23758-15-8.

Studies in the Ganglioside Series. IV. Preparation of 2,3-Di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose and Its Utilization in the Synthesis of Oligosaccharides[1]

DAVID SHAPIRO, Y. RABINSOHN, A. J. ACHER, AND A. DIVER-HABER

Department of Chemistry, The Weizmann Institute of Science, Rehovoth, Israel

Received October 14, 1969

2,3-Di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (V) has been prepared by cyclization of phenyl 2,3,6-tri-*O*-acetyl-4-*O*-*t*-butyl-β-D-glucopyranoside (III) and removal from IV of the protecting *t*-butyl group by trifluoroacetic acid. Compound III was obtained by acid-catalyzed addition of 2-methylpropene to phenyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (II). The use of V as aglycon in the Koenigs–Knorr reaction will permit the synthesis of oligosaccharides containing a glycosidic linkage at C-4 of glucose. This is demonstrated by the synthesis of lactose and of the aminosaccharide 4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-glucopyranose (XIII).

The carbohydrate chain of the gangliosides comprises a tetrasaccharide in which galactose is attached to glucose by a 1 → 4 linkage.[2,3] It is well known that the C-4 hydroxyl group in the *C1* conformation of glucopyranose, although equatorially oriented, exhibits rather low reactivity. Richardson[4,5] has shown that the differential reactivity of the secondary hydroxyls in glucopyranosides is not solely dependent on the conformation. The 4-OH is also sterically hindered by adjacent substituents, especially by the 5-acyloxymethyl group. Because of these features of the glucose molecule, the synthesis of disaccharides of the lactose type has posed a problem ever since. Curtis and Jones,[6] using the open chain form of glucose, condensed 2,3,5,6-di-*O*-isopropylidene-D-glucose diethyl acetal with acetobromogalactose and obtained a mixture of mono- and disaccharides from which lactose could be separated by charcoal and paper chromatography.

During the course of our studies[7–9] on the gangliosides it became imperative to devise a suitably substituted glucose derivative in which the free C-4 hydroxyl would have enhanced reactivity. Earlier investigators recognized the synthetic value of 1,6-anhydro-hexopyranoses. In 1933 Freudenberg[10] coupled unsubstituted 1,6-anhydro-β-D-glucopyranose with acetobromoglucose and obtained a mixture from which cellobiose could be isolated in a 2% yield. Hudson[11] first synthesized lactose *via* its epimer (4-*O*-galactopyranosyl-β-D-mannopyranose), employing 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose as the aglycon. The presence in the mannose molecule of two neighboring *cis* hydroxyls offers a convenient means for selective substitution by the isopropylidene group. However, since the glucose molecule lacks this possibility, we explored a different route for the preparation of a 1,6-anhydro derivative in which the C-4 hydroxyl is free for reaction.

1,6-Anhydro-β-D-glucopyranose exists in the *1C* conformation. Although all of the hydroxyl groups are axially oriented, steric considerations indicate that those in positions 2 and 4 will react preferentially. The C-3 hydroxyl is the most hindered one, owing to the hemiacetal and anhydro rings, and to the C–C linkage at C-5.[12] Indeed, esterification with benzoyl chloride, tosyl chloride, or benzyl chloroformate was found to give high yields of the 2,4-diacyl derivatives,[12,13] and benzylation, even under drastic conditions, likewise produced the 2,4-dibenzyl derivative in appreciable amounts.[14]

We now report the synthesis of 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (V) (Scheme I). The route adapted involves blocking of the C-4 hydroxyl by the *t*-butyl group. This group has been used in peptide synthesis for the protection of hydroxyamino acids and is conveniently introduced by acid-catalyzed addition of 2-methylpropene.[15–17] Except for one case, in which a similar reaction was carried out by a different method and under drastic conditions,[18] no attempt has been made to employ this olefin in carbohydrate chemistry. The acid-catalyzed reaction of *t*-butyl alcohol with glucose was reported to give preferentially the 6-*O*-derivative,[19] whereas the use of *t*-butyl bromide met with little success.[20]

(1) Supported by U. S. National Institutes of Health, PL 480, Agreement No. 425115.

(2) L. Svennerholm, *J. Lipid Res.*, **5**, 145 (1964).

(3) H. Wiegandt, *Angew. Chem. Int. Ed. Engl.*, **7**, 87 (1968).

(4) A. C. Richardson, *Chem. Commun.*, 104 (1965).

(5) J. M. Williams and A. C. Richardson, *Tetrahedron*, **23**, 1369 (1967).

(6) E. J. C. Curtis and J. K. Jones, *Can. J. Chem.*, **37**, 358 (1959).

(7) D. Shapiro, A. J. Acher, and E. S. Rachaman, *J. Org. Chem.*, **32**, 3767 (1967).

(8) A. J. Acher and D. Shapiro, *ibid.*, **34**, 2652 (1969).

(9) D. Shapiro and A. J. Acher, *ibid.*, **35**, 229 (1970).

(10) K. Freundenberg and W. Nagai, *Chem. Ber.*, **66**, 27 (1933).

(11) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1852 (1942).

(12) M. Černý, V. Gut, and J. Pacák, *Collect. Czech. Chem. Commun.*, **26**, 2542 (1961).

(13) R. W. Jeanloz, A. M. C. Rapin, and S. Hakomori, *J. Org. Chem.*, **26**, 3939 (1961).

(14) G. Zemplén, Z. Csürös, and S. Angyal, *Chem. Ber.*, **70**, 1848 (1937).

(15) H. C. Beyerman and J. S. Bontekoe, *Proc. Chem. Soc.*, 249 (1961).

(16) F. M. Callahan, G. W. Anderson, R. Paul, and J. E. Zimmerman, *J. Amer. Chem. Soc.*, **85**, 201 (1963).

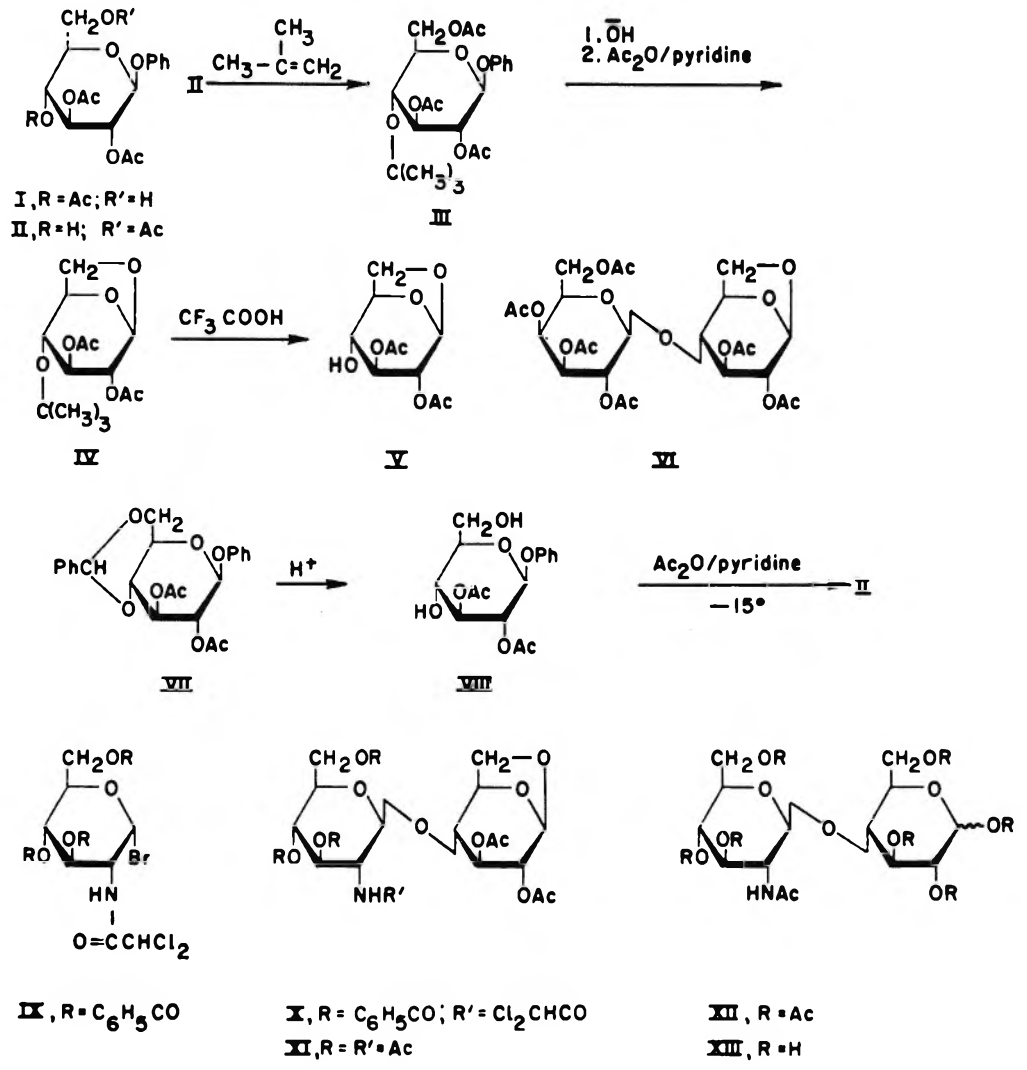
(17) E. Wuensch and J. Jentsch, *Chem. Ber.*, **97**, 2490 (1964).

(18) V. Prey and F. Grundschober, *ibid.*, **95**, 1845 (1962).

(19) A. N. de Beider, E. J. Bourne, and H. Weigel, *Carbohyd. Res.*, **3**, 1 (1966).

(20) J. Kenner and G. N. Richards, *J. Chem. Soc.*, 3019 (1957).

Scheme I



The reaction of II[21,22] with 2-methylpropene in the presence of a catalytic amount of concentrated sulfuric acid proceeded smoothly and afforded phenyl 2,3,6-tri-*O*-acetyl-4-*O*-*t*-butyl-β-D-glucopyranoside (III) in a 72% yield. Ring closure with potassium hydroxide followed by acetylation of the crude reaction product gave 64% 2,3-di-*O*-acetyl-1,6-anhydro-4-*O*-*t*-butyl-β-D-glucopyranose (IV). Removal of the *t*-butyl group with trifluoroacetic acid proceeded smoothly and gave an almost quantitative yield of 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (V).

While this investigation was in progress, another method for the preparation of V was reported which involves protection of the C-4 hydroxyl by the benzyl group. Seib,[22] investigating the acid-catalyzed polymerization of 1,6-anhydro-β-D-glucopyranose, prepared the 4-*O*-benzyl derivative of V *via* cyclization of phenyl-2,3,6-tri-*O*-acetyl-4-*O*-benzyl-β-D-glucopyranoside. The latter compound was prepared by benzylation of I with benzyl bromide in the presence of silver oxide, a reaction which took place with simultaneous 4 → 6 acetyl migration.[21] In our hands this reaction proceeded less satisfactorily. Considerably lower yields were obtained which probably resulted from partial deacetylation, as indicated by tlc.

The key intermediate II was initially prepared by alkaline rearrangement of I according to Helferich.[21] This method proved to be unsatisfactory, the yields being low and inconsistent. An alternative procedure was, therefore, considered. We found that II could be prepared more advantageously *via* the benzylidene derivative VII. Acetylation of VIII with 1 equiv of acetic anhydride under controlled conditions afforded 55% II, after chromatographic separation from the tetraacetate and a small amount of unchanged diacetate.

To simplify the preparation of V, an attempt was made to achieve the desired substitution by direct acetylation of 1,6-anhydro-β-D-glucopyranose. Treatment of the anhydro sugar with 2.5 equiv of acetic anhydride resulted in the formation of nearly equal amounts of the three diesters, in addition to the triacetate (25%). The desired diacetate V was obtained in 13% yield. The structures of the other two diacetates were determined by methylation with diazomethane-boron trifluoroetherate.[23] 2,4-Di-*O*-acetyl-1,6-anhydro-3-*O*-methyl-β-D-glucopyranose gave on deacetylation 1,6-anhydro-3-*O*-methyl-β-D-glucopyranose,[24] whereas 3,4-di-*O*-acetyl-1,6-anhydro-2-*O*-methyl-β-D-

(21) B. Helferich and F. Strauss, *J. Prakt. Chem.*, **142**, 13 (1935).
(22) P. A. Seib, *Carbohyd. Res.*, **8**, 101 (1968).
(23) I. O. Mastronardi, S. M. Flematti, J. O. Deferrari, and E. G. Gros, *ibid.*, **3**, 177 (1966).
(24) R. E. Reeves, *J. Amer. Chem. Soc.*, **71**, 2116 (1949).

glucopyranose led, after ring opening by acetolysis, to 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-α-D-glucopyranose.[23]

In a preliminary communication[25] we have shown that the Koenigs–Knorr reaction of V with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide gave a 49% yield of the hexaacetate VI.[26] Since VI has been earlier converted into lactose in high yield,[26] this route constitutes a new and convenient microscale synthesis of the disaccharide.

The significance of 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose as aglycon is further demonstrated by the synthesis of an amino sugar disaccharde as a model compound. 4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-D-glucose (XIII) was synthesized by condensing V with 3,4,6-tri-*O*-benzoyl-2-deoxy-2-dichloroacetamido-α-D-glucopyranosyl bromide (IX), following the procedure described in previous papers of this series.[7–9] The resulting product X was converted into the N-acetyl derivative XI by alkaline hydrolysis and successive acetylation. Acetolysis of XI led, *via* XII, to the disaccharde XIII. This disaccharide has been obtained recently through enzymatic transfer of N-acetylglucosamine to glucose.[27] Its (N-unsubstituted) α isomer was found in hydrolysates of heparin.[28] It is noteworthy that the yield of the Koenigs–Knorr reaction product of V with IX was considerably lower than that of VI. This observation must be attributed to a steric hindrance due to the bulky molecule of the otherwise highly reactive bromide.

The present results provide a method for the attachment of the disaccharide 4-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactopyranose, recently synthesized in our laboratory,[9] to position 4 of glucose. Such a combination will lead to the trisaccharide inherent in the ganglioside of patients with Tay-Sachs disease[2,3] which presents one of the major objectives of our synthetic studies in this series.

Experimental Section[29]

Phenyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (VII).—A solution of phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside[30] (8 g) in pyridine (30 ml) was treated in the cold with acetic anhydride (10 ml) and left overnight at room temperature. The solution was poured into ice–water; the precipitate was filtered, washed thoroughly with water, and dried, Crystallization from a mixture of chloroform–ethanol (1:10) gave the pure compound (8.6 g, 86%), mp 228–229°, $[\alpha]^{23}D$ −64.2° (*c* 1).

Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.56; H, 5.53.

Phenyl 2,3-Di-*O*-acetyl-β-D-glucopyranoside (VIII).—A solution of VII (20 g) in 60% aqueous acetic acid (350 ml) was kept at 80° for 45 min. The cooled solution was extracted several times with hexane and concentrated *in vacuo*. Tlc [benzene–ethyl acetate (1:2)] of the crystalline residue showed no starting material and only a faint spot of a compound moving more slowly than the major product. Crystallization from a mixture of acetone–ether–hexane gave 13.4 g (84%) of VIII, mp 142–143°, $[\alpha]^{23}D$ −45° (*c* 2).

Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92. Found: C, 56.69; H, 5.90.

Phenyl 2,3,6-Tri-*O*-acetyl-β-D-glucopyranoside (II).—A solution of the diacetyl derivative VIII (6.8 g, 20 mmol) in pyridine (50 ml) was cooled to −20°, and acetic anhydride (2.0 ml) was added in one portion. After 48 hr at −15°, the solution was concentrated *in vacuo*, and the reagents were coevaporated several times with toluene. Chromatography of the residue on silica gel with ethyl acetate–methylene chloride (8:92) gave 2.1 g (24%) of the fully acetylated glycoside. A mixture of the same solvents (15:85) eluted II (4.18 g, 55%) as a homogeneous product. Ethyl acetate–methylene chloride (3:1) removed unreacted material (0.60 g, 9%). The triacetate melted at 134–135° (lit. 130°[21] and 134.5–135.5°[22]); $[\alpha]^{23}D$ −54° (*c* 3.1).

Phenyl 2,3,6-Tri-*O*-acetyl-4-*O*-*t*-butyl-β-b-glucopyranoside (III).—To dry methylene chloride (76 ml) containing concentrated sulfuric acid (0.30 ml) was added at −5° isobutene (23 ml). After the mixture stirred for a few minutes at this temperature, phenyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (3.82 g) was added in one portion. The solution was kept in a well stoppered flask at −2–0° for 1 hr and then overnight at room temperature. The cooled solution was shaken carefully with ice-cold 2.5% sodium hydrogen carbonate, washed with cold water to neutrality, and dried over sodium sulfate. Tlc [benzene–ethyl acetate (3:1)] showed a faint spot of unreacted material and a major faster moving spot. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a silica gel column. The fraction eluted with methylene chloride–ethyl acetate (9:1) yielded 3.17 g (72%) of a homogeneous product. It was crystallized from ethyl acetate–hexane and had mp 139–140°, $[\alpha]^{22}D$ −44.7° (c 2). The nmr spectrum showed signals at τ 2.55–3.15 (five aromatic protons), 7.92, 7.95, and 7.96 (nine acetyl protons), and 8.80 (nine *t*-butyl protons).

Anal. Calcd for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.50; H, 6.63.

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*-*t*-butyl-β-D-glucopyranose (IV).—A solution of III (3.0 g) in 2-methoxyethanol (15 ml) and 15% aqueous potassium hydroxide (35 ml) was refluxed in an oil bath at 100–110° for 24 hr. The cooled solution was neutralized carefully with 2 *N* sulfuric acid and concentrated to dryness under reduced pressure. The remainder was extracted three–four times with boiling absolute alcohol, and the combined extracts were evaporated. The solid residue, dried over phosphorus pentoxide, was dissolved in hot pyridine (10 ml), and acetic anhydride (8 ml) was added to the filtrate. After standing at room temperature overnight, the reaction mixture was concentrated to dryness *in vacuo*, and the last traces of the acylating agent were removed by distilling with several portions of toluene. The residue was passed through a silical gel column. Methylene chloride–ethyl acetate (88:12) eluted a homogeneous product (1.32 g, 64%). After crystallization from ether–hexane, it melted at 140–141°, $[\alpha]^{22}D$ −48.8° (c 2.2), tlc [benzene–ethyl acetate (1:1)] R_f 0.72. The nmr spectrum showed signals at τ 7.85, 7.90 (six acetyl protons) and 8.75 (nine *t*-butyl protons).

Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34. Found: C, 55.60; H, 7.46.

2,3-Di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (V).—To the *t*-butyl derivative IV (800 mg) dissolved in methylene chloride (10 ml) was added trifluoroacetic acid containing 1% water (1 ml). After standing for 15 min at room temperature, the solution was concentrated *in vacuo* and the remainder was treated with distilling toluene at room temperature. Tlc [benzene–ethyl acetate (1:1)] showed no starting material. The residual syrup (850 mg) refused to crystallize. It was chromatographed on silica gel (40 g) and eluted with ethyl acetate–methylene chloride (2:1). The oily product weighed 780 mg (92%), $[\alpha]^{22}D$ −44.6° (*c* 3.5) (lit.[22] $[\alpha]^{22}D$ −45°), tlc [benzene–ethyl acetate (1:1)] R_f 0.28.

Anal. Calcd for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73. Found: C, 48.72; H, 5.70.

Partial Acetylation of 1,6-Anhydro-β-D-glucopyranose.—The anhydro sugar (laevoglucosan,[31] 6.48 g, 0.040 mol) dissolved in pyridine (60 ml) was treated overnight at room temperature with acetic anhydride (9.5 ml, 0.100 mol). After the solution was warmed at 50° for 1 hr, the excess of acylating reagent was removed *in vacuo* by coevaporating several times with toluene. Tlc [benzene–ethyl acetate (1:1)] showed, in addition to some

(25) D. Shapiro, Y. Rabinsohn, and A. Diver-Haber, *Biochem. Biophys. Res. Commun.*, **37**, 28 (1969).

(26) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, **65**, 1848 (1943).

(27) J. A. Rupley and V. Gates, *Proc. Nat. Acad. Sci. U. S.*, **57**, 496 (1967).

(28) M. L. Wolfrom, J. R. Vereellotti, and D. Horton, *J. Org. Chem.*, **28**, 279 (1963).

(29) Details concerning the specification of chemicals and the type of apparatus for physical measurements used in this investigation are given in paper I of this series. Optical rotations were determined in chloroform, unless stated otherwise.

(30) C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, **10**, 184 (1945).

(31) G. H. Coleman, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, p 397.

unreacted material, the presence of triacetyllaevoglucosan (TAL) and of a monoacetyl derivative. Three further spots moving close to each other were assumed to be the three diacetates (R_f: a, 0.44; b, 0.38; c, 0.28). The product was chromatographed on a silica gel column from which the triacetate (2.9 g, 25%) was removed by methylene chloride–ethyl acetate (85:15). A 1:1 mixture of these solvents eluted pure a (140 mg), pure c (190 mg), and mixtures of the isomers totaling 5.25 g (53%). Rechromatography on silical gel with methylene chloride–ethyl acetate (1:1) and on silica gel G with ethyl acetate yielded the following homogeneous compounds.

2,4-Di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (a).—Compound a (1.43 g, 15%) was crystallized from ether, mp 132–133°, $[\alpha]^{22}D$ −70.2° (*c* 3), R_{TAL} 0.65.

Anal. Calcd for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73. Found: C, 49.02; H, 5.55.

3,4-Di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (b).—Compound b (0.980 g, 10%) was crystallized from ethyl acetate–hexane, mp 96–97°, $[\alpha]^{22}D$ −79.5° (*c* 2.2), R_{TAL} 0.57.

Anal. Calcd for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73. Found: C, 48.98; H, 5.61.

Compound c.—This oily product (1.25 g, 13%, R_{TAL} 0.41) was identical in every respect with V.

2,4-Di-*O*-acetyl-1,6-anhydro-3-*O*-methyl-β-D-glucopyranose.—Methylation of compound a with diazomethane–boron trifluoroetherate was effected by the procedure of Mastronardi, *et al.*[23] Methylene chloride–ethyl acetate (3:1) eluted 53% oil which could not be induced to crystallize, $[\alpha]^{22}D$ −57.7° (*c* 1.8), tlc [benzene–ethyl acetate (1:1)] R_f 0.67. The nmr spectrum showed signals at τ 6.52 (three methoxyl protons) and 7.86 and 7.88 (six acetyl protons).

Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.30; H, 6.09.

Deacetylation of the preceding compound in absolute methanol containing a catalytic amount of sodium methylate gave, after crystallization from acetone–pentane, 70% 1,6-anhydro-3-*O*-methyl-β-D-glucopyranose, mp 65–67°, $[\alpha]^{22}D$ −64° (*c* 2.1, acetone) (lit.[24] mp 65–66°, $[\alpha]^{20}D$ −64.8°).

3,4-Di-*O*-acetyl-1,6-anhydro-2-*O*-methyl-β-D-glucopyranose.—Methylation of compound b gave on chromatography (as described above) the pure diacetate (76%) as a waxy solid. After crystallization from ethyl acetate–hexane, the product melted at 45–46°, $[\alpha]^{22}D$ −86.8° (*c* 2.6), tlc [benzene–ethyl acetate (1:1)] R_f 0.58, nmr τ 6.48 (three methoxyl protons) and 7.85 and 7.90 (six acetyl protons).

Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.51; H, 6.15.

Ring opening in the preceding compound was effected by the method of Hudson.[11] The anhydro derivative (150 mg) was treated with a 7:3 mixture (8 ml) of acetic anhydride–acetic acid and concentrated sulfuric acid (0.1 ml) for 4 hr at 50°. Anhydrous sodium acetate (0.5 g) was added, and the mixture was concentrated *in vacuo*. The residue was extracted with chloroform; the extract was washed with water, dried, and evaporated. Crystallization from ethanol gave 155 mg (73%) of 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-α-D-glucopyranose, mp 105–107°, $[\alpha]^{22}D$ +111° (*c* 1.6) (lit.[23] mp 106–108°, $[\alpha]^{20}D$ + 109°).

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*-(3,4,6-tri-*O*-benzoyl-2-deoxy-2-dichloroacetamido-β-D-glucopyranosyl)-β-D-glucopyranose (**X**).—To a solution of 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (V, 0.6 g) in dry benzene–nitromethane (2:1, 30 ml) were added mercuric cyanide (1 g) and the bromide IX[7] (3 g), and the reaction was allowed to proceed with stirring at 40° for 96 hr. The cooled solution was poured into a mixture of ice–water (100 ml) and methylene chloride (200 ml). The organic layer was washed four times with cold water, dried over sodium sulfate, and evaporated *in vacuo* to constant weight. The glycoside (200 mg, 10%) was eluted from a silica gel column with methylene chloride–ethyl acetate (92:8). After crystallization from isopropyl alcohol containing a few drops of ether, it melted at 112°, $[\alpha]^{23}D$ −38° (*c* 1), tlc (ethyl acetate) R_f 1.7. A strong band at 11.2 μ in the ir spectrum indicated the presence of a β-glycoside. The nmr spectrum showed signals at τ 2–2.9 (15 aromatic protons), 4.18 (dichloroacetyl proton), and 7.9 and 8.1 (six acetoxy protons).

Anal. Calcd for $C_{39}H_{37}Cl_2NO_{15}$: C, 56.39; H, 4.49; Cl, 8.54. Found: C, 56.12; H, 4.53; Cl, 8.65.

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranose (**XI**).—To a solution of X (160 mg) in absolute methanol (15 ml) was added at −15° 1 *N* barium methoxide (0.2 ml), and the mixture was allowed to stand in the refrigerator for 4 hr at 3–5°. The methanol was evaporated *in vacuo* at room temperature to about 5 ml, and 1 *N* barium methoxide (4 ml) and water (1 ml) were added. The hydrolysis of the dichloroacetyl group was accomplished after 24 hr at room temperature. The solution was neutralized with methanolic hydrogen chloride and evaporated *in vacuo* to dryness, whereupon the moisture was removed by coevaporation with isopropyl alcohol. The residue, dried thoroughly over phosphorus pentoxide, was shaken with pyridine (10 ml) and acetic anhydride (8 ml) overnight at room temperature. After removal of the acylating agents *in vacuo*, the residue was taken up with methylene chloride (100 ml) and water (50 ml), and the solution was washed with three portions of water (50 ml each). The residue resulting from the evaporation of the dried solution was crystallized from acetone–ether and yielded 110 mg (84%) of XI, mp 194–195°, $[\alpha]^{29}D$ −29.3° (*c* 1.1), tlc (ethyl acetate) R_V 0.31 or R_X 0.18.

1,2,3,6-Tetra-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranose (**XII**).—Opening of the 1,6-anhydro ring was effected as described previously. The disaccharide XI (80 mg) was stirred at 40° with a mixture of acetic anhydride (7 ml), acetic acid (3 ml), and concentrated sulfuric acid (0.05 ml). After 3 hr, anhydrous sodium acetate (0.3 g) was added, the solution was concentrated *in vacuo*, and the reagents were coevaporated with toluene to dryness. The residue was taken up with methylene chloride and passed through a silica gel G column (15 g). The product was obtained by elution with ethyl acetate, yield 77 mg (65%). After crystallization from acetone–ether, it melted at 148–151°, $[\alpha]^{29}D$ +24.0° (*c* 0.5), tlc (ethyl acetate) R_V 0.68 or R_{XI} 2.2.

Anal. Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80. Found: C, 49.97; H, 5.77.

4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-D-glucopyranose (**XIII**).—To a solution of the octaacetyl derivative XII (55 mg) in absolute methanol (10 ml) was added at −15° 1 *N* barium methoxide (0.1 ml) and the mixture was allowed to stand for 4 hr in refrigerator (+5°). Neutralization with Dowex 50-X[8] (2 g) followed by evaporation of the filtrate afforded the crude disaccharide. It crystallized from alcohol on adding a few drops of ether to the warm solution. The disaccharide was homogeneous on tlc [benzene–methanol (1:1)], $R_{lactose}$ 0.95, mp 190–195° (with sintering at 175°), $[\alpha]^{27}D$ +30° (*c* 0.7, water). The infrared spectrum showed bands at 3.0 (OH), 6.05 and 6.45 (amide), and 11.2 μ (β-disaccharide).

Anal. Calcd for $C_{14}H_{25}O_{11}N \cdot H_2O$: C, 41.89; H, 6.78. Found: C, 41.83; H, 6.66.

Registry No.—II, 22348-26-1; III, 23740-46-7; IV, 23740-47-8; V, 22331-11-9; VII, 23740-55-8; VIII, 23740-56-9; X, 23740-57-0; XI, 23740-58-1; XII, 23740-59-2; XIII, 23740-60-5; 2,4-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose, 23740-49-0; 3,4-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose, 23740-50-3; 2,4-di-*O*-acetyl-1,6-anhydro-3-*O*-methyl-β-D-glucopyranose, 23740-51-4; 1,6-anhydro-3-*O*-methyl-β-D-glucopyranose, 23740-52-5; 3,4-di-*O*-acetyl-1,6-anhydro-2-*O*-methyl-β-D-glucopyranose, 23740-53-6; 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-α-D-glucopyranose, 14199-55-4.

The Chemistry of Hydrazides. X. The Reduction of Cyclic and Acyclic Hydrazides with Diborane

HENRY FEUER AND FRANK BROWN, JR.

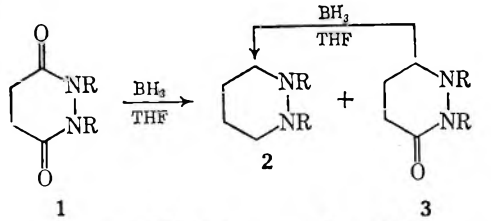
Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received April 29, 1969

1,2-Dialkyl- and 1,2-diarylperhydropyridazine-3,6-diones (**1**) are reduced in high yield to the corresponding 1,2-dialkyl- and 1,2-diarylperhydropyridazines (**2**) on treatment with diborane at 65°. Half-reduced 1,2-dialkylperhydropyridazin-3-ones (**3a–3d**) in addition to the fully reduced compounds **2a–2d** are obtained if reactions are performed at 25°. At higher diborane concentrations (10 equiv) at 65°, compounds **1a–1f** undergo reduction of the carbonyl groups and cleavage of the N–N bond to give the corresponding N,N′-disubstituted 1,4-butanediamines. Temperatures of 129–135° are required to effect reduction of 1,2-diacylhydrazines to the corresponding 1,2-dialkylhydrazines with diborane. On the other hand, the reduction of 1,2-diacyl-1,2-dialkylhydrazines to the corresponding tetraalkylhydrazines requires only a temperature of 65°.

1,2-Disubstituted Perhydropyridazine-3,6-diones.—Recently we presented a new synthesis of 1,2-dialkyl- and 1,2-diarylperhydropyridazine-3,6-diones.[1]

We are now reporting on the reduction of these systems to the corresponding perhydropyridazines (eq 1).



(1)

1

a, R = $(CH_2)_2CH_3$
b, R = $CH(CH_3)_2$
c, R = $CH(CH_3)C_2H_5$
d, R = $(CH_2)_3CH_3$

2

3

e, R = C_6H_5
f, R = $C_6H_4CH_3$-*o*
g, R = H

A survey of the literature revealed that Stetter and Spangenberger[2] reduced 1,2-succinylpyrazolidine and 1,2-succinylpiperidazine to the corresponding cyclic hydrazines in good yield with lithium aluminum hydride. By using the same reagent, E. Hedaya, *et al.*,[3] converted 1,4,6,9-tetraketo[1,2-*a*]pyridazine into perhydropyridazo[1,2-*a*]pyridazine in 10% yield.

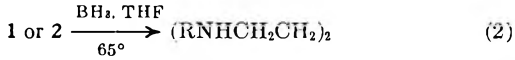
The reduction of 1,2-dialkylperhydropyridazine-3,6-diones **1a–1d** and 1,2-diarylperhydropyridazine-3,6-diones **1e** and **1f** at 65° with a slight excess of borane (5 equiv) in tetrahydrofuran (THF) followed by acidic or basic hydrolysis of the reaction mixture gave the corresponding perhydropyridazines **2a–2f** in high yield.

When reactions were carried out at 25° while employing 5 equiv of borane, the reductions of compounds **1a–1d** were incomplete, because in addition to **2a–2d** there were also obtained the corresponding half-reduced 1,2-dialkylperhydropyridazin-3-ones, **3a–3d** (eq 1).

On the other hand, only compounds **2e** and **2f** were obtained when **1e** and **1f** were treated with borane under similar conditions.

The structure of **3** was indicated by physical data and by the fact that **3b** was readily converted into **2b** in 79% yield on treatment with borane in THF at 25°.

When compounds **1a–1f** were treated with a large excess of borane (10 equiv) in refluxing THF, not only



(2)

4

reduction of both carbonyl groups, but also cleavage of the N–N bond occurred with the formation of N-N′-disubstituted 1,4-diaminobutanes, **4a–4f** (eq 2). It is very likely that the formation of **4** occurred *via* **2**, for **2b** was converted in 65% yield into **4b** under similar reaction conditions.

The reduction of the parent compound perhydropyridazine-3,6-dione (**1g**) with 12 equiv of borane at 65° gave perhydropyridazine (**2g**) in 52% yield as the only compound. No product resulting from the cleavage of the N–N bond was obtained.

1,2-Diacylhydrazines.—The successful reduction of compounds **1** to **3** with diborane prompted us to investigate the reaction with 1,2-diacylhydrazines. If successful, it would provide a convenient one-step preparation of 1,2-dialkylhydrazines.

Hinman[4] reported that 1,2-diacetylhydrazine was reduced with lithium aluminum hydride to 1,2-diethylhydrazine in 26% yield, but that under similar reaction conditions 1,2-dibenzoylhydrazine (**4**) was recovered unchanged.

In this study it was found that reaction temperatures of 129–135° were required to achieve reduction of 1,2-dipropionylhydrazine and 1,2-dibutyrylhydrazine to the corresponding 1,2-dipropylhydrazine (**5**) and 1,2-dibutylhydrazine (**6**) in yields of 65 and 49%, respectively.

In the cases of compound **4** and 1,2-dicyclohexanoylhydrazine, the reaction led to the half-reduced products, 1-benzoyl-2-benzylhydrazine (**7**) and 1-cyclohexanoyl-2-cyclohexylmethylhydrazine (**8**), respectively. Subsequent treatment of **8** with diborane gave the fully reduced 1,2-dicyclohexylmethylhydrazine (**9**) and some cyclohexylmethylamine. Compound **7** also underwent reduction but gave rise to a mixture which could not be separated.

1,2-Diacyl-1,2-dialkylhydrazines.—As in the case of **1**, reduction of 1,2-diacyl-1,2-dialkylhydrazines with diborane occurred already at 65° and led to tetraalkylhydrazines in good yield. Small amounts of half-reduced compounds were also obtained. For instance, in the reduction of 1,2-dipropionyl-1,2-dimethylhydrazine, there was obtained, in addition to 82% 1,2-dipropyl-1,2-dimethylhydrazine (**10**), 14% 1-propionyl-2-propyl-1,2-dimethylhydrazine (**11**). 1,2-Dibenzoyl-

(1) H. Feuer, E. P. Rosenquist, and F. Brown, Jr., *Israel J. Chem.*, **6**, 587 (1968).

(2) H. Stetter and H. Spangenberger, *Chem. Ber.*, **91**, 1982 (1958).

(3) E. Hedaya, R. L. Hinman, V. Schomaker, S. Theodoropulos, and L. M. Kyle, *J. Amer. Chem. Soc.*, **89**, 4875 (1967).

(4) R. L. Hinman, *ibid.*, **78**, 1645 (1956).

1,2-dimethylhydrazine (**12**) gave 60% 1,2-dibenzyl-1,2-dimethylhydrazine (**13**) and 28% N-methylbenzylamine, the latter apparently arising from cleavage of the N—N bond. It is of interest that in the reduction of **12** with lithium aluminum hydride cleavage of the N—C=O rather than the N—N bond occurred for, in addition to **13**, there were isolated 1-benzoyl-1,2-dimethylhydrazine and benzyl alcohol.[4]

Experimental Section

Apparatus.—All diborane reductions were performed in a three-neck flask equipped with a magnetic stirrer, thermometer, reflux condenser, and septum stopple or gas dispersion tube, depending on the method of introducing diborane. Hydrogen evolution was measured by attaching a series of burets through a Dry Ice trap to the outlet of the condenser.

Reagents.—Diborane was generated as described by Brown[5] and solutions of borane in THF were prepared and standardized.

1,2-Disubstituted perhydropyridazine-3,6-diones were prepared by the procedure of Feuer, *et al.*[1] 1,2-Diacyl- and 1,2-diaroylhydrazines were prepared by methods described in the literature. Tetrahydrofuran (THF) was purified by the method of Feuer and Savides.[6] Dimethyl ether of diethylene glycol (Diglyme) was purified by vacuum distillation from $LiAlH_4$.

Equipment.—Infrared spectra were taken with a Perkin-Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on Aerographs A-700 and A-903 using SF-96 on Chromosorb W columns.

1,2-Diisopropylperhydropyridazine. A. From 1,2-Diisopropylperhydropyridazine-3,6-dione (1b).—The following experiment is typical of the procedure employed for preparing 1,2-dialkylperhydropyridazines. To 3.96 g (20.0 mmol) of 1,2-diisopropylperhydropyridazine-3,6-dione in 100 ml of THF at 0° was introduced by means of a syringe 8.3 ml of 12 *N* borane in THF (99.6 mmol of hydride) at such a rate that the temperature did not exceed 5°. The mixture was stirred at 0–5° for 1 hr, allowed to attain room temperature, and refluxed for 24 hr. This operation yielded 5.04 mmol of hydrogen at STP. Recooling the reaction mixture to 0–5°, adding dropwise 20 ml of 20% potassium hydroxide, and refluxing for 1 hr gave an additional 13.21 mmol of hydrogen at STP. Thus a total of 81.4 mmol of hydride was consumed (theory requires 80.0 mmol of hydride).

Extracting the reaction mixture with ether, drying the extract ($MgSO_4$), removing ether, and distilling the residue *in vacuo* gave 2.90 g (85%) of **1,2-diisopropylperhydropyridazine (2b)**: bp 33° (0.2 mm); $n^{20}D$ 1.4581; ir (neat) 2976 cm^{-1} (C–H); nmr (CCl_4) 0.98 [d, 12, $CH(CH_3)_2$], 3.1 [m, 2, $CH(CH_3)_2$], 2.8 (m, 4, $NCH_2CH_2CH_2CH_2N$), and 1.45 ppm (m, 4, $NCH_2CH_2CH_2CH_2N$).

Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.28; H, 12.80; N, 16.30.

When the reaction was carried out at 25° for 24 hr, from 1.98 g (10.0 mmol) of **1b** and 4.4 ml of 12 *N* borane in THF (52.8 mmol of hydride) there was obtained 1.28 g of liquid, bp 28–68° (0.1 mm). Glpc analysis at 180° and 90 ml/min He indicated the presence of two compounds in addition to starting material (6%).

One compound (retention time 8 min) was identified as **2b** (75%), $n^{20}D$ 1.4583.

The second product (retention time 16 min) was **1,2-diisopropylperhydropyridazin-3-one (3b, 8%)**: $n^{21}D$ 1.4754; ir (neat) 2976 (CH) and 1660 cm^{-1} (C=O); nmr (CCl_4) 1.1 [d, 6, $CH_2NCH(C_3)H_2$], 1.2 [d, 6, O=CNCH(CH_3)$_2$], 1.5 (m, 2, $NCH_2CH_2CH_2C$=O), and 4.0 ppm [m, 2, $CH(CH_3)_2$].

Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.20. Found: C, 65.10; H, 11.06; N, 15.38.

B. From 1,2-Diisopropylperhydropyridazin-3-one (3b).—The procedure was similar to that employed in part A. From 0.18 g (0.98 mmol) of **3b** in 10 ml of THF and 1.0 ml of 4.4 *N* borane in THF (4.4 mmol of hydride), there was obtained 0.13 g (79%) of **2b**, bp 33° (0.2 mm), $n^{20}D$ 1.4584. **1,2-Dipropylperhydropyridazine (2a, 82%)** was prepared as above: bp 33° (0.2 mm); $n^{20}D$ 1.4578; nmr (CCl_4) 0.88 [t, 6, $(CH_2)_2CH_3$], 1.42 (m, 4, $CH_2CH_2CH_3$), 2.6 (t, 4, $CH_2CH_2CH_3$), 1.5 [m, 4, $NCH_2(CH_2)_2CH_2N$], and 2.8 ppm [m, 4, $NCH_2(CH_2)_2CH_2N$].

Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.50; H, 12.94; N, 16.47. Found: C, 70.45; H, 12.99; N, 16.56.

1,2-Dipropylperhydropyridazin-3-one (3a, 8%) was prepared as above: bp 60–65° (0.2 mm); $n^{20}D$ 1.4713; nmr (CCl_4) 1.0 [t, 6, $(CH_2)_2CH_3$], 1.45 (m, 4, $CH_2CH_2CH_3$), 1.5 (m, 2, $NCH_2CH_2CH_2C$=O), 2.3 (t, 2, CH_2C=O), and 3.0 ppm (t, 6, NCH_2).

Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.20. Found: C, 65.13; H, 11.03; N, 14.92.

1,2-Di(*sec*-butyl)perhydropyridazine (2c, 81%) was prepared as above: bp 44–46° (0.15 mm); $n^{20}D$ 1.4671; nmr (CCl_4) 0.82 (t, 6, CH_2CH_3), 1.0 (d, 6, $CHCH_3$), 1.42 (m, 4, CH_2CH_3), 1.5 [m, 4, $NCH_2(CH_2)_2CH_2N$], 2.8 [t, 4, $NCH_2(CH_2)_2CH_2N$], and 3.0 ppm [m, 2, $CH(CH_3)C_2H_5$].

Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.51; H, 13.03; N, 14.01.

1,2-Di(*sec*-butyl)perhydropyridazin-3-one (3c, 15%) was prepared as above: $n^{20}D$ 1.4808; nmr (CCl_4) 0.89 (t, 6, CH_2CH_3), 1.05 (d, 3, $CHCH_3$), 1.18 (d, 3, O=CNCHCH_3), 1.5 [m, 4, $CH(CH_3)CH_2CH_3$], 1.6 (m, 2, $NCH_2CH_2CH_2C$=O), 2.2 (m, 2, CH_2C=O), 3.05 (t, 4, NCH_2), 3.1 (m, 1, CH), and 3.75 ppm (m, 1, CH).

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.36; H, 11.32; N, 13.05.

1,2-Dibutylperhydropyridazine (2d, 74%) was prepared as above: bp 41–44° (0.2 mm); $n^{20}D$ 1.4620; nmr (CCl_4) 0.90 (t, 6, CH_3), 1.4 (m, 12, CH_2), 2.6 [t, 4, $NCH_2(CH_2)_2CH_3$], and 2.7 ppm [t, 4, $NCH_2(CH_2)_2CH_2N$].

Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.64; H, 13.39; N, 13.89.

1,2-Dibutylperhydropyridazin-3-one (3d, 15%) was prepared as above: $n^{20}D$ 1.4734; nmr (CCl_4) 0.93 (t, 6, CH_3), 1.4 (m, 10, CH_2), 2.2 (m, 2, CH_2C=O), and 3.0 ppm (m, 6, NCH_2).

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.30; N, 13.19. Found: C, 67.64; H, 11.51; N, 13.24.

Perhydropyridazine (2g, 52%) was prepared as above: bp 52° (18 mm); $n^{20}D$ 1.4858 [lit.[7,8] bp 54° (12 mm); $n^{17}D$ 1.4862]; ir (neat) 3300 (NH) and 2924 cm^{-1} (CH); nmr (CCl_4) 1.58 [m, 4, $NCH_2(CH_2)_2CH_2N$], 2.89 (m, 4, NCH_2), and 3.2 ppm (m, 2, NH).

1,2-Di(*o*-tolyl)perhydropyridazine (2f, 70%) was prepared as above: mp 61–62°; nmr (CCl_4) 1.77 [t, 4, $NCH_2(CH_2)_2CH_2N$], 2.35 (s, 6, CH_3), 3.2 (m, 4, NCH_2), and 7.0 ppm (m, 8, aromatic H).

Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.12; H, 8.13; N, 10.44.

N,N′-Diisopropyl-1,4-diaminobutane. A. From 1,2-Diisopropylperhydropyridazine-3,6-dione.—The following experiment is typical of the procedure employed for preparing N,N′-disubstituted 1,4-diaminobutanes. To 3.96 g (20.0 mmol) of 1,2-diisopropylperhydropyridazine-3,6-dione in 100 ml of THF at 0° was added 32.5 ml of 6.4 *N* borane in THF (208 mmol of hydride). The reaction mixture was stirred at 0–5° for 1 hr and then refluxed for 24 hr. Adding dropwise 30 ml of 10% hydrochloric acid[9] to the reaction mixture at 0–5°, removing THF by distillation, refluxing the aqueous residue for 1 hr, basifying with solid sodium hydroxide, extracting the emulsion with ether, drying the extract ($MgSO_4$), removing ether, and distilling the residue gave 2.66 g (77%) of **N,N′-diisopropyl-1,4-diaminobutane**: bp 45° (0.03 mm) (lit.[10] bp 208.5–218°); $n^{20}D$ 1.4418; ir (neat) 3285 (NH) and 2975 cm^{-1} (CH); nmr (CCl_4) 0.63 (s, 2, NH), and 0.96 ppm [d, 12, $CH(CH_3)_2$].

The dipicrate salt, mp 189–190° (lit.[11] mp 189.5–190°), was prepared by the usual method.[12]

(5) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **81**, 6428 (1959).

(6) H. Feuer and C. Savides, *ibid.*, **81**, 5826 (1959).

(7) P. Baranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).

(8) K. Alder, H. Niklas, R. Aumüller, and B. Olsen, *Justus Liebigs Ann. Chem.*, **585**, 81 (1954).

(9) Only acidic hydrolysis led to pure product. When the hydrolysis was performed in basic medium, the reaction product was contaminated with boron-containing material.

(10) R. G. Shepherd and R. G. Wilkinson, *J. Med. Pharm. Chem.*, **5**, 823 (1962).

(11) A. A. Ryabinin and E. M. Il'ina, *J. Appl. Chem. USSR*, **26**, 369 (1953).

(12) 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., 1960, p 222.

B. **From 1,2-Diisopropylperhydropyridazine.**—The procedure was similar to that employed in part A. From 3.40 g (20.0 mmol) of 1,2-diisopropylperhydropyridazine, 60 ml of THF, and 10 ml of 12.1 *N* borane in THF (121 mmol of hydride), there was obtained 2.23 g (65%) of **N,N'-diisopropyl-1,4-diaminobutane**, bp 45° (0.3 mm), $n^{20}D$ 1.4418, and 0.77 g (23%) of starting material.

By following procedure A, from 1.03 g (3.50 mmol) of 1,2-di(*o*-tolyl)perhydropyridazine-3,6-dione, 30 ml of THF, and 3.1 ml of 11.4 *N* borane in THF (35.5 mmol of hydride), there was obtained 0.79 g (84%) of **N,N'-di(*o*-tolyl)-1,4-diaminobutane**: mp 45°; ir (neat) 3420 (NH) and 2925 cm^{-1} (CH); nmr ($CDCl_3$) 1.2 (s, 2, **NH**), 1.7 (m, 4, $NCH_2CH_2CH_2CH_2N$), 2.1 (s, 6, CH_3), 3.1 (m, 4, $NCH_2CH_2CH_2CH_2N$), and 6.8 ppm (m, 8, aromatic **H**).

The dihydrochloride salt, mp 223°, was prepared by the usual method.[12]

Anal. Calcd for $C_{18}H_{26}N_2Cl_2$: C, 63.34; H, 7.62; N, 8.21; Cl, 20.82. Found: C, 63.08; H, 7.64; N, 8.28; Cl, 20.71.

N,N'-Dipropyl-1,4-butanediamine (74%) was prepared: bp 54–60° (0.27 mm); $n^{20}D$ 1.4469; ir (neat) 3280 (NH) and 2860 cm^{-1} (CH); nmr (CCl_4) 0.68 (s, 2, **NH**), 0.92 (t, 6, CH_3), 1.50 [m, 4, $NCH_2(CH_2)_2CH_2N$], 1.55 (m, 4, $CH_2CH_2CH_3$), 2.58 [t, 4, $NCH_2(CH_2)_2CH_2N$], and 2.60 ppm (t, 4, $CH_2CH_2CH_3$).

The dipicrate salt was prepared, mp 210–212° dec after recrystallization from 95% ethanol.

Anal. Calcd for $C_{22}H_{30}N_8O_{14}$: C, 41.90; H, 4.76; N, 17.78. Found: C, 42.03; H, 5.01; N, 17.96.

N,N'-Di(*sec*-butyl)-1,4-butanediamine (75%) was prepared: bp 54–60° (0.12 mm); $n^{20}D$ 1.4487; ir (neat) 3280 (NH) and 2975 cm^{-1} (CH); nmr (CCl_4) 0.79 (s, 2, **NH**), 0.95 [d, 6, CH(CH_3)], 0.99 (t, 6, CH_2CH_3), 1.4 (m, 8, CH_2), 2.57 (t, 4, NCH_2), and 2.6 ppm (m, 2, **CH**).

The dipicrate salt was prepared, mp 215–216° dec.

Anal. Calcd for $C_{24}H_{34}N_8O_{14}$: C, 43.77; H, 5.17; N, 17.02. Found: C, 44.02; H, 5.45; N, 16.80.

N,N'-Di(*o*-tolyl)-1,4-butanediamine (84%) was prepared: mp 45°; ir (neat) 3420 (NH) and 2925 cm^{-1} (CH); nmr ($CDCl_3$) 1.2 (s, 2, NH), 1.7 [m, 4, $(CH_2)_2$], 2.1 (s, 6, CH_3), 3.1 (m, 4, NCH_2), and 6.8 ppm (m, 8, aromatic H).

The dihydrochloride salt was prepared, mp 223° (from CH_3OH).

Anal. Calcd for $C_{18}H_{26}N_2Cl_2$: C, 63.34; H, 7.62; N, 8.21; Cl, 20.82. Found: C, 63.08; H, 7.64; N, 8.28; Cl, 20.71.

N,N'-Dibutyl-1,4-butanediamine (80%) was prepared: mp 64–66°; ir (melt) 3300 (NH) and 2975 cm^{-1} (CH); nmr (CCl_4) 0.81 (s, 2, **NH**), 0.93 (t, 6, CH_3), 1.4 {m, 12, $[CH_3(CH_2)_2CH_2]_2$-$NHCH_2(CH_2)_2CH_2NH$}, and 2.58 ppm (t, 8, NCH_2).

The dipicrate salt was prepared, mp 213–214° dec.

Anal. Calcd for $C_{24}H_{34}N_8O_{14}$: C, 43.77; H, 5.17; N, 17.02. Found: C, 44.02; H, 5.32; N, 17.23.

1,2-Dipropylhydrazine (5).—The following experiment is typical of the procedure employed for the reduction of 1,2-diacylhydrazines. To 4.32 g (30.0 mmol) of 1,2-dipropionylhydrazine in 240 ml of diglyme at 0° was added 44 ml of 6.25 *N* borane in THF (274 mmol of hydride). The reaction mixture was stirred at 0–5° for 15 min, allowed to attain room temperature, and then heated to 134° for 24 hr. Removing THF and diglyme *in vacuo*, hydrolyzing the residue with 30 ml of 10% hydrochloric acid at 0°, and then refluxing for 1 hr was followed by basifying with sodium hydroxide. Extracting the reaction mixture with ether, drying the extract ($MgSO_4$), filtering, removing ether, and distilling the residue gave 2.27 g (65%) of **1,2-dipropylhydrazine**: bp 149–151°, $n^{20}D$ 1.4297 (lit.[13] bp 149–150°; $n^{20}D$ 1.4287); ir (neat) 3320 cm^{-1} (NH); nmr (CCl_4) 0.95 (t, 6, $CH_2CH_2CH_3$), 1.6 (m, 4, $CH_2CH_2CH_3$), 3.7 (t, 4, $CH_2CH_2CH_3$), and 3.7 ppm (s, 2, **NH**).

1,2-Dibutylhydrazine (6).—From 1,2-dibutyrylhydrazine (5.16 g, 30.0 mmol), diglyme (240 ml), and 44 ml of 6.25 *N* borane in THF (274 mmol of hydride), there was obtained 2.12 g (49%) of 1,2-dibutylhydrazine: bp 190–193°; $n^{20}D$ 1.4317 (lit.[14] bp 192–194°; $n^{20}D$ 1.4346); nmr (CCl_4) 0.95 (t, 6, CH_3), 1.4 (m, 8, CH_2), 3.6 (t, 2, NCH_2), and 3.7 ppm (s, 2, **NH**).

1,2-Dicyclohexylmethylhydrazine (9).—From 2.38 g (10 mmol) of 1-cyclohexanoyl-2-cyclohexylmethylhydrazine (8) dissolved in 23 ml of diglyme and 4.2 ml of 12 *N* borane in THF at 142°, there were obtained 1.21 g (54%) of **1,2-dicyclohexylmethylhydrazine** (9): bp 112–114 (0.2 mm); [lit.[15] bp 112–114° (0.2 mm)]; $n^{20}D$ 1.5010; ir (neat) 3320 (NH) and 2940 cm^{-1} (CH); nmr (CCl_4) 1.1–1.6 (m, 22, C_6H_{11}), 2.76 (d, 4, CH_2), and 4.3 ppm (s, 2, **NH**).

Cyclohexylmethylamine (0.13 g, 6%) was also obtained: bp 28–30° (2 mm); $n^{20}D$ 1.4659 (lit.[16] bp 163.5°; $n^{18}D$ 1.4664); ir (neat) 3300 cm^{-1} (NH); nmr ($CDCl_3$) 1.2–1.6 (m, 11, ring H), 2.4 (m, 2, CH_2), and 2.45 ppm (m, 2, NH_2).

1-Cyclohexanoyl-2-cyclohexylmethylhydrazine (8).—The procedure was similar to that employed for the preparation of **5** except that 7.56 g (30.0 mmol) of 1,2-dicyclohexanoylhydrazine, 125 ml of diglyme, and 22.8 ml of 12 *N* borane in THF (273.6 mmol of hydride) were employed, and that the reaction temperature was 129°. After the usual work-up the ether was removed *in vacuo* and 20 ml of hexane was added to the residue. Cooling to −78° and filtering gave 3.93 g (55%) of **1-cyclohexanoyl-2-cyclohexylmethylhydrazine** (8): mp 97°; ir (neat) 3300 (NH), 2920 (CH), and 1630 cm^{-1} (C=O); nmr (DMSO-d_6) 0.8–1.8 (m, 22, C_6H_{11}), 1.9 (m, 1, CH_2NH), 2.45 (s, 2, CH_2NH), and 3.35 ppm (m, 1, O=C—**NH**).

Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 70.54; H, 10.99; N, 11.75. Found: C, 70.40; H, 11.24; N, 11.77.

Removing hexane from the filtrate and distilling gave 0.50 g (7%) of **9**.

1-Benzoyl-2-benzylhydrazine (7).—The procedure was similar to that described for the preparation of 1-cyclohexanoyl-2-cyclohexylmethylhydrazine (8), except that the reaction was carried out at 149° for 24 hr. After evaporation of the ether extract, there was obtained **1-benzoyl-2-benzylhydrazine** (69%): mp 110° (H_2O); ir (neat) 3300 (NH) and 1640 cm^{-1} (C=O); nmr ($CDCl_3$) 4.0 (m, 4, CH_2NHNHC=O), and 7.4 ppm (m, 10, aromatic **H**).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.05; H, 6.01; N, 12.28.

1-(*p*-Methoxybenzoyl)-2-(*p*-methoxybenzyl)hydrazine (54%) was obtained: mp 135° (50% aqueous EtOH); ir (KBr) 3220 (NH) and 1610 cm^{-1} (C=O); nmr (DMSO-d_6) 1.9 (d, 6, OCH_3), 3.4 (m, 2, $NHCH_2$), 3.9 [m, 2, $(NH)_2$], and 7.2 ppm (m, 8, aromatic **H**).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.05; H, 6.29; N, 9.84.

Acidification of the aqueous layer with 10% hydrochloric acid gave on filtration 34% of starting material.

1-(*p*-Chlorobenzoyl)-2-(*p*-chlorobenzyl)hydrazine (42%) was obtained: mp 138° (40% aqueous EtOH); ir (Nujol) 3280 (NH) and 1640 cm^{-1} (C=O); nmr (DMSO-d_6) 3.2 (s, 2, CH_2NH), 3.9 [m, 2, $(NH)_2$], 7.3 (s, 4, ClC_6H_4CO), and 7.6 ppm (q, 4, $ClC_6H_4CH_2$).

Anal. Calcd for $C_{14}H_{12}N_2OCl_2$: C, 56.95; H, 4.07; N, 9.49; Cl, 24.07. Found: C, 57.08; H, 4.14; N, 9.36; Cl, 23.97.

The usual work-up of the aqueous lager afforded 40% of starting material.

1,2-Dipropyl-1,2-dimethylhydrazine (10).—The following experiment is typical of the procedure employed for the preparation of tetrasubstituted hydrazines. To 5.16 g (30.0 mmol) of 1,2-dipropionyl-1,2-dimethylhydrazine in 200 ml of THF at 0° was added by means of a syringe 24 ml of 6.25 *N* borane in THF (150 mmol of hydride). The reaction mixture was stirred at 0–5° for 15 min, allowed to attain room temperature, and then refluxed for 24 hr. The reaction mixture was recooled to 0°, hydrolyzed by adding dropwise 30 ml of 10% hydrochloric acid, and then refluxed for 1 hr. Basifying with solid sodium hydroxide, extracting with ether, drying the extract ($MgSO_4$), removing ether, and distilling the residue gave two fractions.

One fraction was **1,2-dipropyl-1,2-dimethylhydrazine** (10, 3.53 g, 82%): bp 64–65° (40 mm); $n^{20}D$ 1.4267; ir (neat) 2951 cm^{-1} (CH); nmr (CCl_4) 0.89 (t, 6, $NCH_2CH_2CH_3$), 1.46 (m, 4, $NCH_2CH_2CH_3$), 2.39 (t, 4, $NCH_2CH_2CH_3$), and 2.21 ppm (s, 6, NCH_3).

Anal. Calcd for $C_8H_{20}N_2$: C, 66.60; H, 13.98; N, 19.42. Found: C, 66.60; H, 13.94; N, 19.62.

The other fraction was **1-propionyl-2-propyl-1,2-dimethylhydrazine** (11, 0.68 g, 14%): bp 92–94° (40 mm); $n^{20}D$ 1.4505; ir (neat) 2951 (CH) and 1653 cm^{-1} (C=O); nmr (CCl_4) 0.96 (t, 3, $NCH_2CH_2CH_3$), 1.03 (t, 3, CH_3CH_2C=O), 1.45 (m, 2,

(13) R. Renaud and L. C. Leitch, *Can. J. Chem.*, **32**, 545 (1954).

(14) R. Stollé, *Chem. Ber.*, **34**, 682 (1901).

(15) P. G. Ugryumov, *J. Gen. Chem. USSR*, **10**, 1985 (1940); *Chem. Abstr.*, **35**, 4361[3] (1941).

(16) J. Gutt, *Chem. Ber.*, **40**, 2061 (1907).

$NCH_2CH_2CH_3$), 2.55 (s, 3, NCH_3), 2.82 (s, 3, NCH_3), 2.42 (t, 2, $NCH_2CH_2CH_3$), and 2.58 ppm (q, 2, $CH_3CH_2C{=}O$).

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.72; H, 11.47; N, 17.70. Found: C, 60.86; H, 11.50; N, 17.90.

1,2-Dipropyl-1,2-diethylhydrazine.—By following the usual procedure, there was obtained **1,2-dipropyl-1,2-diethylhydrazine** (82%): bp 74–76° (10 mm); $n^{20}D$ 1.4322; nmr (CCl_4) 0.88 [t, 6, $N(CH_2)_2CH_3$], 1.0 (t, 6, NCH_2CH_3), 1.38 (m, 4, $NCH_2CH_2CH_3$), 2.43 (t, 4, $NCH_2CH_2CH_3$), and 2.40 ppm (q, 4, NCH_2CH_3).

Anal. Calcd for $C_{10}H_{24}N_2$: C, 69.70; H, 14.04; N, 16.26. Found: C, 69.81; H, 14.26; N, 16.30.

When the reaction mixture was refluxed during the reduction only for 2 hr instead of 24 hr, there was also obtained **1-propionyl-2-propyl-1,2-diethylhydrazine** (10%): bp 58° (0.31 mm); $n^{20}D$ 1.4533; ir (neat) 2990 (CH) and 1653 cm^{-1} (C=O); nmr (CCl_4) 0.90 [t, 3, $N(CH_2)_2CH_3$], 1.0 (t, 3, $O{=}CNCH_2CH_3$), 1.05 (t, 3, $O{=}CCH_2CH_3$), 1.38 (m, 2, $NCH_2CH_2CH_3$), 2.40 (q, 2, NCH_2CH_3), 2.50 (t, 2, $NCH_2CH_2CH_3$), 2.70 (q, 2, $OCCH_2CH_3$), and 3.23 ppm (q, 2, $OCNCH_2CH_3$).

Anal. Calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.45; H, 12.12; N, 15.07.

1,2-Diethyl-1,2-dimethylhydrazine.—By following the typical procedure, there was obtained from 4.32 g (30 mmol) of 1,2-diacetyl-1,2-dimethylhydrazine 2.61 g (75%) of 1,2-diethyl-1,2-dimethylhydrazine: bp 92–94°; $n^{20}D$ 1.4091 [lit.[4] bp 93–94° (752 mm); $n^{27}D$ 1.4121]; ir (neat) 2950 and 2800 cm^{-1} (CH); nmr (CCl_4) 1.02 (t, 6, CH_2CH_3), 2.22 (s, 6, NCH_3), and 2.48 ppm (q, 4, CH_2CH_3).

When the reduction mixture was refluxed for only 2 hr instead of 24 hr, the major product was identified by glpc analysis as the half-reduced 1-acetyl-2-ethyl-1,2-dimethylhydrazine (46% yield): $n^{20}D$ 1.4423; ir (neat) 2960, 2850 (CH), and 1665 cm^{-1} (CO); nmr (CCl_4) 1.01 (t, 3, CH_3CH_2), 2.03 (s, 3, CH_3CO), 2.55 (s, 3, NCH_3), 2.7 (q, 2, CH_2CH_3), and 2.78 ppm (s, 3, H_3CNCO).

Anal. Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.27; H, 10.91; N, 21.26.

Tetraethylhydrazine and 1-Acetyl-1,2,2-triethylhydrazine.—From 1,2-diacetyl-1,2-diethylhydrazine, there were obtained **tetraethylhydrazine** (70%), bp 56–58° (46 mm) [lit.[17] bp 52–53° (42 mm)], $n^{20}D$ 1.4215, and **1-acetyl-1,2,2-triethylhydrazine** (8%): bp 34–36° (0.33 mm); $n^{20}D$ 1.4498; ir (neat) 2950 (CH) and 1653 cm^{-1} (CO); nmr (CCl_4) 1.02 [t, 6, $N(CH_2CH_3)_2$], 1.17 (t, 3, $O{=}CNCH_2CH_3$), 2.0 (s, 3, $CH_3C{=}O$), 2.72 [q, 4, $N(CH_2CH_3)_2$], and 3.20 ppm (q, 2, $O{=}CNCH_2CH_3$).

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.72; H, 11.47; N, 17.70. Found: C, 60.48; H, 11.61; N, 17.86.

1,2-Dibenzyl-1,2-dimethylhydrazine (13).—From 1,2-dibenzoyl-1,2-dimethylhydrazine was obtained **13** (60%): bp 110–112° (0.1 mm); $n^{20}D$ 1.5566 [lit.[4] bp 118–120° (0.15 mm), $n^{20}D$ 1.5538]; nmr (CCl_4) 2.3 [s, 6, $N(CH_3)_2$], 3.7 [s, 4, $N(CH_2)_2$], and 7.3 ppm (s, 10, aromatic **H**). **N-Methylbenzylamine** (28%) was also obtained: bp 50–52° (3 mm); $n^{20}D$ 1.5242; ir (neat) 3350 cm^{-1} (NH); nmr (CCl_4) 1.9 (s, 1, **NH**), 2.3 (s, 3, NCH_3), 3.7 (s, 2, NCH_2), and 7.3 ppm (s, 5, aromatic **H**).

Registry No.—Diborane, 19287-45-7; **2a**, 23359-97-9; **2b**, 23346-48-7; **2c**, 23346-49-8; **2d**, 23346-50-1; **2f**, 23346-51-2; **2g**, 505-19-1; **3a**, 23346-53-4; **3b**, 23346-54-5; **3c**, 23346-55-6; **3d**, 23346-56-7; **4a**, 23346-57-8; **4a** dipicrate, 23346-58-9; **4c**, 23346-59-0; **4c** dipicrate, 23359-98-0; **4d**, 19435-69-9; **4d** dipicrate, 23346-61-4; **4f**, 23346-62-5; **4f** dihydrochloride, 23346-63-6; **7**, 1215-52-7; **8**, 23337-87-3; **10**, 23337-88-4; **11**, 23337-89-5; 1-(*p*-methoxybenzoyl)-2-(*p*-methoxybenzyl)hydrazine, 23359-99-1; 1-(*p*-chlorobenzoyl)-2-(*p*-chlorobenzyl)hydrazine, 23337-90-8; 1,2-dipropyl-1,2-diethylhydrazine, 23337-91-9; 1-propionyl-2-propyl-1,2-diethylhydrazine, 23337-92-0; 1,2-diethyl-1,2-dimethylhydrazine, 23337-93-1; 1-acetyl-1,2,2-triethylhydrazine, 23389-69-7.

Acknowledgment.—We thank the Purdue Research Foundation for financial support of part of this work.

(17) O. Westphal and M. Eucken, *Chem. Ber.*, **76B**, 1137 (1943).

Hydroxamic Acids and N-Hydroxyimides Related to Pyridine, Pyrazine, and Quinoxaline

CHARLES D. HURD AND VICTOR G. BETHUNE[1]

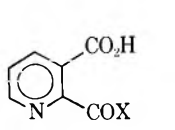
Department of Chemistry, Northwestern University, Evanston, Illinois

Received January 28, 1969

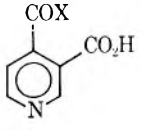
The *o*-carboxyhydroxamic acids **1b**, **2b**, **8a**, and **9a** were prepared and subjected to Lossen rearrangement. In an inert medium, the isocyanate intermediate from **1b** gives the cyclic anhydride **3**, which reacts readily with water or methanol. In the presence of methanol, *o*-amino esters were obtained in all cases, indicating that cyclization of the isocyanate is more rapid than its reaction with methanol. Rearrangement of N-(benzoyloxy)-quinolinimide **12b** and N-(benzoyloxy)cinchomeronimide **14b** gave amino acids **4a** and **15**, respectively.

In this study we have extended our earlier findings[2] on the Lossen rearrangement of *o*-carboxyhydroxamic salts. The 3-carboxyhydroxamic acids **1b** and **2b** were obtained from the corresponding methyl esters **1a** and **2a** by reaction with hydroxylamine. The esters were obtained by treatment of quinolinic and cinchomeronic anhydrides, respectively, with methanol. We were unable to isolate the isomeric methyl 2-carboxynicotinate from brief heating of quinolinic anhydride in methanol,[3] but both isomeric benzyl esters were obtained with benzyl alcohol.

The benzoyl hydroxamates **1c** and **2c** were prepared from the acids with benzoyl chloride, and were converted into the monosodium salts for rearrangement. On heating in toluene the salts gave mixtures of the cyclic anhydrides **3**[4] and **6** and the amino acids **4a** and **7a**. The aminonicotinic acid presumably arose from traces of water; a sample of the salt of **1c** that had been stored for a week gave only **4a** (76%). The rearrange-



1a, X = OCH_3
b, X = NHOH
c, X = $NHOCOC_6H_5$



2a, X = OCH_3
b, X = NHOH
c, X = $NHOCOC_6H_5$

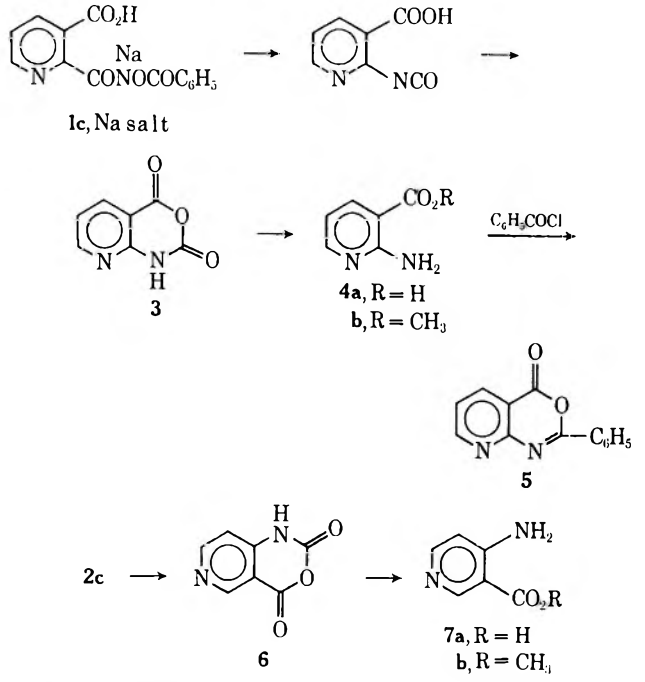
(1) Abbott Fellow, 1962–1963; Lubrizol Fellow, 1963–1965.

(2) C. D. Hurd, C. M. Buess, and L. Bauer, *J. Org. Chem.*, **17**, 865 (1952); **19**, 1140 (1954).

(3) J. Kenyon and K. Thaker, *J. Chem. Soc.*, 2531 (1957).

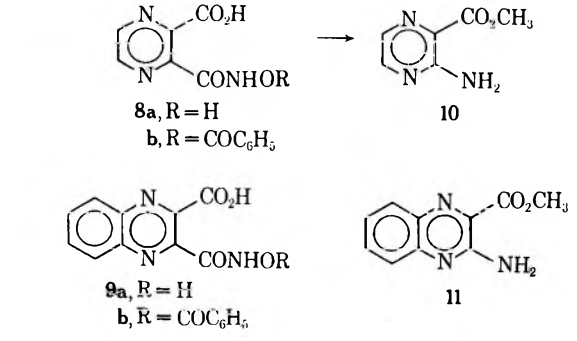
(4) An alternative preparation of **3** by $Pb(OAc)_4$ oxidation of 2-carbamylnicotinic acid has recently been described by A. L. J. Beckwith and R. J. Hickman, *ibid.*, *C*, 2756 (1969).

ment of **1b**, as the disodium salt, was also carried out in cold aqueous solution with benzenesulfonyl chloride[5] to give **4a**. The azlactone **5** was obtained from **4a** with excess benzoyl chloride.



The anhydrides **3** and **6** undergo hydrolysis or alcoholysis much more rapidly than isatoic anhydride, which can be recrystallized from alcohol. Treatment of **3** or **6** with warm methanol gives **4b** and **7b**. These esters are also obtained by heating the benzoylhydroxamic salts in toluene–methanol (8:1). The formation of **4b** and **7b**, rather than the methyl carbamates, HOOC-(NC_5H_3)NHCOOCH$_3$, when methanol is present during the rearrangement, demonstrates that cyclization of the intermediate isocyanates to **3** and **6** is much more rapid than reaction of the isocyanate with methanol.

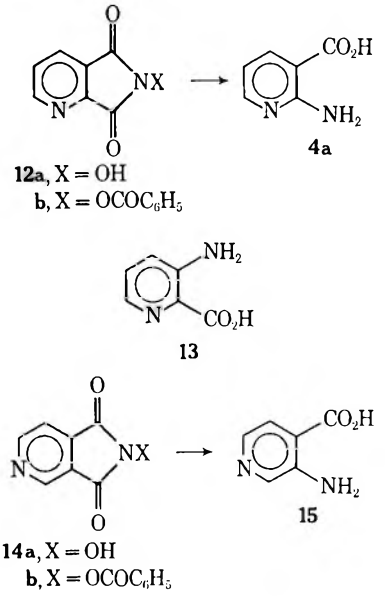
o-Carboxyhydroxamic acids **8a** and **9a** were obtained from pyrazine- and quinoxaline-2,3-dicarboxylic anhydrides by treatment with hydroxylamine in methanolic sodium methoxide. The benzoyl derivatives of **8** and **9** and the sodium salts contained water or methanol of crystallization. Heating the methanolates in toluene gave the amino esters **10** and **11**, presumably again by attack of methanol on the cyclic anhydride.



For comparison with the *o*-carboxyhydroxamic esters, the N-hydroxyimides **12a** and **14a** were prepared from **1b** and **2b**, respectively, in refluxing thionyl chloride. Only a low yield of **12** was obtained from the reaction of quinolinic anhydride and hydroxylamine. The hydroxyimide structures were confirmed by ir bands at 5.6 and 5.7–5.8 μ, and formation of a bright red color in base, paralleling the properties of N-hydroxyphthalimide.[6] The benzoates **12b** and **14b** were prepared by direct benzoylation or by cyclization of **1c** and **2c** with thionyl chloride.

Rearrangement of **14b** led to 3-aminoisonicotinic acid (**15**) in 54% yield, attack of base evidently occurring predominately at the C-4 carbonyl. This result parallels the course of the Hofmann rearrangement of **14** (X = H) to **15** with NaOBr or NaOCl.[7]

With **12b**, the Lossen rearrangement product isolated in 43% yield was 2-aminonicotinic acid (**4a**). The related Hofmann rearrangement has been reported[8] to give 3-aminopicolinic acid (**13**) with NaOCl, but, with excess NaOBr, both **4a** and **13** have been isolated.[9]



The reactivity of the C-4 carbonyl in **14b** and the C-2 carbonyl in **12b** should be comparable, and little difference was observed in the time required for the two rearrangements. It is surprising, therefore, that **4a**, arising from C-3 attack, rather than **13**, appears to be the major product from **12b**.

Experimental Section

Microanalyses for C, H, and N were done by Micro-Tech Laboratories, Skokie, Ill. Quinolinic anhydride, mp 136–136.5°, cinchomeronic anhydride, mp 75–77°, 2,3-pyrazinedicarboxylic anhydride, mp 224–225° dec with darkening at 170°, 2,3-quinoxalinedicarboxylic anhydride, mp 253° dec, and methyl 3-carboxypicolinate (**1a**), mp 122–123°,[3] were synthesized by known methods.

Sodium 2-(Methoxycarbonyl)nicotinate.—Equimolar (0.03) parts of methanol solutions of **1a** and CH_3ONa were mixed. When the salt started to separate from the 30 ml of solution, 130 ml of absolute ether–hexane (4:9)w as added: yield of rinsed and dried salt, 5.8 g (94%).

Anal. Calcd for $C_8H_6NO_4Na$: Na, 11.21. Found: Na, 11.14.

(5) C. D. Hurd and L. Bauer, *J. Amer. Chem. Soc.*, **76**, 2791 (1954); L. Bauer, *J. Org. Chem.*, **21**, 1182 (1956).

(6) L. Bauer and S. V. Miarka, *J. Amer. Chem. Soc.*, **79**, 1983 (1957); *J. Org. Chem.*, **24**, 1293 (1959).

(7) S. Blumenfeld, *Monatsh. Chem.*, **16**, 703 (1895). S. Gabriel and J. Colman, *Ber.*, **35**, 2831 (1902). K. Blanchard, *et al.*, *Bull. Johns Hopkins Hosp.*, **91**, 339 (1952); *Chem. Abstr.*, **47**, 10536 (1953).

(8) E. Sucharda, *Ber.*, **58**, 1727 (1925); E. Ochiai and I. Arai, *J. Pharm. Soc. Jap.*, **59**, 458 (1939).

(9) L. Fibel and P. Spoerri, *J. Amer. Chem. Soc.*, **70**, 3908 (1948).

Quinolinic Anhydride and Benzyl Alcohol.—A mixture of the anhydride (14.9 g), the alcohol (13.0 g), and benzene (100 ml) was heated at reflux for 2 hr, whereby some of the ester precipitated. On cooling, 15 g (58%) of ester, mp 151–152°, was obtained. Recrystallization from ethanol–water gave long needles, mp 152–153°. The substance is believed to be benzyl 3-carboxypicolinate by analogy to similar reactions[3,10] of quinolinic and 3-nitrophthalic anhydrides with alcohols.

Anal. Calcd for $C_{14}H_{11}NO_4$: N, 5.45; neut equiv, 257.2. Found: N, 5.28; neut equiv, 255.2.

The benzene filtrate was concentrated and the residue was dissolved in ethyl acetate. Hexane, added to incipient cloudiness, promoted formation of small, colorless cubic crystals after several days at 0°; yield 5 g (19%), mp 89–90°. After recrystallization from ethyl acetate–hexane, mp 90–91°. This was considered to be benzyl 2-carboxynicotinate. Mixture melting point of the 2- and 3-benzyl esters was 75–125°.

Anal. Calcd for $C_{14}H_{11}NO_4$: N, 5.45; neut equiv, 257.2. Found: N, 5.18; neut equiv, 256.

Disodium 3-Carboxypicolinohydroxamate.—A cool solution of **1a** (0.065 mol in 50 ml of CH_3OH) was added to 0.078 mol of hydroxylamine and 0.13 mol of CH_3ONa in 110 ml of methanol. [Alternatively, sodium 2-(methoxycarbonyl)nicotinate may be used with no added CH_3ONa.] The desired disodium salt precipitated during 6 hr, when 75 ml of dry ether–hexane (1:2) was added to complete the precipitation: yield, 12.7–13 g (86–88%) after drying *in vacuo* over P_2O_5.

Anal. Calcd for $C_7H_4N_2O_4Na_2$: Na, 20.34. Found: Na, 20.48, 20.22.

Disodium 3-Carboxyisonicotinohydroxamate.—This was made in the same way from **2a**; yield 92%. Ester **2a** was prepared from cinchomeronic anhydride and methanol following directions of Kaas.[11]

Anal. Calcd for $C_7H_4N_2O_4Na_2$: Na, 20.34. Found: Na, 21.01.

Disodium 3-Carboxy-2-pyrazinecarbohydroxamate.—A solution of hydroxylamine (0.24 mol) in 225 ml of methanol was added to a solution of 2,3-pyrazinedicarboxylic anhydride in 350 ml of methanol. Then 200 ml of methanol containing 0.24 mol CH_3ONa was slowly added. A bright yellow, gelatinous mass soon separated. After 30 min, ether and pentane were added and the salt was collected, rinsed (ether), and dried; yield, 95%.

Anal. Calcd for $C_5H_3N_3O_4Na_2$: Na, 20.25. Found: Na, 20.15.

Disodium 3-Carboxy-2-quinoxalinecarbohydroxamate.—The same plan was followed; yield 96%. It was also an orange, gelatinous mass.

Anal. Calcd for $C_{10}H_5N_3O_4Na_2$: Na, 16.54. Found: Na, 16.82.

The free hydroxamic acids gave intense violet red colors with $FeCl_3$ solution.

3-Carboxypicolinohydroxamic Acid, 1b.—This acid was made by suspending 1 g of its disodium salt in 50 ml of ethyl acetate, adding 2 ml of cold 5 *N* HCl, and shaking the mixture. The solid that separated was crystallized from water; yield 0.4 g, mp 164° dec. It was insoluble in ethyl acetate and chloroform. Infrared (KBr), with strong peaks noted unless designated otherwise as m (medium), w (weak), or b (broad): 3.10–3.90 (b), 5.90 (b), 6.30, 6.65, 6.85, 7.05, 7.50, 7.60, 8.40 (m), 8.60 (m), 9.10, 9.35 (m), 9.60, 9.90 (w), 10.90, 11.85 (w), 12.15, 12.50, 14.12, 14.50 (m), 15.27 (m) μ.

Anal. Calcd for $C_7H_6N_2O_4$: N, 15.38. Found: N, 15.22.

3-Carboxyisonicotinohydroxamic Acid, 2b.—To a solution of the disodium salt (2 g) in 12 ml of cold water was added 3.5 ml of 5 *N* HCl. After cooling and scratching the walls of the container the acid separated: yield, air dried, 1.6 g; mp 178–179° dec; after vacuum drying for 24 hr at 77°, mp 179–180° dec. Attempts to purify **2b** by recrystallization were fruitless. The original crude product, mp 179–180°, analyzed acceptably for H (only 0.04% low) but was 1.3% low for carbon. This uncrystallized material was taken directly to the benzoylation step.

3-Carboxy-2-pyrazinecarbohydroxamic Acid, 8a.—The method given for **2b** worked well for **8a**; yield 0.82 g of colorless cubes from 1 g of the disodium salt. After recrystallization from ethanol–water, the melting point was 151–152° dec. It was soluble in alcohol and hot water but dissolved with difficulty in ethyl acetate. Analysis showed that **8a** is a monohydrate, stable for 17 hr under diminished pressure at 80°: ir 3.12, 3.30, 3.55, 5.82, 6.01, 6.15 μ, and 12 other bands.

Anal. Calcd for $C_6H_5N_3O_4 \cdot H_2O$: N, 20.89. Found: N, 20.68.

3-Carboxy-2-quinoxalinecarbohydroxamic Acid, 9a.—Addition of dilute HCl to a solution of 3 g of the disodium salt in 25 ml of water to a pH of about 1 caused separation of 2 g of the monohydrate of **9a**. Its melting point was 213–216° dec when heated slowly in a capillary tube, or at 206–208° dec if placed in a bath preheated to 200°. Attempted recrystallization lowered the melting point. Ir showed 3.40 (b), 5.90, 6.00, 6.70 (w), 7.21 (w), 9.50 (m), 13.20 μ.

Anal. Calcd for $C_{10}H_7N_3O_4 \cdot H_2O$: C, 51.95; H, 3.05. Found: C, 51.68; H, 3.36.

Benzoylations.—Each of the four disodium salts described above was dissolved in water. To each solution cooled to 0–5° and stirred, was added gradually during 1 hr equivalent amounts of benzoyl chloride and 2 *N* NaOH solution. At the completion of reaction, the ferric chloride color tests were negative.

To the water solution was added 1.3 volumes of hexane–benzene (1:1) followed by an excess (about 1.5 equiv) of 5 *N* HCl. The solid which separated was collected on a filter, washed well, dried, and recrystallized.

3-Carboxypicolino(benzoylhydroxamic) Acid, 1c.—This compound was obtained in a yield of 79%: mp 138–140° dec; melting point after crystallization from ethyl acetate–hexane, 141–143° dec; second recrystallization, 144.5–145° dec; ir 3.12, 3.24–3.92 (b), 5.68 (ester), 5.91 (acid), 6.00 μ (amide), and 18 other bands.

Anal. Calcd for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.81; H, 3.73; N, 9.77.

3-Carboxyisonicotino(benzoylhydroxamic) Acid, 2c.—This compound was obtained in a yield of 78%, mp 171–172° dec. For analysis it was recrystallized from dimethylformamide–water and was dried *in vacuo* over P_2O_5, mp 173–174° dec. This is close to the melting point of **2b** but the mixture melting point of the two ranged from 163 to 175°. Compound **2c** is insoluble in water, benzene, ethyl acetate, and is recrystallized with difficulty from alcohol: ir 3.10, 5.70, 5.87, 5.98, 6.25, 6.85 (m), 8.00, 9.50 (b), 11.80, 14.00 μ.

Anal. Calcd for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.15; H, 3.82; N, 9.96.

3-Carboxy-2-pyrazine(benzoylcarbohydroxamic) Acid, 8b.—This compound was obtained as colorless needles after crystallization from ethanol–water in a yield of 62%, mp 151–152° dec, and was unchanged after drying for 12 hr at 80° *in vacuo* over P_2O_5. The compound is a hydrate. Its mixture melting point with **8a** hydrate was 139–142° dec: ir 2.80 (w), 3.15, 3.32, 5.65 (ester), 5.85 (acid), 5.95 μ (amide), and 16 other bands.

Anal. Calcd for $C_{13}H_9N_3O_5 \cdot H_2O$: C, 51.15; H, 3.63; N, 13.77; neut equiv, 305.2. Found: C, 51.33; H, 3.73; N, 13.68; neut equiv, 302.0.

Dehydration of the Hydrate.—A mixture of 10 ml of toluene and 0.5 g of **8b** hydrate was refluxed for 15 min, then half of the toluene was distilled. The resulting solid (0.35 g) melted at 163–164° dec and gave mmp 159–161° with the monohydrate.

Anal. Calcd for $C_{13}H_9N_3O_5$: neut equiv, 287.2. Found: neut equiv, 290.6.

3-Carboxy-2-quinoxaline(benzoylhydroxamic) Acid, 9b.—Yield was 67% after recrystallization from ethyl acetate–hexane, mp 168–170° dec. The analytical sample was again recrystallized and kept at 80° *in vacuo* for 17 hr: mp 170–171° ir 3.00 (b), 5.70, 5.80, 5.29, 6.20 (m) μ, and 11 other bands.

Anal. Calcd for $C_{17}H_{11}N_3O_5$: C, 60.53; H, 3.29; N, 12.46; neut equiv, 337.3. Found: C, 60.45; H, 3.34; N, 12.46; neut equiv, 335.6.

Salts of the Benzoyl Derivatives.—Acids **1c**, **2c**, **8b**, and **9b** (0.5–1.5 g) were dissolved in methanol. Then 1 equiv of sodium, dissolved in methanol, was added. After cooling to 0°, ether–pentane (1:2) was added to complete the precipitation of the monosodium salts. The disodium salt of **1c** was made in the same way, using 2 equiv of CH_3ONa. The salts of **8b** and **9b** were methanolates, stable toward treatment *in vacuo* over P_2O_5 for 12 hr. Yields of monosodium salts were 86% from **1c** (92% for the disodium salt), 93% from **8b**, 82% from **9b**. The yield from **2c** was low (53%) because of the large volume of methanol required for solution. A 92% yield was obtained from 3 g of **2c** by dissolving it in 5 ml of warm dimethylformamide (*cf.* 80 ml of methanol), then at 15° adding 1 equiv of Na in 100 ml of metha-

(10) R. Wegschneider and A. Lipschitz, *Monatsh. Chem.*, **21**, 787 (1900); D. Cram and F. Elhafez, *J. Amer. Chem. Soc.*, **74**, 5846 (1952).

(11) K. Kaas, *Monatsh. Chem.*, **23**, 250 (1902).

nol, and completing the precipitation of the salt at 0° by use of dry ether. All compounds gave satisfactory analytical values for Na, including the methanolates **8b** and **9b**.

Rearrangement of Disodium 3-Carboxypicolinohydroxamate with Benzenesulfonyl Chloride.—To a solution of the disodium salt of **1b** in 30 ml of water (2°) was added 8 ml of 15% NaOH; 7.1 g of benzenesulfonyl chloride was then added dropwise. After stirring at 20–25° for 1 hr, the aqueous layer was extracted with 20 ml of benzene and was acidified (HCl) to pH 5. A precipitate (0.76 g) of 2-aminonicotinic acid formed on cooling: mp 290° dec (block) after recrystallization from water. It was identical with that obtained below.

Rearrangements of Monosodium Salts of 1c, 2c, 8b, and 9b in Water.—Samples of 1–2 g of the salts were dissolved in 10–30 ml of water and heated at 100° for 30–60 min. After cooling the solutions, 1 equiv of dilute HCl was added. The solid which formed was filtered off, dried, and extracted with benzene to remove benzoic acid. The remaining amino acid was recrystallized.

From **1c** was obtained 54% 2-aminonicotinic acid, mp 286–287° dec (see below); from **2c**, a 46% yield of 4-aminonicotinic acid,[12] melting point taken on a melting block, 338–341° dec; from **9b**, an 86% yield of 3-amino-2-quinoxalinecarboxylic acid,[13] mp 210° dec. The salt from **8b** (2 g) was largely unchanged after boiling the solution for 3 min. After acidification, 1.2 g of **8b** hydrate separated.

Rearrangements of Monosodium Salts in Toluene. 2-(Carboxyamino)nicotinic Cyclic Anhydride (3) from 1c.—Heating a suspension of 1 g of the Na salt of **1c** in 20 ml of dry toluene at 100° for 1 hr caused evolution of CO_2 [detected by $Ba(OH)_2$ solution]. After cooling and filtering, the residue was rinsed with benzene and extracted with warm water. The undissolved part was 0.19 g of **3** or 36%, mp 208–210° dec. Beckwith and Hickman[4] report mp 217–219° for **3**, recrystallization solvent unspecified. Our compound possessed the same four ir bands which they reported (Nujol mull, 3.18, 3.25, 5.42, 5.65 μ) and our spectrum (KBr) showed these additional bands: 5.70, 6.20, 6.55 (w), 7.00, 7.40, 7.80 (m), 8.10 (m), 9.70, 10.10, 10.75 (m), 12.00 (w), 12.70, 13.30, 14.00, 14.60 (w), 15.00 (m) μ. Our product was insoluble in benzene, ethyl acetate, or chloroform; attempted recrystallizations were unsuccessful.

When **3** was heated in water, 2-aminonicotinic acid separated, mp 287–290° dec. After heating in methanol, concentrating this solution, adding water, and cooling, methyl 2-aminonicotinate[14] separated, mp 84.5–85°, ir 5.92 μ.

The toluene filtrate from **3** was acidified, evaporated to dryness, and extracted with benzene to remove 0.25 g of benzoic acid. Extraction of the remainder with water left 0.18 g (40%) of 2-aminonicotinic acid (**4a**). It was recrystallized from hot water and dried: mp 289–290° dec (block) with gradual heating, or 308–310° dec when heating was started at 300° (lit. values range from 295 to 310°; ir 3.10, 3.40 (b), 5.87 μ (carboxyl), and 8 other bands.

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.29. Found: C, 52.00; H, 4.62; N, 20.47.

2-Phenyl-4H-pyrido[2,3-*d*][1,3]oxazin-4-one, 5.—A mixture of **4a** (0.5 g), dry pyridine (8 ml), benzene (12 ml), and benzoyl chloride (0.5 ml) was heated for 30 min at 60–70°. The resulting green solution was poured into water. After the usual work-up and recrystallization from cyclohexane, 0.4 g of **5** was obtained as colorless needles: mp 145–146°; ir 5.71, 6.19, 6.27 μ and 11 other bands.

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; Found: C, 69.27; H, 3.70.

4-Aminonicotinic Acid (7a) from 2c.—A suspension of 2.68 g of the monosodium salt of **2c** in 60 ml of dry toluene was refluxed for 2 hr. Some CO_2 was evolved. The solid, presumably mainly **6**, was collected. It dissolved completely in 10 ml of water with gas evolution (CO_2). After acidifying and extraction with ether, 0.72 g (59%) of **7a**, mp 333–335° dec (block) was obtained. Crystallization from water gave fine needles: mp 338–340° (lit.[12] 340° dec); ir 3.05, 3.20, 4.00 (b), 6.00, 6.10, 6.40, 7.10, 7.50, 8.72 (m), 9.20 (w), 9.75 (w), 10.90 (w), 11.80 (m), 12.30 (m), 14.70 (b) μ.

Rearrangement in Toluene–Methanol.—Refluxing 1.0 g of the monosodium salt of **2c** in 40 ml of dry toluene and 5 ml of absolute methanol for 7 hr, then filtration and evaporation of the filtrate left a residue which was crystallized from alcohol–water to give 0.3 g of **7b**, mp 172–173°, lit.[12] mp 173°.

Methyl 3-Amino-2-pyrazinecarboxylate (10) from 8b.—A suspension of the monosodium salt of **8b**-methanolate and 30 ml of toluene was heated at reflux for 3 hr (CO_2 was evolved). The mixture was filtered and the filtrate was evaporated. The yellow residue (0.55 g, 40%) was crystallized from 95% ethanol yielding long yellow needles of **10**: mp 171–172°;[15] ir 2.90, 5.90 μ. Treatment with ammonia gave the amide, mp 237–238° (lit.[15] 239°). The toluene-insoluble residue gave 0.29 g (24%) of 3-amino-2-pyrazinecarboxylic acid [mp 208–210° dec (lit.[16] 210°); ir 2.92, 3.03, and 5.86 μ] after acidification and processing.

The sodium salt of **8b** rearranged comparably in refluxing xylene, giving methyl 3-amino-2-pyrazinecarboxylate (40%) and 3-amino-2-pyrazinecarboxylic acid (18%).

Rearrangement of 9b.—A suspension of 2.95 g of the monosodium salt methanolate of **9b** was refluxed in toluene for 3 hr. After filtration, the residue was acidified to give 0.9 g (63%) of 3-amino-2-quinoxalinecarboxylic acid:[13] mp 209–211° dec after recrystallization from acetic acid–water; ir 2.90 (m), 3.10 (m), 5.91 μ, and 8 other bands. Evaporation of the toluene filtrate left a residue that was recrystallized from methanol to give 0.52 g (33%) of **11**: mp 216–217° (lit.[13] mp 218–219°); ir: 2.87, 3.00, 5.88 μ, and 12 other bands.

N-Hydroxyquinolinimide, 12a.—Gentle heating of a suspension of 2.8 g of **1b** in 20 ml of thionyl chloride caused a vigorous reaction which subsided after 30 min. After refluxing for 30 min more, excess $SOCl_2$ was removed *in vacuo*. The residue was rinsed with benzene, air dried, and crystallized from 2-propanol; yield 2 g (80%), mp 229–230° dec. The compound gave no color with $FeCl_3$ but it instantly became bright red on addition of 2% NaOH solution, This color gradually disappeared on standing. For analysis, it was recrystallized from 2-propanol and dried *in vacuo* at 100° over P_2O_5: mp 230–231° dec; ir 3.80 (b), 5.55, 5.60, 5.80, 6.20 μ, and 10 other bands.

Anal. Calcd for $C_7H_4N_2O_3$: C, 51.22; H, 2.46; N, 17.07. Found: C, 51.51; H, 2.62; N, 16.83.

Quinolinic Anhydride and Hydroxylamine.—To an aqueous solution of 0.027 mol of hydroxylamine was added 0.025 mol of quinolinic anhydride. The solution was heated at 100° for 1 hr, then cooled. One gram (20%) of solid separated; this was shown to be **1c** by melting point and mixture melting point (163–164° dec) and ir spectrum. A further crop of product appeared to be a mixture of **1b** and quinolinic acid.

N-Benzoyloxyquinolinimide, 12b.—A precipitate formed at once as 0.3 ml of benzoyl chloride was added to a solution of 0.3 g of **12a** in 3 ml of dry pyridine. The mixture was heated 20 min at 60–70° (precipitate redissolved), then was cooled. The solid was removed, rinsed with 5% $NaHCO_3$ solution, dried, and crystallized from ethanol to form 0.35 g of fine needles: mp 156–157° (a second crystallization brought the melting point to 159–160°); ir 5.55 (w), 5.65, 5.75, 6.25 μ and, 8 other bands.

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00. Found: C, 63.08; H, 3.22.

Compound **12b** was synthesized also in 82% yield by direct reaction of 2.6 g of **1c** and 15 ml of refluxing $SOCl_2$. After latter was removed under reduced pressure, the residue was rinsed with pentane, and crystallized from alcohol; 2 g of product was obtained, mp and mmp 157–158°.

3-Carboxypicolino(benzoylhydroxamic) Acid (1c) from 12a and Benzoyl Chloride.—To the intensely red suspension formed by adding 1.8 g of **12a** to a solution of 0.45 g of NaOH in 10 ml of water (2°) was added, with stirring, 1.6 g of benzoyl chloride during 20 min. The suspension became almost colorless. After 10 min more, another 0.4 ml of benzoyl chloride was added, the mixture was stirred for 30 min, and the now homogeneous mixture was acidified (HCl) to a congo red endpoint. The precipitate was collected, rinsed with both water and ether, dried, and crystallized from ethyl acetate–hexane to give 1.65 g (52%) of **1c**, mp 142–143°.

Rearrangement of 12b.—To a suspension of 2 g of **12b** in 20 ml of water at 10° was added 6 ml of 10% NaOH solution. When the solid had dissolved, the solution was heated at 100° for 45

(12) A. Kirpal, *Monatsh.*, **23**, 239 (1902); G. B. Bachman and R. Barker, *J. Org. Chem.*, **14**, 97 (1949). Both list 340° dec.

(13) A. Philips, *Ber.*, **28**, 1657 (1895) lists 210° dec; A. Gowenlock, G. Newbold, and F. Spring, *J. Chem. Soc.*, 622 (1945), list 212–213° dec.

(14) A. Kirpal, *Monatsh. Chem.*, **21**, 957 (1900); G. Koller, *Ber.*, **60**, 408 (1927).

(15) R. Ellington, R. Henry, and F. McDonald, *J. Amer. Chem. Soc.*, **67**, 1711 (1945).

(16) S. Gabriel and A. Sonn, *Ber.*, **40**, 4850 (1907).

min. Dilution with acetic acid and cooling produced a precipitate which was collected on a filter and extracted with ether. The residue was recrystallized from water yielding 0.45 g (43%) of 2-aminonicotinic acid, **4a**, mp 286–288° dec.

N-Hydroxycinchomeronimide, 14a.—The synthesis paralleled that of **12a**. From 1 g of **2b** and 8 ml of $SOCl_2$ was obtained 0.8 g of crude residue, insoluble in benzene. Crystallization from acetic acid gave 0.72 g (80%) of **14a**: mp 232–233° dec; ir 4.00 (b), 5.55, 5.60, 5.80, 6.20, 11.20, 14.00 μ.

Anal. Calcd for $C_7H_4N_2O_3$: C, 51.22; H, 2.46; N, 17.07. Found: C, 51.10; H, 2.75; N, 16.81.

N-Benzoyloxycinchomeronimide, 14b.—The method described for **12b** was followed; the warm reaction mixture was poured onto ice before collecting the solid product. From 0.3 g of **14a** was obtained 0.3 g (94%) of **14b**; after crystallization from ethanol, the melting point was 191–192°; ir 5.55 (w), 5.65, 5.75, 6.20 (m) μ, and 8 other bands.

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00; N, 10.45. Found: C, 62.31; H, 2.94; N, 10.69.

The same compound was obtained in 83% yield from **2c** and thionyl chloride.

Rearrangement of 14b.—**14b** (1 g), insoluble in 10 ml of cold water, was brought into solution by 3 ml of 10% NaOH solution. After heating at 100° for 30 min, it was cooled and acidified (HCl) to pH 5. The precipitate was collected, dried, ether extracted to remove benzoic acid, and crystallized from water to yield 0.28 g (54%) of 3-aminoisonicotinic acid[7] (15), mp 299–302° dec (block). After another crystallization the melting point was 307–309° dec; ir 3.00, 3.10, 4.10, 4.70 (b), 6.15, 6.28 μ, and 9 other bands. A mixture of this acid and 4-aminonicotinic acid (mp 340° dec) melted at 265–285° dec.

Registry No.—Sodium 2-(methoxycarbonyl)nicotinate, 23410-97-1; benzyl 3-carboxypicolinate, 23410-98-2; benzyl 2-carboxynicotinate, 23410-99-3; disodium 3-carboxypicolinohydroxamate, 23411-00-9; disodium 3-carboxy-2-pyrazinecarbohydramate, 23411-01-0; disodium 3-carboxy-2-quinoxalinecarbohydroxamate, 23411-02-1; **1b**, 23411-03-2; **1c**, 23411-04-3; **2b**, 23411-05-4; **2c**, 23411-06-5; **3**, 21038-63-1; **4a**, 5345-47-1; **5**, 23411-09-8; **8a**, 23411-10-1; **8b**, 23411-11-2; **9a**, 23411-12-3; **9b**, 23411-13-4; **12a**, 23439-87-4; **12b**, 23411-14-5; **14a**, 23439-88-5; **14b**, 23411-15-6.

Reactions of 2-Acetoacetylaminopyridines with Triethyl Orthoformate and Zinc Chloride

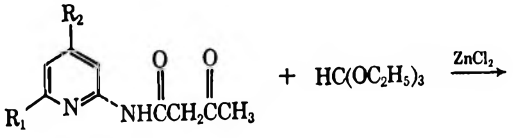
MICHAEL C. SEIDEL, GLENN C. VAN TUYLE, AND W. DAVID WEIR

Rohm and Haas Company, Spring House, Pennsylvania 19477

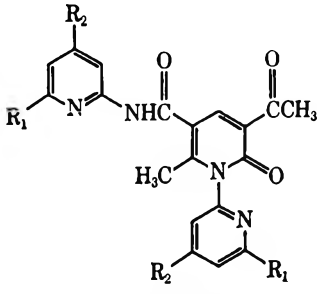
Received September 18, 1969

The reaction of 2-acetoacetylaminopyridines with triethyl orthoformate and zinc chloride did not yield the expected ethoxymethylene derivatives, but dimeric products, such as **2**, containing 2 mol of the starting material and one CH moiety. The scope of the reaction was explored. Mixed dimers were obtained upon addition of other acetoacetamides to the reaction mixture. A mechanism explaining these results is proposed.

In an attempt to prepare the ethoxymethylene derivative of 2-acetoacetylaminopyridine (**1**) by reaction with triethyl orthoformate, acetic anhydride, and zinc chloride, the condensation product **2** was obtained in modest yield. The yield could be raised to 69% by the use of ethanol instead of acetic anhydride as solvent; a much higher yield of the analogous product was obtained with the 6-methylpyridine **3**.

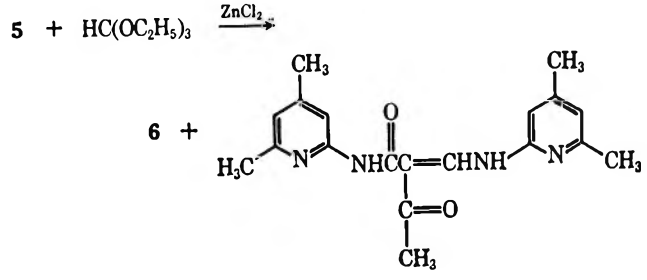


1, $R_1 = R_2 = H$
3, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = R_2 = CH_3$



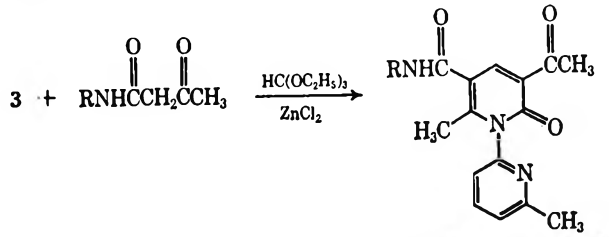
2, $R_1 = R_2 = H$ (69%)
4, $R_1 = CH_3$; $R_2 = H$ (91%)
6, $R_1 = R_2 = CH_3$ (12%)

Several 2-acetoacetylaminopyridines were used in this reaction (see Table I for details); 2-acetoacetylaminothiazole gave an analogous product. 2-Acetoacetylamino-4,6-dimethylpyridine was the only compound giving two isolable products. In addition to **6** (12%) a 17% yield of **7** was isolated.



7 (17%)

Addition of 2 mol of *p*-chloroacetoacetanilide to the reaction mixture gave rise to a mixed dimer. Com-



8, R = *p*-ClC_6H_4 (59%)
9, R = *n*-C_3H_7 (12%)
12, R = *t*-C_4H_9 (70%)

pound **8** crystallized from the reaction mixture and was uncontaminated with a possible isomer or with **4**.

TABLE I
2-ACETOACETYLAMINOPYRIDINES

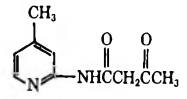
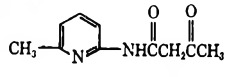
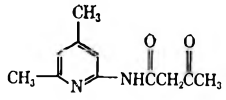
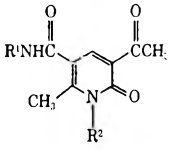
Compound	Structural formula	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
28		$C_{10}H_{12}N_2O_2$	57	121–123°	62.48	6.30	14.58	62.78	6.28	14.59
3		$C_{10}H_{12}N_2O_2$	77	100.5–102.5	62.48	6.30	14.58	62.62	6.41	14.61
5		$C_{11}H_{14}N_2O_2$	98	Oil	64.07	6.84	13.59	64.11	7.16	14.19

TABLE II
3-ACETYL-6-METHYL-2-PYRIDONE-5-CARBOXYLIC ACID 2-PYRIDYLAMIDES



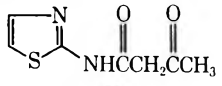
Compound	R^1	R^2	A^a	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Other	Mol wt	Found, % C	Found, % H	Found, % N	Found, % Other	Mol wt
2	2-Pyridyl	2-Pyridyl	8.32	$C_{19}H_{16}N_4O_3$	69	228–229	65.51	4.63	16.05	O, 13.78	348	65.70	4.57	16.01	O, 13.75	357 ± 6[b]
29	5-Chloro-2-pyridyl	5-Chloro-2-pyridyl	8.63	$C_{19}H_{14}Cl_2N_4O_3$	79	216–219	54.69	3.38	13.43		417	54.45	3.20	13.57		400 ± 4[b]
30	4-Methyl-2-pyridyl	4-Methyl-2-pyridyl		$C_{21}H_{20}N_4O_3$	30	235–236.5	67.01	5.36	14.89			67.10	5.20	14.61		
4	6-Methyl-2-pyridyl	6-Methyl-2-pyridyl	8.38	$C_{21}H_{20}N_4O_3$	91	252.5–253	67.01	5.36	14.89		376	67.11	5.37	14.94		377 ± 7[b]
31	2-Thiazolyl	2-Thiazolyl	8.87	$C_{15}H_{12}N_4O_3S_2$	76	259.5–260.5	49.38	3.36	15.55	S, 17.80	360	50.11	3.42	15.54	S, 17.49	373 ± 2[b]
6	4,6-Dimethyl-2-pyridyl	4,6-Dimethyl-2-pyridyl	8.28	$C_{23}H_{24}N_4O_3$	12	253–255	68.30	5.98	13.85			68.15	6.09	13.67		
8	4-Chloro-phenyl	6-Methyl-2-pyridyl	8.30	$C_{21}H_{18}ClN_3O_3$	59	231–233	63.72	4.57	10.62	Cl, 8.96		63.74	4.69	10.66	Cl, 9.07	
19	6-Methyl-2-pyridyl	4-Chloro-phenyl	8.5	$C_{21}H_{18}ClN_3O_3$	25	215–218	63.72	4.57	10.62			63.70	4.58	10.39		
12	*t*-Butyl	6-Methyl-2-pyridyl		$C_{19}H_{23}N_3O_3$	70	243.5–245.5	66.84	6.79	12.31			66.79	7.07	12.30		
9	*n*-Propyl	6-Methyl-2-pyridyl		$C_{18}H_{21}N_3O_3$	12	215.7	65.88	6.47	12.84			66.06	6.70	12.77		
32	Phenyl	2-Pyridyl		$C_{20}H_{17}N_3O_3$	40	230–232	69.15	4.93	12.10			69.54	4.87	12.12		
33	Phenyl	6-Methyl-2-pyridyl		$C_{21}H_{19}N_3O_3$	57	210–212	69.79	5.30	11.63			69.53	5.37	11.70		

[a] *A*, nmr absorption of lone hydrogen in pyridone ring (in parts per million). [b] Ebullioscopic determination in acetone.

Mixed dimers **32** and **33** were obtained using **1** and **3** with acetoacetanilide (see Table II).

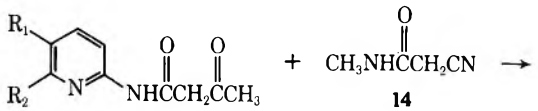
When **3** was treated with triethyl orthoformate and $ZnCl_2$ in the presence of a fourfold excess of N-*n*-propylacetoacetamide, **4** was isolated in 21% yield together with 12% **9**; when a twofold excess was used, a 15% yield of **10** was the only product isolated. Using a fourfold excess of N-*t*-butylacetoacetamide, a 70% yield of a product could be isolated which by tlc was pure **12**.

Other active methylene compounds were added to the reaction mixture of substituted 2-acetoacetylaminopyridine, triethyl orthoformate, and zinc chloride in ethanol. The results were threefold: either (a) the added compound did not influence the normal reaction at all, or (b) it interfered in the reaction without showing up in the end product, or, in one case, (c) a mixed compound was formed. (a) When cyanoacetamide or ethyl acetoacetate was added in a twofold excess, **1** and 2-acetoacetylaminothiazole (**13**) gave rise



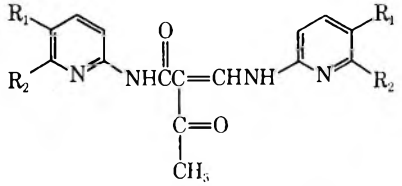
13

to undiminished yields of the normal 1:1 products, the added compounds not influencing the reaction at all. (b) Another type of result was obtained when a twofold excess of N-methylcyanoacetamide (**14**) was added.



14

3, $R_1 = H; R_2 = CH_3$
15, $R_1 = Cl; R_2 = H$



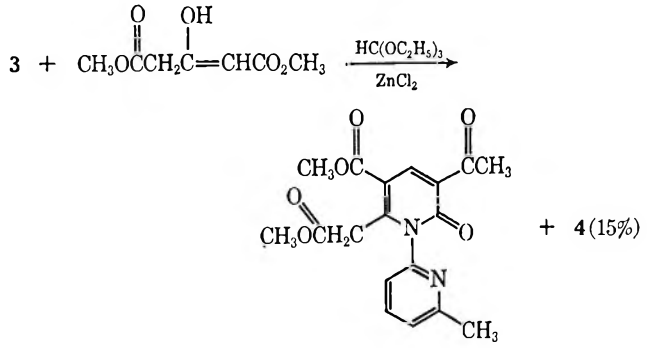
10, $R_1 = H; R_2 = CH_3$ (95%)
16, $R_1 = Cl; R_2 = H$ (68%)

The N-methylcyanoacetamide did not show up in the product but, obviously, it had profoundly influenced the reaction. (c) The reaction of **3** with triethyl ortho-

TABLE III
2-ACETYL-3-PYRIDYLAMINOACRYL-2-PYRIDYLAMIDES

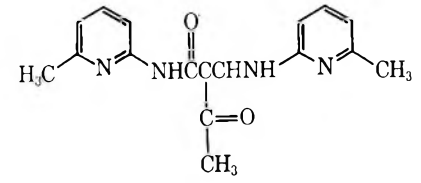
Compound	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7	$C_{19}H_{22}N_4O_2$	17	226–228	67.44	6.55	16.56	67.40	6.55	16.58
10	$C_{17}H_{18}N_4O_2$	15, 91	187.5–189	65.79	5.85	18.05	65.87	5.86	18.11
16	$C_{15}H_{12}Cl_2N_4O_2$	68	235–237	51.28	3.42	15.91	51.55	3.60	15.77

formate in the presence of dimethyl acetonedicarboxylate gave rise to the ring closed compound **17**.

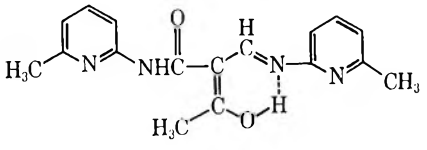


17 (45%)

Confirmation of Structural Assignments. 1. Compound 10.—The ir spectrum of this compound dis-



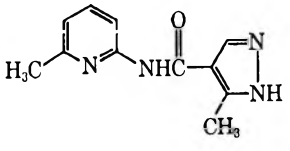
10



10a

plays an "insufficient amount" of carbonyl absorption, one band at 6.05 and a small shoulder at 5.95 μ. It may therefore, exist mainly in the form **10a**. Supporting this is the presence of three strong bands at 6.25, 6.40, and 6.55 μ.

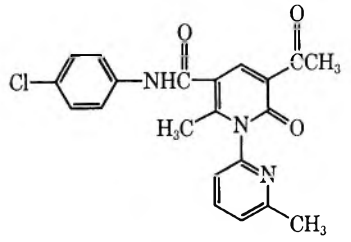
The structure of **10** was also supported by the reaction with hydrazine which resulted in the formation of **18** in 62% yield.



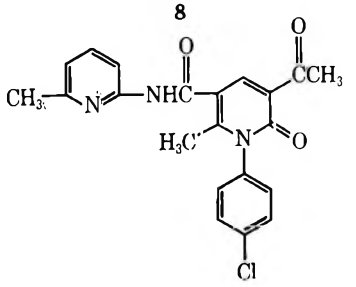
18

The structures of **7** and **16** (see Table III) were assigned by analogy to **10**.

2. Compound 8.—The question here is whether the compound obtained by reaction of **3** with *p*-chloroacetoacetanilide in triethyl orthoformate has structure **8** or **19**.

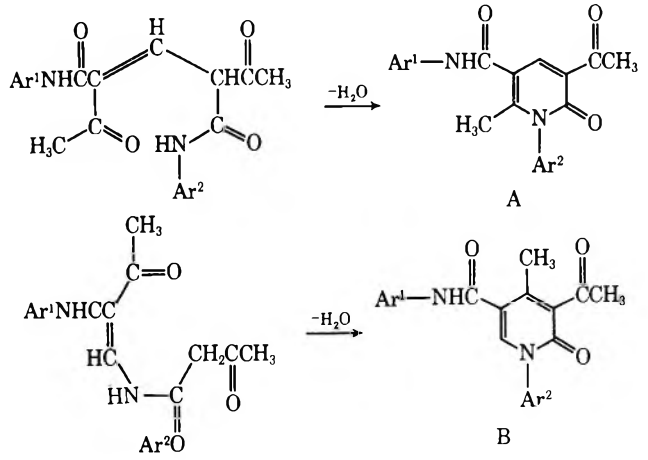


8

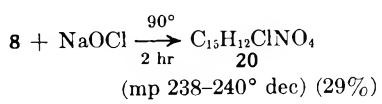


19

The methyl group on the pyridone ring could be in the 6 position as shown in **8** and **19**, or in the 4 position. Ring closure could occur in two ways, one leading to A (**8** or **19**) and the other leading to B.



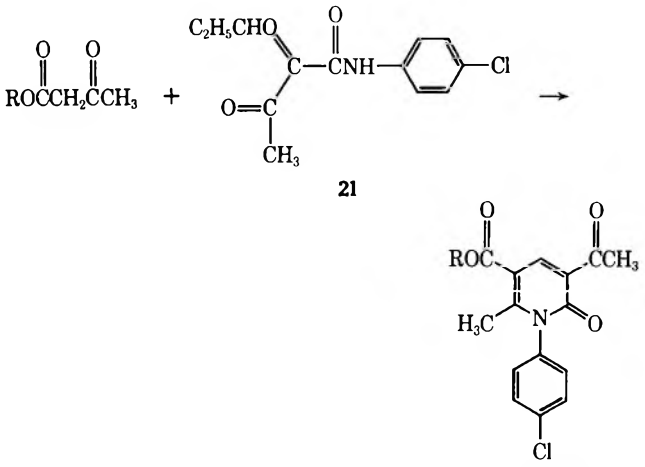
Hydrolysis with either strong aqueous base or acid led to destruction of the compound. Treatment with aqueous sodium hypochlorite in basic solution led to a new compound having lost the amino pyridine part of the molecule.



(mp 238–240° dec) (29%)

The compound was acidic, phenolic (positive $FeCl_3$ test) but could not be methylated with either diazomethane or dimethyl sulfate. The ir spectrum showed the typical features of a six-membered enol chelate ring. The nmr spectrum showed the presence of two equivalent acetyl groups.

Several acetoacetic esters were condensed with **21** to form the esters **22a**–**22c** (listed in Table IV).

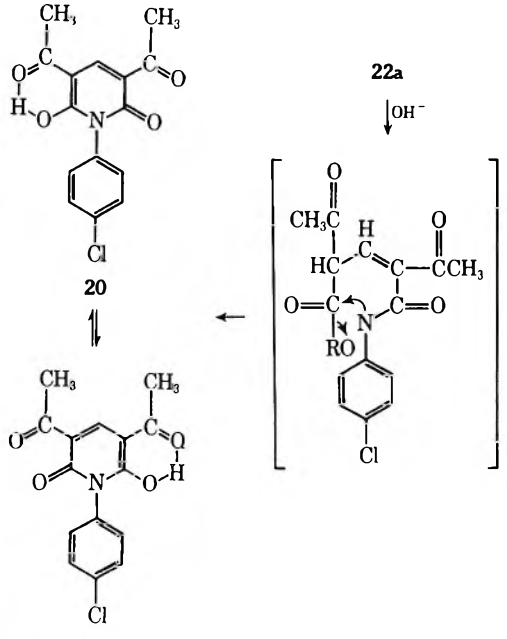


21

22a, R = C_2H_5–
b, R = t-C_4H_9–
c, R = CH_3
d, R = H

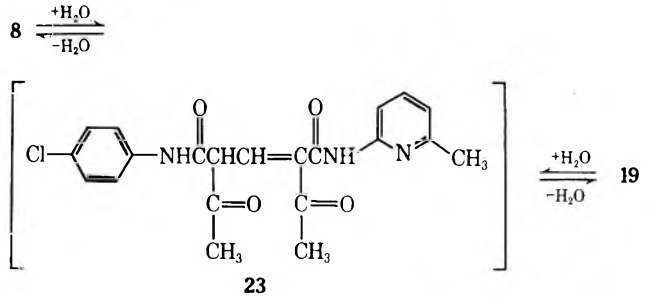
When **22a** was treated with methanolic NaOH and then acidified, a compound identical with **20** was isolated in 82% yield. The fact that it was not identical with the expected acid, **22d**, was shown by preparing **22d** *via* acid hydrolysis of **22b**. The acid **22d** had a melting point of 272.5–274.5° dec and gave **22c** on treatment with diazomethane.

The formation of **20** involved a base-catalyzed rearrangement of the pyridone ring in **22a** and **8**.



The same compound, **20**, is formed by the action of basic NaOCl on **8**. Attachment of a positive chlorine on the pyridine ring labilizes the amide linkage to the point where, after base-catalyzed ring opening, an analogous displacement can occur, leading to **20**. The identity of the products from the two sources established the position of the methyl group on the pyridone ring in **8**.

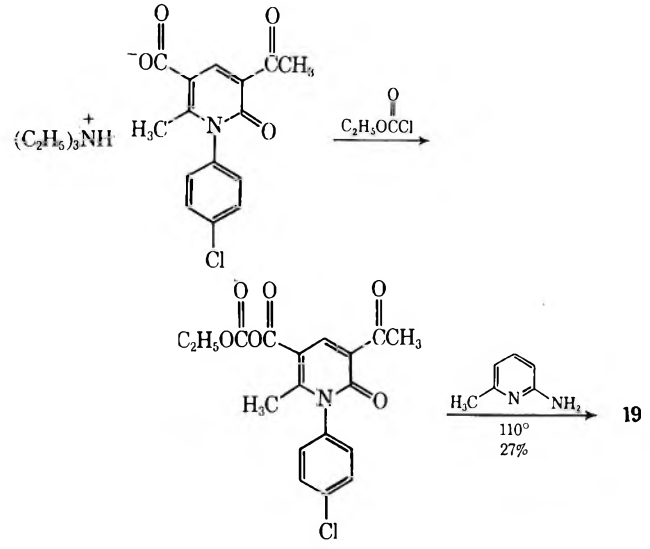
At this point, it would appear that formula **19** is the correct one for the triethyl orthoformate derived compound since in the formation of **20** the 6-methyl-2-aminopyridine group was lost, but, after base-catalyzed ring opening, both **8** and **19** can be expected to give tautomeric forms of the same intermediate **23**. The



23

intermediate **23** could obviously ring close in two directions to give either starting material.

In order to pin down the structure of **19**, it was made from the acid **22d** by using a mixed anhydride method.

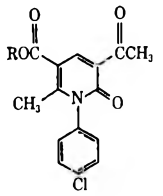


The compound melted at 216–218°, and it depressed the melting point of **8**. Once **19** was available the mother liquors from the preparation of **8** were worked up on an effort to find traces of **19**. Using tlc, no such traces could be found.

In the acidic reaction medium of the triethyl orthoformate reaction, then, no **19** is formed. Base, however, should transform **8** into **19** and *vice versa*, if **23** is formed under these conditions. Using NaOH in ethanol, at room temperature, **8** was partially isomerized into **19**. The compound dissolved rapidly upon addition of the base and the product isolated on acidification after 2 hr was largely **19** (by tlc). After two recrystallizations, a 30% yield of pure **19** was obtained.

Mechanism of Formation of 2 and 8, and Their Analogs.—The zinc chloride catalyzed reaction between 2-acetoacetylaminopyridines and triethyl orthoformate yielding dimeric pyridones of type **2** is unexpected.

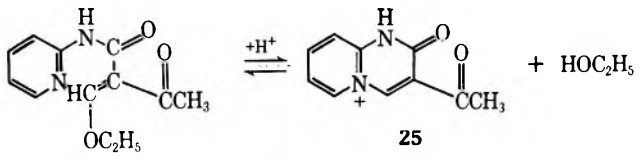
TABLE IV
3-ACETYL-6-METHYL-2-PYRIDONE-5-CARBOXYLIC ACID DERIVATIVES



Compound	R	A[a]	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
22a	Ethyl	8.34	$C_{17}H_{16}ClNO_4$	42	185–186.5	61.17	4.83	4.20	61.37	4.70	4.13
22b	*t*-Butyl		$C_{19}H_{20}ClNO_4$	69	228 dec	63.07	5.57	3.87	63.40	5.44	3.68
22d	H	8.26	$C_{15}H_{12}ClNO_4$	83	272.5–274.5	58.93	3.96	4.58	59.04	4.25	4.45
22c	Methyl		$C_{16}H_{14}ClNO_4$	85	207.4	60.10	4.41	4.38	60.03	4.23	4.18

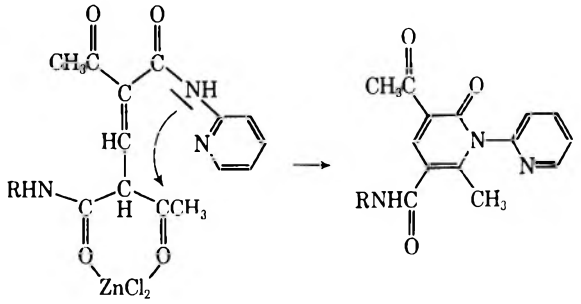
[a] *A*, nmr absorption of lone hydrogen on pyridone ring in parts per million.

It is reasonable to assume that an ethoxymethylene derivative **24** is formed initially. The favorable



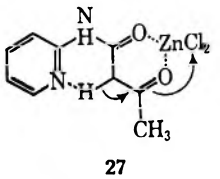
24 **25**

steric arrangement of **24**, however, makes the ethoxy group labile and acid-catalyzed removal of ethanol should give **25**. These reactions should be reversible under the reaction conditions. When **25** reacts with another mole of starting material instead of ethanol, dimeric products can be formed. If the methylene carbon of **1** condenses with **25** to give **26**, ring closure to the observed products can occur.



26

An interesting phenomenon concerns the preference of the acetoacetylaminopyridine to react with itself instead of reacting with other acetoacetamides. Only an excess of *p*-chloroacetoacetanilide gives rise to **8** as the sole product. Only an excess of *t*-butylacetoamide prevents completely the formation of **4**. This may be due to assistance by the pyridine ring nitrogen, facilitating the reaction of the reactant with **25**. This assistance would be removal or partial removal of a proton from the methylene group as shown in **27**.



27

Compounds such as **7**, **10**, and **16** probably are formed when the starting 2-acetoacetylamino pyridine partially solvolyzes and the free 2-aminopyridine reacts with **25**.

Experimental Section

All melting points are uncorrected. The microanalyses were carried out by Mr. C. W. Nash and his associates.

Acetoacetamides.—The acetoacetamides used as starting materials were prepared by reaction of the appropriate amine with diketene in toluene. N-*n*-propylacetoacetamide,[1] **1**,[2] 2-acetoacetylamino-5-chloropyridine,[3] **11**,[4] and **13**[5] have already been described.

The properties were in accord with those described in the literature. Other acetoacetamides are listed in Table I.

General Procedure for the Reaction of Acetoacetylaminopyridines with Triethyl Orthoformate. 5-Acetyl-2-methyl-1-(6-methyl-2-pyridyl)-N-(6-methyl-2-pyridyl)-6-(1H)-oxonicotinamide (4) (Table II).—A solution of 58 g (0.3 mol) of 2-acetoacetylamino-6-methyl pyridine (**3**), 1 g of $ZnCl_2$ in 180 ml of absolute ethanol, and 70 ml of triethyl orthoformate was refluxed for 4 hr, then cooled, and filtered. The product was recrystallized from Methyl Cellosolve, yield 51 g.

5-Acetyl-1-(*p*-chlorophenyl)-2-methyl-N-(6-methyl-2-pyridyl)-6-(1H)-oxonicotinamide (19) (Table II).—To a slurry of 12.5 g (0.04 mol) or **22d** in 200 ml of toluene, 4.1 (0.04 mol) of triethylamine was added. Ethyl chloroformate (4.5 g, 0.04 mol) was added to the solution. The resultant mixture was left standing for 1 hr. Then 4.5 g (0.04 mol) of 2-amino-6-methylpyridine was added and the mixture was refluxed for 2 hr, whereupon excess water was added and ice cooling was applied. The product was filtered off and recrystallized from ethanol, yield 6 g.

Methyl 5-Acetyl-2-carbomethoxymethyl-1-(6-methyl-2-pyridyl)-6(1H)-oxonicotinate (17).—A solution of 19.2 g (0.1 mol) of 2-acetoacetylamino-6-methylpyridine (**3**), 34 g (0.2 mol) of dimethylacetone dicarboxylate, and 1 g of $ZnCl_2$ in 150 ml of abolute ethanol and 60 ml of triethyl orthoformate was refluxed for 4 hr. After the mixture cooled in the refrigerator overnight, 11.5 g of **4** was isolated by filtration. The filtrate was evaporated and the residue was taken up in a small amount of ethanol. The precipitated product was recrystallized from ethanol, yield 32 g (45%), mp 171.7°.

Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.62; H, 5.06; N, 7.72.

1-Acetyl-2-ethoxy-(*p*-chloro)acrylanilide (21).—A solution of 30 g (0.124 mol) of 2-carbethoxy-(*p*-chloro)acetanilide,[6] 30 ml each of triethyl orthoformate and acetic anhydride, and 2 g of $ZnCl_2$ was refluxed for 3 hr. The product crystallized on cooling overnight in the refrigerator and was recrystallized from methanol yield 23 g of **21** (61%), mp 130–132°.

(1) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 225 (1961).
(2) Beilsteins Handbuch, Vol. 22, p I 630.
(3) V. F. Kucherov, *J. Gen. Chem. USSR*, **20**, 1890 (1950); *Chem. Abstr.*, **45**, 2951*h* (1951).
(4) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).
(5) I. G. Farbenindustrie A.-G., German Patent 607,623 (Jan 3, 1935).
(6) F. D. Chattaway and F. A. Mason, *J. Chem. Soc.*, **97**, 339 (1910).

Anal. Calcd for $C_{13}H_{14}ClNO_3$: C, 56.47; H, 5.42; N, 4.70. Found: C, 56.74; H, 5.41; N, 4.79.

3-Methyl-4-(6-methyl-2-pyridyl)carbamoylpyrazole (18).—A solution of 9.5 g (0.03 mol) of **10** and 5 g (0.1 mol) of hydrazine hydrate in 100 ml of ethanol was refluxed for 3 hr. It was then poured into water and the solution was acidified with acetic acid. The precipitated crystals were recrystallized from ethanol, 4 g (62%), mp 236–239°.

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.60; N, 25.91. Found: C, 61.33; H, 5.57; N, 25.75.

3-Acetyl-5-carbo-*t*-butoxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridone (22b) (Table IV).—To a slurry of 26.7 g (0.1 mol) of **21** and 25 g (0.158 mol) of *t*-butyl acetoacetate in ice-cooled ethanol (150 ml), 6 g of $NaOCH_3$ (0.11 mol) was added. The solution became almost clear before the product crystallized. After 2 hr in an ice bath, the mixture was filtered and the product was washed with ethanol, yield 25 g.

3-Acetyl-5-carboxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridione (22d) (Table IV).—Compound **22b** (20 g, 0.055 mol) was dissolved in 100 ml of concentrated H_2SO_4 by heating the mixture to 60°, whereupon it was left to stand at room temperature for 30 min. The solution was poured into ice water and filtered. The product was recrystallized from methanol–water, yield 14 g.

1-(*p*-Chlorophenyl)-3,5-diacetyl-6-hydroxy-2-pyridone (20). 1.—A slurry of 44 g (0.112 mol) of **8** in 400 ml of Clorox and 80 g of 50% aqueous NaOH was heated on a steam bath for 2 hr. Most of the starting material dissolved. The mixture was then cooled by addition of ice and acidified with concentrated HCl. The product was filtered off and recrystallized from ethanol, yield 10 g (29%), mp 238–240° dec.

2.—Compound **22a** (20 g, 0.06 mol) was added to a solution of 70 ml of methanol, 50 ml of water, and 30 g of 50% aqueous NaOH. The mixture was heated gently until the solid was dissolved and then left standing overnight. The product was filtered after acidification with concentrated HCl and recrystallized from ethanol, yield 15 g (82%).

Anal. Calcd for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.56. Found: C, 58.68; H, 4.10; N, 4.40.

Registry No.—**2**, 23600-24-0; **3**, 16867-47-3; **4**, 23646-59-5; **5**, 23600-26-2; **6**, 23600-27-3; **7**, 23600-28-4; **8**, 23646-60-8; **9**, 23600-29-5; **10**, 23600-30-8; **12**, 23646-61-9; **16**, 23600-31-9; **17**, 23600-32-0; **18**, 23600-33-1; **19**, 23646-64-2; **20**, 23600-34-2; **21**, 23600-35-3; **22a**, 23600-36-4; **22b**, 23600-37-5; **22c**, 23600-38-6; **22d**, 23600-39-7; **28**, 23600-40-0; **29**, 23646-62-0; **30**, 23646-63-1; **31**, 23674-48-8; **32**, 23600-41-1; **33**, 23600-42-2.

Acknowledgment.—We gratefully acknowledge the encouragement of this work by Dr. Charles L. Levesque.

Fluorinated Aminoimidazolines. Synthesis and Determination of Tautomeric Structure

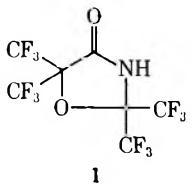
WILLIAM J. MIDDLETON AND CARL G. KRESPAN

Contribution No. 1592 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

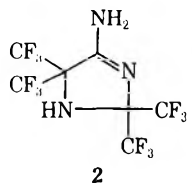
Received August 29, 1969

Hexafluoroacetone imine reacts with sodium cyanide to give 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), a compound that possesses pronounced pharmacological activity as a central nervous system depressant and muscle relaxant. This imidazoline has unexpected chemical and thermal stability. The ^1H nmr spectrum of ^{15}N-labeled **2** shows that it exists primarily as the amino tautomer, and not as the imino tautomer **16**, and indicates restricted rotation for the amino group because of the contribution of ionic resonance form **17** or solvent complexing. The preparation of several analogs, including 4-amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (**9**), 4-amino-2,2,5,5-tetramethyl-3-imidazoline (**12**), and 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**13**), is also described.

In earlier studies aimed at the synthesis of heterocyclic compounds highly substituted with fluoroalkyl groups, it was found that sodium cyanide reacts with 2 equiv of hexafluoroacetone to yield the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone



1

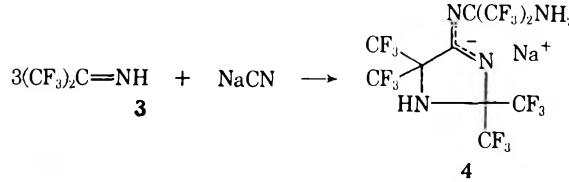


2

(**1**).[1] In continuing these studies, we have investigated the related reactions of cyanide with imines of fluoro ketones in attempts to prepare analogous heterocyclic compounds containing more nitrogen. One of the compounds that resulted from this study, 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), has been shown in laboratory and clinical studies to possess pronounced pharmacological activity as a central nervous system depressant and muscle relaxant.[2]

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **32**, 951 (1967).

Reactions of Cyanide with Fluoro Ketone Imines.—Hexafluoroacetone imine (**3**) reacts readily and exothermally with a suspension of sodium cyanide in a polar solvent such as dimethyl sulfoxide, dimethylformamide, or acetonitrile at temperatures as low as −30° to give the 3:1 adduct **4**. Regardless of which reagent is in excess or the mode of addition, the 3:1 adduct is always formed.

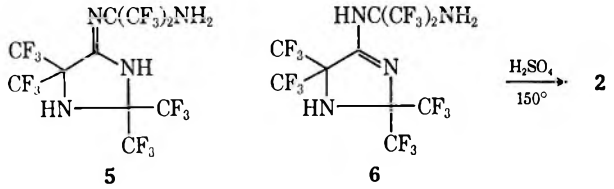


3 **4**

This behavior is in contrast to the reaction of hexafluoroacetone with sodium cyanide, which could be stopped at either a 1:1 adduct or a 2:1 adduct and which never formed a 3:1 adduct.[1] Acidification of **4**

(2) J. L. Claghorn and J. D. Schoolar, *Current Therap. Res.*, **10**, 279 (1968); I. M. Levine, P. B. Jossmann, D. F. Friend, and J. DeAngelis, *Clin. Pharmacol. Therap.*, **9**, 448 (1968); R. Clark, T. E. Lynes, W. A. Price, J. P. Marvel, D. H. Smith, and V. G. Vernier, *The Pharmacologist*, **10**, 197 (1968).

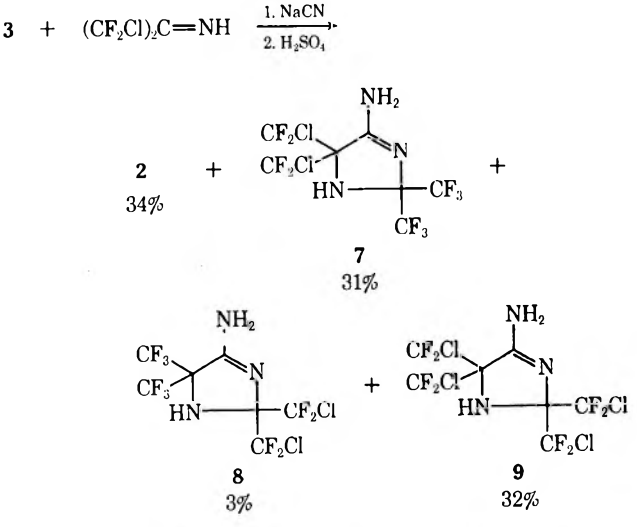
gave an easily sublimable heterocycle. Although two different tautomeric structures (**5** and **6**) can be written for this compound, the imidazoline structure **6** has been tentatively assigned on the basis of analogy to related compounds to be described later in this and a following paper.[3]



5 **6**

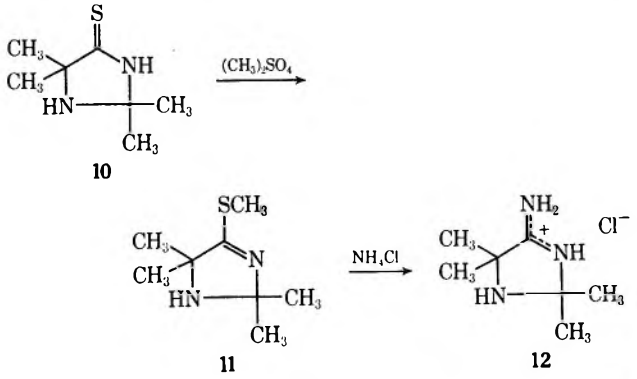
One unit of imine can be removed from **6**, either by pyrolysis or hydrolysis with concentrated sulfuric acid at 150°. The resulting aminoimidazoline **2** possesses exceptional thermal, hydrolytic, oxidative, and other chemical stability. Examples of this stability follow. (1) **2** can be dissolved in hot (150°) concentrated sulfuric acid or 20% oleum and recovered unchanged after dilution with water. No salt formation occurs in aqueous solutions with acids. (2) **2** is inert to oxidizing reagents such as chlorine, bromine, hydrogen peroxide, and peracids, and hypochlorites even at 100°. (3) **2** will not react with anhydrous hydrazine, even when held at reflux temperature for several days. (4) **2** shows remarkable thermal stability, even up to 500°. At higher temperatures, it can be pyrolyzed to CF_3CN, CHF_3, and C_2F_6.

Other similar 4-aminoimidazolines were prepared by the reaction of sodium cyanide with different imines, including the imines of chloropentafluoroacetone, 1,3-dichlorotetrafluoroacetone, pentafluoroacetone, and perfluorocyclopentanone (see Experimental Section). Imidazolines derived from two different imines were also prepared by adding sodium cyanide to a mixture of two fluoro ketone imines; all four possible imidazolines are formed, but not in the statistical proportion. For example, reaction of sodium cyanide with an equimolar mixture of 3 and $(CF_2Cl)_2C{=}NH$ gave imidazolines **2**, **7**, **8**, and **9** in the ratio 34:31:3:32, respectively.



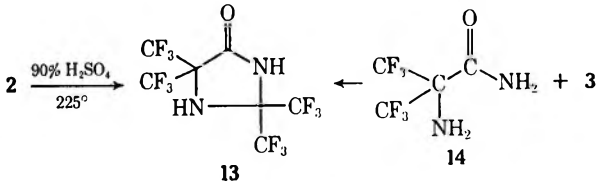
These imidazolines were separated by distillation and subsequent hydrolysis of their corresponding isocyanate derivatives.[3] which were formed by treatment of the imidazoline mixture with oxalyl chloride. Other mixed imidazolines were also prepared from **3** and $CF_3C(=NH)CF_2Cl$ and from **3** and $CF_3C(=NH)CF_2H$. In all cases, the isomer which contained the *gem*-trifluoromethyl groups on the 2-carbon position of the ring predominated (see Experimental Section).

The nonfluorinated analog of **2** could not be prepared by this method, since acetone imine is not stable. However, it was prepared and isolated as the hydrochloride salt (**12**) by reaction of the thio ether **11** with ammonium chloride. The thio ether was prepared by alkylation of the known thiolactam **10**[4] with methyl sulfate. This imidazoline possesses drastically different properties than **2** in that it forms salts with acids, is easily oxidized and hydrolyzed, and is thermally unstable.



10 **11** **12**

Structure Proof for 2.—The surprising inertness of **2** is consistent with its reported low toxicity when used as a pharmaceutical agent,[2] since hydrolysis or other degradation could lead to toxic materials such as fluoride ions. However, this inertness tends to cast doubt on the assigned structure. For this reason, a detailed study of the structure was undertaken. A proof of the skeletal structure was accomplished by the conversion of **2** into the lactam **13** by extremely vigorous hydrolysis with 90% sulfuric acid at 225°. The lactam **13** was independently synthesized by the condensation of hexafluoroacetone imine (**3**) with the amino amide **14**.



13 **14**

The ^{19}F nmr spectrum is also in agreement with the assigned structure **2**. Two signals of equal area were observed, each split into septets by *ca.* 5 Hz. Since the spin–spin coupled fluorine atoms are six bonds apart, this relatively large coupling constant may indicate a through-space interaction. This observed coupling constant is believed to be an average value between those of the *cis*- and the *trans*-trifluoromethyl groups; so the spectrum appears as an A_6X_6 pattern instead of the expected $A_3A'_3X_3X'_3$ pattern.

The higher field septets of both **2** and **13** are assigned so the trifluoromethyl groups in the 2 position, consistent with earlier observations that *gem*-trifluoromethyl groups flanked by N and/or O consistently

(3) W. J. Middleton, D. M. Gale, D. W. Wiley, and C. G. Krespan, *J. Org. Chem.*, **35**, 1485 (1970).

(4) J. C. Christian, *ibid.*, **22**, 396 (1957).

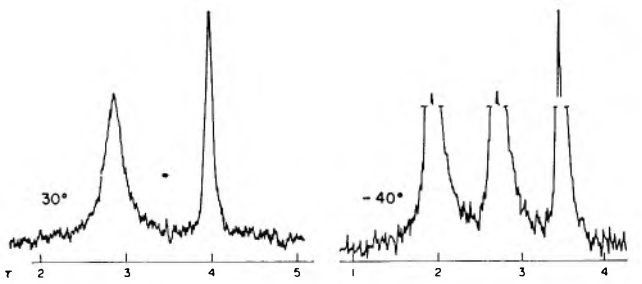
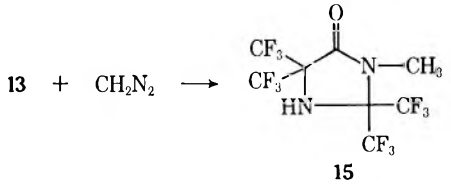


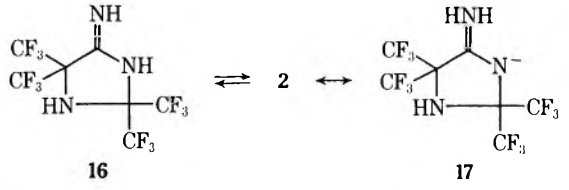
Figure 1.—Proton magnetic resonance spectra at 60 MHz of **2** at 30 and −40° in acetone-d_6.

appear at higher field than those attached to only one such atom in otherwise similar situations.[5] For example, the resonance for $(CF_3)_2C(NH_2)_2$ is 8.7 ppm higher field than that of amino amide **14**. This assignment is also supported by the ^1H–^{19}F spin–spin coupling observed between the methyl group and the higher field trifluoromethyl groups of methyllactam **15**, which was prepared by the action of diazomethane on **13**.



15

Tautomeric Determination.—It is possible to write another tautomeric structure (**16**) for **2** in which the double bond is shifted to an exocyclic position.



16 **17**

Attempts to prove by classical methods which of these two tautomeric structures best represents the compound were indecisive. In alkylation experiments, derivatives of both forms (**2** and **16**) that would be incapable of tautomerization could be prepared,[3] but the spectral and chemical properties of these derivatives were too similar to allow an assignment by analogy of an *exo* or an *endo* double bond to the parent. However, a detailed study of the proton nmr spectra of **2** did allow a definite tautomeric assignment to be made.

At temperatures above 25° in solvents or in the melt, the ^1H nmr spectrum of **2** shows two broad absorptions in the ratio of 2:1 (Figure 1). The protons causing the larger, lower field absorption exchanged rapidly with D_2O, whereas the sharper, higher field peak remained in the presence of D_2O until an acid was added. This spectrum does not differentiate between structures **2** and **16** (or an equilibrium mixture), for the larger peak could either be due to the amino group of **2** or be an exchange-averaged peak owing to H-3 and the imino H in structure **16**.

At lower temperature the lower field peak splits into two distinct peaks of equal area about 46 Hz apart

(5) See, *e.g.*, W. J. Middleton and/or C. G. Krespan, *et al.*, *J. Org. Chem.*, **30**, 1398, 1402 (1965); **32**, 948, 951 (1967); **33**, 1002 (1968); *J. Amer. Chem. Soc.*, **86**, 4948 (1964); **88**, 3617 (1966); **90**, 6813 (1968).

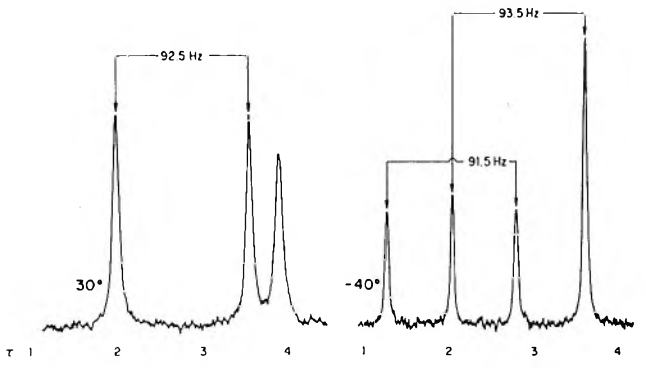


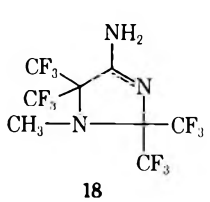
Figure 2.—Proton magnetic resonance spectra at 60 MHz of 4-(^{15}N-amino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline at 30 and −40° in acetone-d_6.

(Figure 1). Again, this result could be explained on the basis of either structure. If **16** were correct, the cooling could have slowed down the exchange rate so that averaging no longer occurred. If structure **2** were correct, restricted rotation about the exocyclic carbon–nitrogen bond due to a contribution of resonance from **17** (similar to that observed for amides) would be implied.

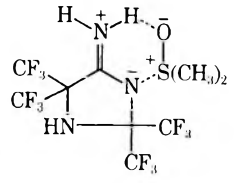
By observing the spin–spin coupling between nitrogen and hydrogen, this problem was resolved. Unfortunately, ^{14}N–^1H coupling is difficult to observe because of the quadrupole associated with ^{14}N. Isotropic ^{15}N has no quadrupole, however, and furthermore has a spin of $^1/_2$ (like ^1H). For the purpose of observing the ^1H nmr spectrum, **2** containing a ^{15}N label was prepared from ^{15}N-labeled sodium cyanide.

The labeled sample incorporated the ^{15}N exclusively as the exocyclic nitrogen, as shown by its complete loss when the sample was hydrolyzed to the lactam **13**. No scrambling of the ^{15}N occurred between the exocyclic nitrogen and the ring nitrogen in the 3 position, as would have been expected if a rearrangement similar to the Chapman rearrangement observed in the reaction of sodium cyanide with hexafluoroacetone[1] had occurred. This lack of rearrangement may reflect the fact that there is no driving force to form a more stable anion as there is in the case of the hexafluoroacetone reaction.

In the 30° ^1H nmr spectrum of the labeled sample of **2** (Figure 2), a sharp doublet (J_{NH} = 92.5 Hz, measured at both 60 and 40 MHz) now appeared in the place of the broad signal of the two easily exchangeable hydrogens. In the spectrum at −40°, this doublet became two doublets (J_{NH} = 91.5 and *ca.* 93.5 Hz). The coupling constant of the later doublet could not be measured exactly because the high-field leg overlapped the signal of the H in the 1-ring position. To remove this complication, the ^{15}N-labeled 1-methyl derivative **18**



18



19

was prepared[3] and its spectra were recorded at 25 and −40° (Figure 3).

The spectrum of **18** at 30° showed a single doublet (J_{NH} = 93.5 Hz) and at −40° two doublets (J_{NH} = 94.0 and 89.5 Hz). These spectra of the ^{15}N-labeled compounds clearly show that both of the easily exchangeable hydrogens in **2** and **18** are directly bound to the ^{15}N, since the coupling constants are large and are consistent with values to be expected for directly bound hydrogens.[6] Imino structures such as **16** are therefore eliminated, since the NH coupling would be expected to have a low value for the hydrogen not directly bound to ^{15}N in this structure.

The two separately observable peaks for the amino group in the low-temperature spectra of **2** must therefore result from restricted rotation about the C–N bond due to a contribution of ionic resonance from **17**. The observed values of the coupling constants indicate a large amount of s character in the hybridization of the NH bonds (closer to sp^2 than sp^3),[6] consistent with structure **17**.

The temperature necessary to cause the appearance of the two separate peaks appears to vary with solvent polarity. In dimethyl sulfoxide, the most polar solvent examined, the two peaks appeared at 10°. The formation of a complex such as **19** could aid in causing the restricted rotation. This conclusion was supported by the isolation of a stable 1:1 complex of **2** with dimethyl sulfoxide that could be recrystallized from benzene.

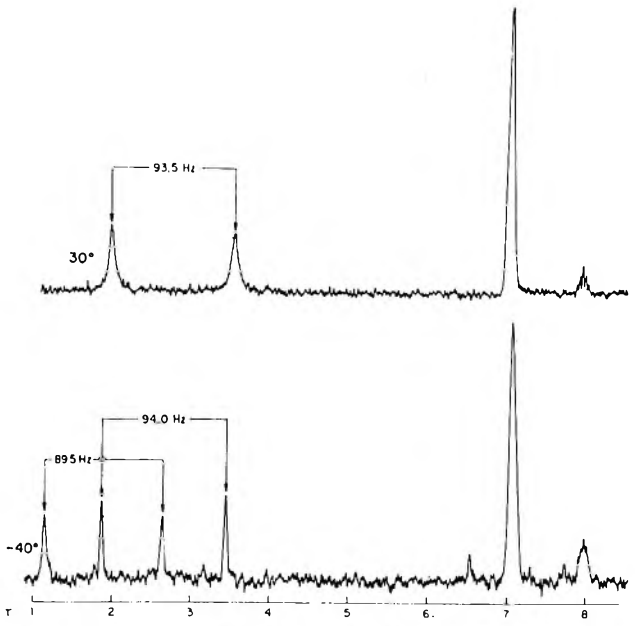


Figure 3.—Proton magnetic resonace spectra at 60 MHz of **18** at 30 and −40° in acetone-d_6.

Experimental Section[7]

4-[1-Amino-2,2,2-trifluoro-1-(trifluoromethyl)ethylamino]-2,-2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6).—Hexafluoroacetone imine (**3**), 20 ml (*ca.* 30.8 g, 0.187 mol), at −10°, was slowly distilled into a stirred suspension of 3.06 g (0.0625 mol) of powdered sodium cyanide in 50 ml of dimethyl sulfoxide. An exothermic reaction ensued. The rate of addition of the imine was adjusted so that the temperature of the reaction mixture did not rise above 65°. At the end of the addition (20 min being required) the reaction mixture became homogenous. The mixture was cooled to 20° and then poured into 500 ml of water containing 100 ml of aqueous 10% hydrochloric acid. The aqueous phase was decanted from the oil that separated, and the oil was washed with water until it solidified. This solid was collected on a filter, pressed dry, and then dried in a vacuum desiccator over P_2O_5, crude yield 24.1 g (74%). Recrystallization from pentane gave **6** as colorless prisms: mp 45–46°; ^{19}F nmr ($CDCl_3$) δ 72.8 (septet, 6 F, J_{HF} = 5 Hz), 77.9 (septet, 6 F, J_{HF} = 5 Hz), and 79.8 ppm (s, 6 F); ^1H nmr ($CDCl_3$) τ 4.5 (broad singlet, 1 H), 6.43 (broad singlet, 1 H), and 6.92 ppm (s, 2 H); ir (KBr) 5.97 μ (C=N).

Anal. Calcd for $C_{10}H_4F_{18}N_4$: C, 23.00; H, 0.77; F, 64.49. Found: C, 23.21; H, 0.91; F, 65.23.

4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (2).—A 47.1-g sample of **6** was dissolved in 100 ml of concentrated sulfuric acid, and the stirred solution was heated slowly to 150° and held at that temperature for 10 min. Frothing occurred during the heating period. The solution was cooled to 20° and poured over 1 l. of crushed ice. The white solid that formed was collected on a filter after the ice melted and was washed with water. Recrystallization from alcohol–water (1:2) gave 31.5 g (98%) of **2** as long, colorless needles: mp 159.7–160.4°; bp 194° (760 mm); ir (KBr) 5.90 μ (C=N); ^{19}F nmr (acetone) δ 71.5 (septet, 6 F, J_{HF} = 4.7 Hz) and 76.5 ppm (septet, 6 F, J_{HF} = 4.7 Hz); ^1H nmr (dimethyl sulfoxide-d_6) τ 2.80 (broad singlet, 2 H) and 3.94 (sharper singlet, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 357 (0.13), 338 (4.8), 288 (100), 219 (46), 173 (11), and 69 (30). Neutralization equivalents were determined by titration with tetra-*n*-butylammonium hydroxide in pyridine.

Anal. Calcd for $C_7H_3F_{12}N_3$: C, 23.55; H, 0.85; F, 63.85; N, 11.77; neut equiv, 357. Found: C, 23.72; H, 10.03; F, 63.86; N, 11.99; neut equiv, 356.7, 352.3, 351,3.

4-Amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (9).—Powdered sodium cyanide, 11.8 g (0.24 mol), was added portionwise over 15 min to a stirred solution of 47.5 g (0.24 mol) of 1,3-dichlorotetrafluoroacetone imine in 80 ml of dimethylformamide cooled to 0°. As the addition proceeded, the reaction mixture warmed slightly, and the rate of addition was adjusted so that the temperature remained below 10°. After the addition, the reaction mixture was poured into 200 ml of aqueous 10% hydrochloric acid, and the oil that separated was washed with water and dissolved in 50 ml of fuming sulfuric acid (20% SO_3). The sulfuric acid solution was heated to 150°, cooled, and poured over 200 ml of crushed ice. The solid that formed was collected on a filter, washed with water, and dried in air. Sublimation at 150° (0.5 mm) gave 26.5 g (78%) of **9** as a crystalline solid: mp 126–133°; ^{19}F nmr (acetone) δ 53.5 (m, 2 F), 55.1 (m, 2 F), 58.3 (m, 2 F), and 58.8 ppm (m, 2 F); ^1H nmr (acetone-d_6) τ 4.09 (1 H) and 2.9 ppm (2 H); ir (KBr) 5.94 μ (C=N).

Anal. Calcd for $C_7H_3Cl_4F_8N_3$: C, 19.87; H, 0.72; Cl, 33.53; F, 35.93; N, 9.84. Found: C, 20.22; H, 0.89; Cl, 33.85; F, 35.91; N, 9.61.

4-Amino-2,5-bis(chlorodifluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline.—This compound was prepared in 70% yield by a procedure similar to that used to prepare **9**, except that chloropentafluoroacetone imine was used in place of the dichloroimine, and was obtained as a white, crystalline powder: mp 120–122° (sealed capillary); ^{19}F nmr (acetone) δ 57.3 (m, 2 F), 62.1 (m, 2 F), 69.7 (m, 3 F) and 73.9 ppm (m, 3 F); ^1H nmr (acetone-d_6) τ 4.09 (1 H) and 2.9 ppm (2 H); ir (KBr) 5.94 μ (C=N).

Anal. Calcd for $C_7H_3Cl_2F_{10}N_3$: C, 21.56; H, 0.77; Cl, 18.18; F, 48.72; N, 10.77. Found: C, 21.94; H, 0.98; Cl, 18.03; F, 48.71; N, 10.79.

12-Amino-6H-hexadecafluoro-6,13-diazadispiro[4.1.4.2]tridec-12-ene.—This compound was prepared in 70% yield by a procedure similar to that used to prepare **9**, except that perfluorocyclopentanone imine was used in place of the dichloroimine, and was obtained as a white, crystalline powder: mp 168–171° (sealed capillary); ir (KBr) 5.92 (C=N) and 6.23 μ (NH_2); ^{19}F nmr (acetone-d_6) δ 120–140 ppm (m); ^1H nmr (acetone-d_6) τ 3.03 (NH_2) and 4.43 ppm (NH).

4-Amino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline (20).—This compound was prepared by a procedure similar to that used to prepare **9**, except that pentafluoroacetone

(6) G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 5564 (1964).

(7) Proton nmr spectra were obtained with a Varian A-60 spectrometer. Peak center positions are reported as τ values in parts per million. Fluorine nmr spectra were obtained with a Varian A56-60 spectrometer. Peak center positions are reported in parts per million upfield from $CFCl_3$ used as an internal reference.

imine[8] was used in place of the dichloroimine, and was obtained as a white, crystalline powder (mixture of two isomers): mp 142–144°; ^{19}F nmr (acetone) δ 72.8 (m, 3 F), 77.1 and 77.7 (multiplets, total 3 F), 127.0 (m, 2 F), and 131.0 ppm (m, 2 F); ^1H nmr (acetone-d_6) δ 3.56 (t, 1 H), 3.98 (t, 1 H), 5.12 (broad, 1 H) and 3.0 ppm (very broad, 2 H); ir (KBr) 5.91 μ (C=N).

Anal. Calcd for $C_7H_5F_{10}N_3$: C, 26.18; H, 1.57; F, 59.17; N, 13.08. Found: C, 26.49; H, 1.45; F, 59.15; N, 12.92.

4-Amino-5,5-bis(chlorodifluoromethyl)-2,2-bis(trifluoromethyl)-3-imidazoline (7).—Powdered sodium cyanide, 6.53 g (0.133 mol), was added portionwise over 30 min to a stirred solution of 33.0 g (0.2 mol) of hexafluoroacetone imine and 39.6 g (0.2 mol) of 1,3-dichlorotetrafluoroimine in 150 ml of dimethylformamide cooled to −30°. The reaction mixture was stirred for 1 hr at −30°, warmed to 25°, and mixed with 200 ml of 10% hydrochloric acid. The organic layer was washed twice with water and then dissolved in 40 ml of fuming sulfuric acid (20% SO_3). The solution was heated to 150°, cooled, and poured over crushed ice. The solid that formed was collected on a filter, washed with water, dried, and sublimed at 150° (10 mm) to give 33.0 g (64% total yield) of a mixture of imidazolines (**2**, **7**, **8**, and **9**), mp 118–155°.

A solution of 30.0 g of this mixture in 100 g of oxalyl chloride was stirred at 25° for 3 days and then distilled. There was obtained 9.10 g of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline,[3] 8.65 g of 4-isocyanato-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline,[3] and 9.02 g of 4-isocyanato-5,5-bis(chlorodifluoromethyl)-2,2-bis(trifluoromethyl)-3-imidazoline, bp 104–105° (8 mm), ir (liquid) 4.40 μ (NCO). The ^{19}F nmr spectrum of the latter imidazoline indicated that this sample also contained a minor amount (8–9%) of the isomeric 4-isocyanato-2,2-bis(chlorodifluoromethyl)-5,5-bis(trifluoromethyl)-3-imidazoline, for the sample had two absorptions in the CF_3 region: δ 76.0 (multiplet, relative area 91–92%) and 71.2 ppm (multiplet, relative area 8–9%).

Anal. Calcd for $C_8HCl_2F_{10}N_3O$: C, 23.10; H, 0.24; Cl, 17.05; F, 45.67. Found: C, 23.23; H, 0.57; Cl, 17.07; F, 45.37.

A 6-g sample of the dichloroisocyanate was mixed with 25 ml of concentrated sulfuric acid. Gas was evolved. Water, 2 ml, was added, and the solution was heated to 150°, cooled, and poured over 25 ml of crushed ice. The solid that formed was collected on a filter, washed with water, dried, and sublimed at 110° (10 mm) to give 5.25 g of **7** as a white, crystalline powder, mp 129–132° (sealed capillary), ir (KBr) 5.90 μ (C=N). The ^{19}F nmr spectrum in acetone indicated that the sample also contained 8–9% isomeric 4-amino-2,2-bis(chlorodifluoromethyl)-5,5-bis(trifluoromethyl)-3-imidazoline (**8**), because the sample had two absorptions in the CF_3 region: δ 76.2 (multiplet, 91–92%) and 71.1 ppm (multiplet, 8–9%).

Anal. Calcd for $C_7H_3Cl_2F_{10}N_3$: C, 21.56; H, 0.77; Cl, 18.18; F, 48.72; N, 10.77. Found: C, 20.98; H, 0.64; Cl, 18.01; F, 48.64; N, 10.67.

4-Amino-5- (and -2-) chlorodifluoromethyl)-2,2,5- (and- 2,5,5-)-tris(trifluoromethyl)-3-imidazoline.—A 69:31 mixture of these isomers was prepared and purified in a manner similar to that of **7** and **8**, using hexafluoroacetone imine and chloropentafluoroacetone imine as the starting imines. This mixture was obtained as a white solid, mp 124–128°. The ^{19}F nmr spectrum in acetone showed multiplets for CF_2Cl at δ 58.0 (69%) and 62.6 ppm (31%) and multiplets for at δ 72.0 and 76.7 (ratio 1:2, total area of CF_3 region, 69%) and 70.2 and 74.5 ppm (ratio 2:1, total area of CF_3 region, 31%).

Anal. Calcd for $C_7H_3ClF_{11}N_3$: C, 22.53; H, 0.81; Cl, 9.49; F, 55.95; N, 11.24. Found: C, 22.69; H, 0.82; Cl, 8.87; F, 55.92; N, 11.17.

4-Amino-2-(difluoromethyl)-2,5,5-tris(trifluoromethyl)-3-imidazoline (21) and 4-Amino-5-(difluoromethyl)-2,2,5-tris(trifluoromethyl)-3-imidazoline (22).—Sodium cyanide, 7.55 g (0.15 mol), was added portionwise to a solution of 16.5 ml (0.15 mol) of hexafluoroacetone imine and 22.0 g (0.15 mol) of pentafluoroacetone imine in 100 ml of dimethylformamide cooled to −30°. The addition required 30 min. The reaction mixture was stirred for 1 hr at 25° and then mixed with 300 ml of 5% hydrochloric acid. The oil that precipitated was separated, washed with water, and dissolved in 50 ml of fuming sulfuric acid. The acid solution was heated quickly to 150°, cooled, and poured over ice. The solid that formed was collected on a filter, washed with water, and sublimed at 100° (10 mm) to give 11.1 g of a mixture of imidazolines. Gas chromatographic analysis (fluorosilicone column) indicated that this mixture was composed of 25.2% **2**, 10.4% **22**, 57.6% **21**, and 4.9% **20**.

A 2.8-g sample of **21** was isolated by preparative gas chromatography: mp 142–144°; ^{19}F nmr (acetone) δ 72.8 (m, 3 F), 77.7 (m, 6 F), and 137.3 ppm (m, 2 F); ^1H nmr (acetone-d_6) τ 3.53 (triplet, J = 53 Hz, CF_2H), 2.88 (broad singlet, NH), and 4.53 ppm (broad singlet, NH_2).

Anal. Calcd for $C_7H_4F_{11}N_3$: C, 24.79; H, 1.19; F, 61.36; N, 12.39. Found: C, 24.39; H, 1.21; F, 61.53; N, 12.50.

A 0.33-g sample of **22** was isolated by preparative gas chromatography: mp 152–154°; ^{19}F nmr (acetone) δ 72.8 (m, 6 F), 77.5 (m, 3 F), and 135.3 ppm (m, 2 F).

Anal. Calcd for $C_7H_4F_{11}N_3$: C, 24.79; H, 1.19. Found: C, 24.47; H, 1.19.

2,2,5,5-Tetramethyl-4-methylthio-3-imidazoline (11).—Dimethyl sulfate, 31.5 g (0.25 mol), was added dropwise with vigorous stirring to a solution of 31.65 g (0.2 mol) of 2,2,5,5-tetramethylimidazolidine-4-thione[4] (**10**) in 200 ml of aqueous 5% sodium hydroxide at 25°. The temperature of the reaction mixture rose to 45° in 30 min. The reaction mixture was cooled and extracted with 200 ml of ether in three portions. The ether extracts were dried ($MgSO_4$) and distilled to give 24.1 g (68%) of **11** as a colorless liquid: bp 71–72° (8.8 mm); $n^{25}D$ 1.4878; ^1H nmr (neat) τ 7.61 (singlet, SCH_3), 8.74 (singlet, 2 CH_3), 8.67 (singlet, 2 CH_2), and 8.06 ppm (singlet, NH).

Anal. Calcd for $C_8H_{16}N_2S$: C, 55.77; H, 9.36; N, 16.26; S, 18.61. Found: C, 55.67; H, 9.49; N, 16.27; S, 18.72.

A higher boiling fraction, bp 72–78° (8.8 mm), was redistilled to give 2.3 g of 1,2,2,5,5-pentamethyl-4-methylthio-3-imidazoline as a colorless liquid: bp 79–80° (8.7 mm); $n^{25}D$ 1.4927; ^1H nmr (neat) τ 7.66 (singlet, CH_3), 7.74 (singlet, CH_3), 8.79 (singlet, 2 CH_3), and 8.86 ppm (singlet, 2 CH_3).

Anal. Calcd for $C_9H_{18}N_2S$: C, 58.04; H, 9.74; N, 15.04; S, 17.21. Found: C, 57.76; H, 9.76; N, 15.02; S, 17.46.

4-Amino-2,2,5,5-tetramethyl-3-imidazoline Hydrochloride (12). A stirred mixture of 17.2 g (0.1 mol) of 2,2,5,5-tetramethyl-4-methylthio-3-imidazoline, 5.89 g (0.11 mol) of powdered ammonium chloride, and 100 ml of ethanol was heated at reflux for 14 days. During this time, methanethiol was slowly evolved. An additional 100 ml of ethanol was added, and the mixture was filtered while hot. The filtrate was cooled, and the solid that separated was collected on a filter, washed with ether, and recrystallized five times from ethanol to remove unreacted ammonium chloride. There was obtained 9.8 g of **12** as colorless crystals: mp 162–165° dec; ir (KBr) 5.89 μ (C=N); ^1H nmr (D_2O) τ 8.471 (singlet, 2 CH_3), 8.472 (singlet, 2 CH_3), and 5.2 ppm (DOH, exchange peak, 4 H).

Anal. Calcd for $C_7H_{16}ClN_3$: C, 47.32; H, 9.08; Cl, 19.96; N, 23.65. Found: C, 47.11; H, 9.19; Cl, 20.18; N, 24.00.

Aminobis(trifluoromethyl)acetamide (14).[9]—A solution of 3.6 g of aminobis(trifluoromethyl)acetonitrile,[10] 1 ml of water, and 20 ml of concentrated sulfuric acid was allowed to stand at room temperature for 3 days and then poured into 50 g of ice. The solution was extracted three times with 50-ml portions of ether, and the ether extracts were combined and dried ($MgSO_4$). Evaporation of the ether gave 2.2 g (56%) of the amide **14** as a colorless solid: mp 58–59°; ^{19}F nmr (acetone) 75.0 ppm (singlet); ^1H nmr (acetone-d_6) τ 2.63 (singlet, NH_2) and 7.04 ppm (singlet, NH_2).

Anal. Calcd for $C_4H_4F_6N_2O$: C, 22.87; H, 1.92; F, 54.26. Found: C, 23.18; H, 1.82; F, 53.73.

2,2,5,5-Tetrakis(trifluoromethyl)-4-imidazolidinone (13).—A mixture of 5.0 g (0.0238 mol) of aminobis(trifluoromethyl)-acetamide and 15 g (0.09 mol) of hexafluoroacetone imine was heated in a Hastelloy bomb at 150° for 12 hr. The bomb was cooled and vented, and nitrogen was bubbled through the liquid contents until they solidified. Sublimation of this solid at 100° (0.3 mm) gave 7.03 g (83%) of the imidazolidinone **13** as a crystalline, white powder: mp 107–108°; ir (KBr) 5.65 μ (C=O); ^{19}F nmr (acetone) δ 72.7 (septet, J = 4.5 Hz, 2 CF_3) and 78.1 ppm (septet, J = 4.5 Hz, 2 CF_3); ^1H nmr (acetone-d_6) τ 5.0 (singlet, NH) and 3.3 ppm (singlet, NH); mass spectrum (70 eV) m/e (rel intensity) 339 (0.14), 289 (72), 288 (56), 226 (47), and 69 (100).

Anal. Calcd for $C_7H_2F_{12}N_2O$: C, 23.47; H, 0.56; F, 63.67; N, 7.83. Found: C, 23.76; H, 0.91; F, 63.26; N, 7.50.

(8) W. J. Middleton, U. S. Patent, 3,342,864 (1967).

(9) We are indebted to Dr. D. M. Gale for this experiment.

(10) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

3-Methyl-2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**15**).—A 3% solution of diazomethane in ether was added portionwise to a solution of 5.0 g of **13** in 10 ml of ether until nitrogen evolution ceased. The ether was evaporated under a stream of nitrogen, and the solid residue was recrystallized from alcohol to give 4.0 g of **15** as colorless crystals: mp 164–165° (sealed capillary); ir (KBr) 5.71 μ (C=O); ^{19}F nmr (acetone) δ 72.8 (septet, J = 4.4 Hz, 2 CF_3) and 75.3 ppm (septet, J_{FF} = 4.4 Hz, split further to quartets, J_{FH} = 0.9 Hz, 2 CF_3); ^{1}H nmr ($CDCl_3$) τ 6.83 (septet, J = 0.9 Hz, CH_3) and 3.25 ppm (singlet, NH).

Anal. Calcd for $C_8H_4F_{12}N_2O$: C, 25.82; H, 1.08; F, 61.27; N, 7.53. Found: C, 26.05; H, 1.30; F, 61.28; N, 7.81.

Hydrolysis of 4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**).—A solution of 100 g of **2** and 25 ml of water in 250 ml of concentrated sulfuric acid was heated at 225° in a sublimation apparatus for 5 days. The sublimate, most of which formed after the first day, was mixed with 200 ml of aqueous 5% sodium hydroxide. The solid that did not dissolve was collected on a filter and washed with water to give 5.8 g of unhydrolyzed **2**. The filtrate was made acidic with 10% hydrochloric acid, and the solid that precipitated was collected on a filter, washed with water, dried, and sublimed at 150° (5 mm) to give 33.2 g (33% conversion, 92% yield) of 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**13**), identical by melting point and ir and nmr spectrum with an authentic sample. The sulfuric acid solution after cooling was poured over 1 l. of crushed ice and the solid that precipitated was collected on a filter, washed with water, and dried to give 58.0 g of unhydrolyzed **2**.

Dimethyl Sulfoxide Complex (**19**).—Dimethyl sulfoxide, 3.91 g (0.05 mol), was added to a solution of 17.86 g (0.05 mol) of **2** in 25 ml of ether. Heat was evolved, and a white solid precipitated. The solid was collected on a filter, dried in air (17.8 g), and recrystallized from benzene to give 15.7 g (72%) of the 1:1 complex as large, colorless prisms: mp 125–126°; ^{19}F nmr (acetone-d_6) δ 72.1 (septet, J = 5 Hz) and 76.7 ppm (septet, J = 5 Hz); ^{1}H nmr (acetone-d_6) τ 2.70 (NH_2), 3.72 (NH), and 7.42 ppm (singlet, 2 CH_3).

Anal. Calcd for $C_9H_9F_{12}N_3OS$: C, 24.83; H, 2.09; F, 52.39; N, 9.66; S, 7.37. Found: C, 25.18; H, 2.17; F, 52.15; N, 9.94; S, 7.47.

Pyrolysis of 2.[9]—Samples of **2** were pyrolyzed over quartz in a glpc–pyrolysis set-up from 200 to 650°. Little decomposition occurred below 500°; at 600° decomposition was moderate and at 750° it was complete. The products were isolated and shown to be a mixture of CF_3CN, CHF_3, and C_2F_6 by ir analysis.

^{15}N-Labeled 2.—A sample of **2** containing labeled nitrogen in the 4-amino group was prepared using ^{15}N-labeled (98.7%) sodium cyanide: mass spectrum (70 eV) m/e (rel intensity) 358 (0.1, parent − ^{15}N), 339 (5), 289 (100), 220 (47), and 69 (30). Hydrolysis of this sample with sulfuric acid gave the lactam **13**, which contained no ^{15}N as determined from its mass spectrum, which is identical with that of **13** prepared by other methods.

Registry No.—**2**, 23757-42-8; **2** (^{15}N labeled), 23758-03-4; **6**, 14372-88-4; **7**, 23757-44-0; **8**, 23757-45-1; **9**, 23757-46-2; **11**, 23757-47-3; **12**, 23757-48-4; **13**, 23757-49-5; **14**, 14316-86-0; **15**, 23829-37-0; **18**, 23757-51-9; **19**, 23757-52-0; **20**, 23757-53-1; **21**, 23757-96-2; **22**, 23757-97-3; 4-amino-2,5-bis(chlorodifluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline, 23757-98-4; 2-amino-6H-hexadecafluoro-6,13-diazadispiro[4.1.4.2]tridec-12-ene, 23757-99-5; 4-amino-5-chloro(difluoromethyl)-2,2,5-tris(trifluoromethyl)-3-imidazoline, 23758-00-1; 4-amino-2-chloro(difluoromethyl)-2,5,5-tris(trifluoromethyl)-3-imidazoline, 23758-01-2; 1,2,2,5,5-pentamethyl-4-methylthio-3-imidazoline, 23758-02-3.

Fluorinated Aminoimidazolines. Reactivity of the Nitrogen Functions

W. J. MIDDLETON, D. M. GALE, D. W. WILEY, AND C. G. KRESPAN

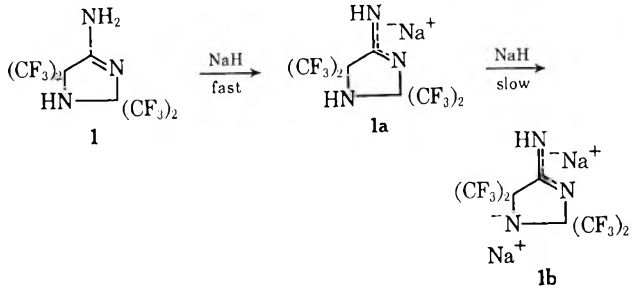
Contribution No. 1598 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received August 29, 1969

The very stable amino and amidino functions of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**1**) are attacked by strong acids and bases. Electrophilic alkylating agents such as dimethyl sulfate tend to attack at the 3 position, while nitration and acylation occur on the 4-amino group. Mono- and dianions stable at 25° can be prepared and used to react with **1** at the 1 position and on the 4-amino group. Appropriate combinations of these techniques allowed synthesis of all the nine possible methylated derivatives of **1**. The 4-nitramino and 4-isocyanato derivatives (**10** and **28**) are particularly useful intermediates.

The exceptional stability of 4-amino-2,2,5,5-tetrakis(polyfluoroalkyl)-3-imidazolines and their availability from fluorimines and cyanide ion[1] prompted a study of their properties. The discovery of the pronounced pharmacological activity of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**1**) coupled with low toxicity[2] provided further incentive for a detailed investigation of the chemistry of these new fluorinated heterocycles.

Anion Formation with Strong Bases.—Although measurement of pH in protic systems established the near neutrality of **1**, the amidine function serves as a donor in the formation of strong hydrogen-bonded complexes with acceptors such as dimethyl sulfoxide and diethyl oxalate.[1] In aprotic media, salt formation with strong base does occur, so that monoanion **1a** forms easily with 1 equiv of sodium hydride–glyme or sodium methoxide–dimethyl sulfoxide.



Excess (threefold) sodium hydride and **1** in glyme formed **1a** at 25° and dianion **1b** at 60° or higher. Anion **1b** is stable at 25°, and **1b** is moderately stable at 84°

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **35**, 1480 (1970).

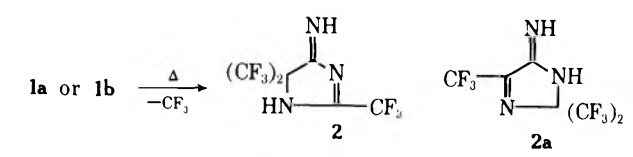
(2) The pharmacological studies on **1** as a skeletal muscle relaxant and central nervous system depressant are being reported separately. See I. M. Levine, P. B. Jossmann, D. G. Friend, and V. DeAngelis, *Chim. Pharmacol. Therap.*, **9**, 448 (1968); J. L. Claghorn and J. C. Schoolar, *Current Therap. Res.*, **10**, 279 (1968); R. Clark, T. E. Lynes, W. A. Price, J. P. Marvel, D. H. Smith, and V. G. Vernier, *The Pharmacologist*, **10**, 197 (1968).

TABLE I
SYNTHESES OF METHYLATED 4-AMINO-2,2,5,5-TETRAKIS(TRIFLUOROMETHYL)-3-IMIDAZOLINES AND 4-IMINO-2,2,5,5-TETRAKIS(TRIFLUOROMETHYL)IMIDAZOLIDINES[a]

Product	Starting materials	Conditions	Isolation	Yield, %	Mp or bp, °C (mm)	Ir bands, μ
3	Na salt of **1** [from NaH and 7.0 g (0.02 mol) of **1**] + 3.5 g of CH_3I	Refluxed overnight in 50 ml of glyme	Distillation	40	75 (10)	2.90 (m) and 3.08 (w) for NH; 6.00 (s) for C=N[b]
17	10.0 g (0.028 mol) of **1** + 20 ml of $(CH_3)_2SO_4$	Heated rapidly to boiling (*ca.* 188°)	Hydrolyzed hot with 50 ml of H_2O, then neutralized with 10% NaOH; fractional recrystallization from pentane to separate from **18**	21 (as mixture with **18**)	121–122	2.95 (m) and 3.17 (m) for NH; 5.95 (s) for C=N
17	13.5 g (0.041 mol) of **1** + 6.0 g of $(CH_3)_3OBF_4$	Stirred and refluxed for 6 hr in 80 ml of CH_2Cl_2	Washed with aq Na_2CO_3; recrystallized from 1:1 water–ethanol, then from pentane	65	...	...
16	Na salt of **8** [from 7.5 g (0.02 mol) and 1.2 g of $NaOCH_3$] + 4.5 g of CH_3I	10 min at 25° in 50 ml of $(CH_3)_2SO$	Diluted with 300 ml of H_2O and extracted with ether; preparative gc at 100° on silicone 200	32	71.5–73	2.87 (m) and 2.91 (m) for NH; 6.01 (s) for C=N
4	10.0 g (0.028 mol) of **1** + 30 ml of $(CH_3)_2SO_4$	8 hr at 200° under autogenous pressure	Hydrolyzed hot with 10 ml of H_2O, then neutralized with aq NaOH; portion soluble in ether–pentane isolated by gc along with **18** using silicone 200 column	7	30–33	2.88 (m) for NH; 6.12 (s) for C=N[c]
20	9.25 g (0.025 mol) of **8** + 11 ml of $(CH_3)_2SO_4$	Heated rapidly to 170° and exothermic reaction (185°) allowed to occur	Hydrolyzed hot with 10 ml of 35 H_2O, neutralized with aq NaOH and steam distilled; preparative gc on silicone 200 column at 100° to separate from **19**		Soft, waxy solid	2.96 (m) for NH 5.95 (s) for C=N[c]
18	See **4** above	...	...	66 (as mixture with **17**)	48–49	3.0 (m, broad) for NH; 5.92 (s) for C=N
5	10.7 g (0.03 mol) of **1** treated in three separate successive reactions with 1.78 g (0.033 mol) of $NaOCH_3$ and 4.97 g (0.035 mol) of CH_3I in each reaction	Each reaction run for 10 min at 5° in 75 ml of $(CH_3)_2SO$	Each diluted with 350 ml of H_2O and lower layer collected; product of third treatment purified by preparative gc on silicone 200 at 85°	50	37.5–39	6.13 (s) for C=N
19	Na salt of **18** [from 5.77 g (0.015 mol) and 1.35 g of $NaOCH_3$] + 4.5 g of CH_3I	20 min at 25° in 35 ml of $(CH_3)_2SO$	Diluted with 150 ml of H_2O; bottom layer purified by preparative gc on silicone 200 at 85°	46	<0	5.85 (s) for C=N[b]
19	See **20** above	...	...	29	...	...

[a] All compounds gave satisfactory elemental analyses. Mass spectra and nmr analyses support the assigned structures. [b] CCl_4 solution. [c] Neat liquid.

(reflux in glyme). Prolonged reflux of **1b** in glyme caused slow decomposition to a four-component product mixture. The major component was **2**, formed by leavage of a trifluoromethyl anion from one or both of the salts of **1**.

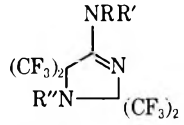


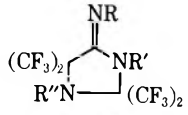
A conjugated structure with two kinds of hydrogen is indicated by the ultraviolet and proton nmr spectra, and structure **2** is favored for the product over alternative structure **2a** on the basis of acidity and the fluorine nmr spectrum. Solubility in dilute sodium hydroxide, the means by which **2** is isolated from **1** and by-products, is more in keeping with formation of a completely conjugated anion than the cross-conjugated anion which would result from **2a**. Loss of a trifluoromethyl group from the 2 position is also indicated by the loss of high-field fluorine nmr signal for **2** compared with **1**.[1]

Alkylations of Imidazoline Anions.—All the methylated derivatives of **1** prepared under basic conditions are given in Table I. Alkylation of the salt **1a** (prepared with 1 equiv of sodium methoxide in dimethyl sulfoxide) with methyl iodide at 25° gave predominantly the 4-methylamino isomer **3**. Although this might be a kinetic result, it is taken as confirmation of delocalized structure **1a** rather than that with a charge at the 1 position. Independent evidence that amidine hydrogen is more acidic than amine hydrogen in **1** was obtained by nmr. In deuterioacetone with D_2O, both protons of the 4-amino group of **1** exchanged within 1 hr at 25°, whereas the 1-position proton required catalysis. The preference for substitution in **1a** on the 4-amino group rather than at the 3 position apparently results from the considerable steric crowding around the

3 position indicated by Stuart–Briegleb models. The proportions of product methylated at the 4-amino-, 3, and 1 positions was 60:2:1, with intermediate amounts of dimethylated products. Of the dimethylated products, the 4-(N,N-dimethylamino) compound **4** predominated. Repeated methylation of **1** led to the 1-methyl-4-(N,N-dimethylamino) compound **5**.

Anion **1a** derived from **1** with sodium hydride in glyme also was methylated to give mainly **3**. This procedure was used to obtain pure **3** (Table I). Similar alkylations with a spectrum of functionally substituted alkyl halides gave imidazolines monosubstituted on the 4-amino group (**6**) in up to 80% yield (Experimental Section).

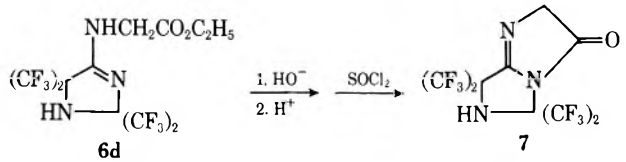




3, R = CH_3; R′ = R″ = H
4, R = R′ = CH_3; R″ = H
5, R = R′ = R″ = CH_3
6a, R = $CH_2CH_2N(CH_3)_2$; R′ = R″ = H
b, R = $CH_2C_6H_5$; R′ = R″ = H
c, R = $CH_2CH{=}CH_2$; R′ = R″ = H
d, R = $CH_2CO_2C_2H_5$; R′ = R″ = H
9, R = R′ = H; R″ = C_2H_5
16, R = H; R′ = R″ = CH_3

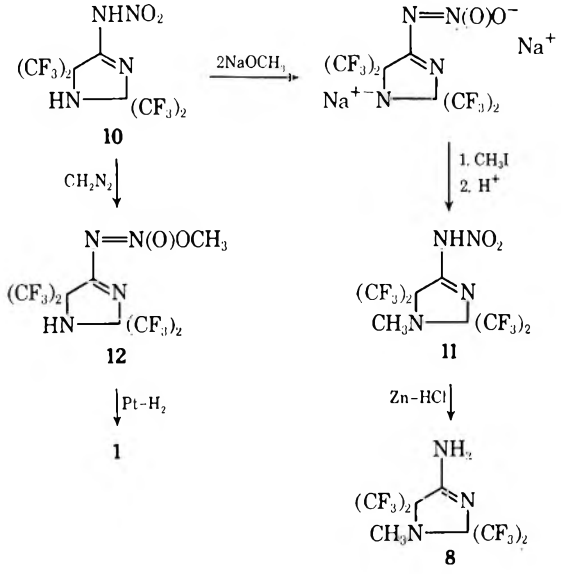
19, R = R′ = R″ = CH_3
20, R = H; R′ = R″ = CH_3

In addition to correlation of spectral parameters for these products with those of **1** and the preparation of all the possible methylated isomers (Table I), the structure of **6d** is supported by its easy cyclization to lactam **7**.



6d **7**

Preparation of the 1-methyl (**8**) and 1-ethyl (**9**) derivatives was accomplished by alkylation of the disodium salt of 4-nitramino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**10**) (see below). The monoanion of **10** is unreactive toward halides; alkylation of the disodium salt gives the 1-methyl derivative **11** in good yield.

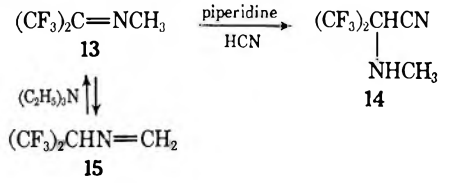


10 **12** **1** **11** **8**

The nitro group was removed by chemical reduction to give 4-amino-1-methyl-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**8**). A similar procedure gave the 1-ethylated product, **9**.

Starting material **10** in these syntheses is derived in good yield from nitration of the very stable parent, **1**, with fuming nitric acid. These vigorous conditions simply convert the 4-amino group in **1** into a nitramino group. The N-nitro compound **10** is very acidic and its anion has low nucleophilicity, but the free acid methylates easily with diazomethane to give **12**, a derivative of the *aci* form. Reductive cleavage of **12** regenerates **1**, showing that methylation occurred at the 4-amino group of **1**.

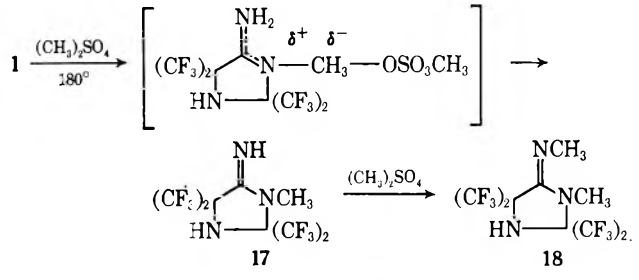
An alternative possibility for preparation of the methylated imidazolines, in particular the 1-methyl derivatives, was by reaction of cyanide ion with N-methylhexafluoroacetone imine (**13**). The first step in the synthesis, addition of cyanide to form the aminonitrile **14**, was demonstrated. However, attempts to condense more than 1 mol of **13** with cyanide under aprotic conditions gave instead the methylene compound, **15**, in high yield. A base-catalyzed prototropic shift occurred, and under equilibrium conditions, **15** was produced as the major component.



13 **14** **15**

With the 1-methyl derivative **8** as a starting material, alkylation with methyl iodide under basic conditions provided a route to the 1-methyl-4-(N-methylamino) derivative, **16** (Table I).

Alkylations with Strong Electrophiles.—Direct methylation of **1** can be accomplished at high temperatures (170–200°) with dimethyl sulfate. In contrast to the monoalkylation of the anion, attack occurs mainly at the 3 position, presumably because of effective stabilization of positive charge in the transition state leading to **17**. Under the forcing conditions of the reaction, a second methyl group can be introduced, this time on the 4-imino nitrogen, to give 3-methyl-4-(N-methylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (**18**). Further methylation of **18** led to the 1,3-dimethyl-4-(N-methylimino) derivative, **19**.



17 **18**

A similar reaction starting with the 1-methyl compound **8** leads to the 1,3-dimethyl derivative **20**, attack at the 3 position again occurring preferentially.

Trimethyloxonium fluoroborate proved to be a better reagent than dimethyl sulfate for introducing a 3-methyl substituent into **1**. Reaction occurred under mild conditions with good selectivity, and yields were

TABLE II

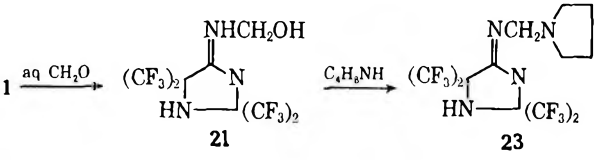
PRODUCTS FROM 4-ISOCYANATO-2,2,5,5-TETRAKIS(TRIFLUOROMETHYL)-3-IMIDAZOLINE[a]

Coreactant	Conditions	Product	Mp or bp, °C (mm)	Yield, %	$\lambda_{max}^{CH_3CN}$, mμ (ε)
$LiAlH_4$	24 hr at 25° in ether	3[b]	75 (10)	38	...
CH_3OH	Ether solvent	29b	125–129	76	<210
$(CH_3)_2NCH_2CH_2OH$	Ether solvent	29c	136–141	62	252 (12,800)
1	Ether solvent	29a	203–205	100	...
CH_3CH_2SH	Ether solvent	29d	115–117	76	...
$C_6H_5COOCH_2CH_3$	Reflux for 3 days, neat, 28 as dimer	32d	80 (0.3)	26	...
p-$(CH_3)_2$-NC_6H_4CHO	Reflux for 1 hr, neat, 28 as dimer	32b	138–142	68	258 (7100) 304 (2600) 315 (1900) 420 (38,700)
$HCON(CH_3)_2$	Reflux for 2 hr, neat, 28 as dimer	32c	113–115	84	281 (23,800)
$(CH_3)_2NCSN(CH_3)_2$	Reflux for 1 hr, neat, 28 as dimer	32e	121–129	36	262 (18,000)

[a] All compounds gave satisfactory elemental analyses. Nmr spectra support the assigned structures. [b] Product identical with 3 prepared by methylation of 1.

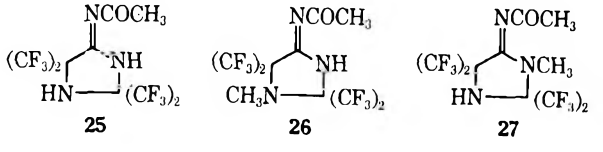
high. This reaction could be extended to ethylation with triethyloxonium fluoroborate, just as the reaction with dimethyl sulfate could also be accomplished with diethyl sulfate. Various combinations of the methods described above were used to prepare all the possible mono-, di-, and trimethyl derivatives of 1. The syntheses are given in Table I.

Mannich Reaction.—Condensation of 1 with formaldehyde proceeded readily to the methylol derivative, 21, and a higher formaldehyde condensation product, the 4-(N-hydroxymethoxy) derivative 22. In the presence of various secondary amines, Mannich products were obtained in high yield. As an example, formaldehyde–pyrrolidine converted 1 into the 4-(N-pyrrolidylmethylamino) derivative, 23. Compound 23 was converted into water-soluble hydrochloride and methiodide salts.



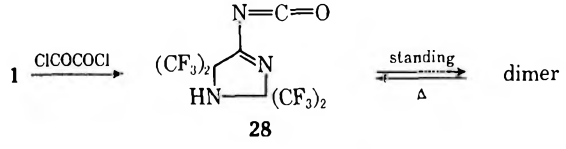
The imidazolines with fluorinated groups other than trifluoromethyl[1] generally undergo the same reactions as 1. An example is the Mannich reaction on 4-amino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline to give 24 (see Experimental Section).

Acylation.—Just as with the Mannich reaction, 1 underwent substitution on the 4-amino group with acid halides. Reaction proceeded slowly because of the very low basicity of 1, but high yields were attained with long reaction times. Acetyl chloride gave with 1 a product formulated as the 4-acetamido compound 25, although the acidity of this product makes the location of the ionizable proton uncertain. A stable tetraethylammonium salt of 25 was readily prepared. The corresponding benzoyl derivative of 1 was prepared, as were many other acylation products.



The 1-methyl compound 8 and the 3-methyl compound 17 also gave acylation products (26 and 27) resulting from attack at the exocyclic nitrogen. Benzenesulfonylation of 1 occurred normally on the 4-amino group.

Formation and Reactions of the Isocyanate.—Oxalyl chloride, as an acid halide, attacked 1 at the 4-amino position to form as the final product 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (28). This highly reactive isocyanate dimerized on standing at room temperature. Above the decomposition point of 152–154°, dimer was shown to crack cleanly to regenerate isocyanate 28, thus serving as a convenient source of 28 for many reactions (Table II).

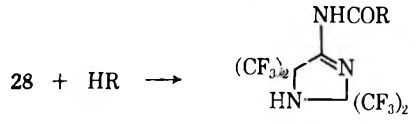


The dimer of 28 may have the normal 1,3-diazetidinedione structure for an isocyanate dimer, as indicated by its pyrolysis back to 28. However, the nmr, infrared, and ultraviolet spectra are also in accord with the isomeric 1,3-oxazetidinone structure, which can be theoretically derived from cycloaddition of the C=N bond of one isocyanate group to the C=O of a second isocyanate group. The dimer exhibits two ir bands (5.51 and 5.71 μ) which could arise from either coupled vibrations of two small-ring carbonyl groups or a carbonyl group plus an imino group on a small ring. Uv absorption at 228 mμ might result from either structure. Nmr bands for ^{19}F show the two imidazoline rings to be different, as they would be in an oxazetidinone and as they might be for steric reasons in a diazetidinedione. An example of the latter case wherein two imidazoline rings are fixed in nonequivalent positions in space was found in the urea 29a derived from isocyanate 28. With water or with an equivalent amount of 1, 28 forms the urea 29a in which the ^{19}F nmr bands are distinct for the trifluoromethyls on each ring.

Isocyanate formation and dimerization were general for the fluorinated imidazolines. 4-Isocyanato-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (30) and

its dimer are described in the Experimental Section as an additional example.

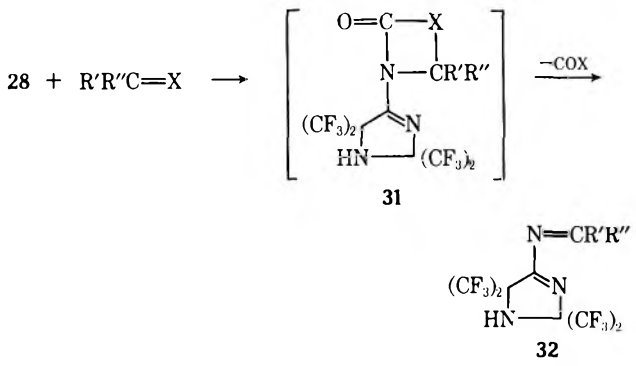
Isocyanate **28** reacted vigorously with active hydrogen compounds to form the corresponding carbamoyl derivatives, **29** (Table II). As noted above, reaction even occurred readily with the amino group in **1**.



29a, RH = **1**
b, R = OCH_3
c, R = $OCH_2CH_2N(CH_3)_2$
d, R = SCH_2CH_3
e, R = $N[CH(CH_3)_2]_2$

The products **29** have an acidic proton, and those derived from amines can give the ammonium salts directly. For example, the diisopropylammonium salt of the N,N-diisopropylurea **29e** was formed from **28** and excess diisopropylamine.

The highly reactive isocyanate group in **28** also reacted easily with carbonyl and thiocarbonyl functions. The initial products in these cases may have been cycloadducts **31**, but loss of CO_2 or COS occurred spontaneously with formation of unsaturated products **32**. Even the ester carbonyl in ethyl benzoate participated in the reaction (Table II).



31

32

a, X = O; R′ = H; R″ = C_6H_5
b, X = O; R′ = H; R″ = $C_6H_4N(CH_3)_2$-*p*
c, X = O; R = H; R″ = $N(CH_3)_2$
d, X = O; R = OCH_2CH_3; R′ = C_6H_5
e, X = S; R = R′ = $N(CH_3)_2$

Reduction of **28** provided a chemical proof of structure for the monomethyl compound **3**. Lithium aluminum hydride converted the isocyanate group, which must be at the 4 position on the imidazoline ring, into an N-methyl compound identical with **3** obtained earlier by methylation under basic conditions.

Spectral Correlations.—In addition to the chemical evidence and to the synthesis of all the possible methylated isomers, spectral correlations tend to confirm the structures assigned to the compounds we have described.

Proton nmr positions for the various NH groups are solvent sensitive, tending to be grouped in the range of τ 5–7 for neat samples and samples in solvents of low polarity. Pronounced shifts to low field occurred with acceptor solvents such as acetone and dimethyl sulfoxide, and resolution of the different types of NH was improved. Examination of the data for alkyl derivatives of **1** shows that in the polar acceptor solvents, hydrogen in the 1 position of either imidazolines or imidazolidines generally appeared in the range of τ 3.7–4.1. The more acidic hydrogen on the 4-amino group of the imidazolines appeared at lower field in the range of τ 2.3–3.0; the 4-imino hydrogen in imidazolidines were at still lower field, *ca.* τ 2.0. The NH chemical shifts in other derivatives are consistent with this classification, with the additional observation that the increased acidity caused by a nitro, acyl, or other negative substituent on the 4-amino group produced a downfield shift for the nearby NH to the region of τ −0.5 to 1.0.

Fluorine nmr shifts, as noted before,[1] were characterized by a higher field position for the trifluoromethyl groups in the 2 position (72–78 ppm) than in the 5 position (67–74 ppm). Long-range coupling between these sets was consistently around 5 Hz. No indication of an AA′BB′ pattern was seen.

Infrared absorption bands for the endocyclic imino group attached to an amino group occurred near 5.9 μ. With one alkyl substituent on the 4-amino group, absorption occurred near 6.0 μ, and with a 4-dialkylamino group near 6.1 μ. The exocyclic imino group gave rise to a band near 5.95 μ, while the 4-alkylimino group gave a band near 5.85 μ.

Experimental Section[3]

4-Imino-2,5,5-tris(trifluoromethyl)-2-imidazoline (2).—To a slurry of 8.1 g (0.34 mol, from 15 g of 54% NaH–Nujol washed with benzene) of sodium hydride in 300 ml of glyme was added a solution of 36 g (0.1 mol) of **1** in 50 ml of glyme at −10°. One equivalent of gas was evolved immediately. The mixture was refluxed for 6 hr while an additional 1.6 equiv of gas were evolved. The resulting dark mixture was cooled and treated at 5° with 10 ml of methanol to destroy excess sodium hydride and then with 200 ml of 2 *N* hydrochloric acid followed by 400 ml of water.

The acidic mixture was extracted with five 75-ml portions of ether and the ethereal solution was concentrated under reduced pressure to give a dark brown tar. Steam distillation afforded 8.2 g of a mixture of starting material and **2**. The crude mixture was dissolved in ether and extracted with three 15-ml portions of 1 *N* sodium hydroxide. The combined basic solutions were extracted twice with ether, neutralized with aqueous HCl, and extracted with ether to afford 4.5 g (16%) of **2**, mp 152–154°. An analytical sample, mp 154–155°, was obtained by three recrystallizations from methylene chloride followed by sublimation at 120° (15 mm): ir 2.88, 3.01 (NH), 5.96, 6.17, and 6.35 μ (C=N); uv $\lambda_{max}^{ethanol}$ 285 mμ (ϵ 7300); ^{1}H nmr τ 0.4 (NH) and 1.0 ppm (NH); ^{19}F nmr 73.2 (singlet, 1, CF_3) and 73.3 ppm (singlet, 2, CF_3).

Anal. Calcd for $C_6H_2F_9N_3$: C, 25.1; H, 0.7; F, 59.6; N, 14.6. Found: C, 24.9; H, 1.4; F, 59.5; N, 14.5.

4-(N-Benzylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6b).—A 7-g sample (0.02 mol) of **1** dissolved in 10 ml of glyme was added at <10° to 1 g (0.02 mol) of 54% sodium hydride–mineral oil in 50 ml of glyme. The stirred suspension was refluxed for 2 hr. Later studies showed that 1 equiv of H_2 is evolved at ice-bath temperature but that refluxing the sodium salt in glyme, even for several days, has no adverse effect. The suspension was cooled and 4 g (0.023 mol) of benzyl bromide was added at <10°. The mixture was refluxed for 22 hr, cooled, and filtered to remove the sodium bromide formed, and the filtrate

(3) Melting points and boiling points are uncorrected. Proton nmr spectra were obtained with a Varian A-60 spectrometer on deuterioacetone solutions with tetramethylsilane as an internal standard. Peak center positions for ^{1}H are reported as τ parts per million. Fluorine nmr spectra were obtained with a Varian A56-60 spectrometer on deuterioacetone solutions with trichlorofluoromethane as an internal standard. Peak center positions for ^{19}F are reported in parts per million upfield from $CFCl_3$. Ir spectra were determined in KBr wafers with a Perkin-Elmer 21 spectrophotometer. Mass spectra were taken at 70 eV on a CEC 21-103C instrument.

was distilled through a spinning-band column. The product was **6b**: yield 6.3 g (70%); bp 120° (10 mm); ^{1}H nmr τ 2.35 (broad, 1, NH), 2.68 (5, C_6H_5), 3.85 (broad, 1, NH), and 5.30 ppm (doublet, 2, J_{HH} = 6.0 Hz, CH_2); ^{19}F nmr 72.8 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 78.1 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_{14}H_9F_{12}N_3$: C, 37.6; H, 2.0; F, 51.1; N, 9.4; mol wt, 447. Found: C, 37.6; H, 2.1; F, 50.9; N, 9.4; mol wt, 447 (mass spectrum).

4-(N-Allylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6c).—Using the above procedure for **6b**, but substituting 3 g (0.025 mol) of 3-bromopropene for benzyl bromide, a 6.1-g (75%) sample of **6c** was prepared: bp 87° (25 mm); ^{1}H nmr (CCl_4) τ 3.7–5.1 (multiplet, 4, NH and $CH{=}CH_2$), 5.9 (multiplet, 2, CH_2), and 6.4 ppm (1, NH); ^{19}F nmr 72.8 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 77.8 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_{10}H_7F_{12}N_3$: C, 30.2; H, 1.8; F, 57.4; N, 10.6; mol wt, 397. Found: C, 30.2; H, 2.2; F, 56.9; N, 10.4; mol wt, 397 (mass spectrum).

4-N-[2-(Dimethylamino)ethyl]amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6a).—The sodium salt of 1, 7.0 g (0.02 mol), was prepared as above. An additional 1 equiv (1 g) of 54% sodium hydride–mineral oil and 4.85 g (0.021 mol) of β-(dimethylamino)ethyl bromide hydrobromide were added successively at <10°. The mixture was refluxed for 24 hr, cooled, and filtered. The product, bp 80–85° (7 mm), yield 5.0 g (58%), solidified on standing, mp 47–53°. A sample was purified *via* the hydrochloride: mp 58–61°; ^{1}H nmr τ 3.40 (broad, 1, NH), 3.90 (broad, 1, NH), 6.50 (triplet, 2, J_{HH} = 6.0 Hz, CH_2), 7.46 (triplet, 2, J_{HH} = 6.0 Hz, CH_2), and 7.78 ppm (singlet, 6, CH_3); ^{19}F nmr 75.5 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 78.6 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_{11}H_{12}F_{12}N_4$: C, 30.9; H, 2.8; F, 53.2; N, 13.1; mol wt, 428. Found: C, 30.4; H, 2.6; F, 53.4; N, 13.9; mol wt, 428 (mass spectrum).

Preparation of 4-[N-(Ethoxycarbonylmethyl)amino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6d) and Cyclization to 6,7-Dihydro-5,5,7,7-tetrakis(trifluoromethyl)-5H-imidazo[1,5-*a*]-imidazol-3-(2H)-one (7).—A 4-g sample (0.024 mol) of ethyl bromoacetate was substituted for benzyl bromide in the above procedure for **6b** to give 4.8 g (50%) of the 4-N-ethoxycarbonylmethyl derivative: mp 74–78°; ^{1}H nmr τ 2.60 (broad, 1, NH), 3.80 (broad, 1, NH), 5.81 (doublet, 2, J_{HH} = 5.5 Hz, CH_2), 5.82 (quartet, 2, J_{HH} = 7.0 Hz, CH_2CH_3), and 8.76 ppm (triplet, 3, J_{HH} = 7.0 Hz, CH_2CH_3); ^{19}F nmr 73.0 (septet, 1, J_{FF} = 5.0 Hz, CF_3), and 78.2 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_{11}H_9F_{12}N_3O_2$: C, 29.8; H, 2.1; F, 51.5; N, 9.5. Found: C, 30.4; H, 2.2; F, 50.9; N, 9.6.

A 10-g sample (0.023 mol) of **6d** was refluxed with 100 ml of 10% sodium hydroxide solution until the mixture became homogeneous (*ca.* 1 hr). The cooled reaction mixture was mixed with 100 g of ice and acidified to pH 2 with concentrated hydrochloric acid. The solid thus formed was extracted with ether, and the ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the ether gave a residue which was purified by mixing with excess (*ca.* 50 ml) 5% sodium bicarbonate solution. The basic solution was extracted with ether to remove starting material, cooled, and acidified to pH 2. The purified acid was collected on a filter, sucked dry, and washed with pentane. The white acid, pK_a = 5.48, yield 6.48 g (69%), had a melting point of 133–135°.

Anal. Calcd for $C_9H_5F_{12}N_3O_2$: C, 26.0; H, 1.2; F, 54.9; N, 10.1; neut equiv, 415. Found: C, 26.2; H, 1.2; F, 54.9; N, 10.3; neut equiv, 413.

An 8-g sample (0.019 mol) of the above acid was dissolved in 50 ml of thionyl chloride and the resulting solution was heated at reflux for 8 hr. The reaction mixture was evaporated to dryness under reduced pressure. The yellow residue was sublimed at 150° (1 mm) and then recrystallized from ether–pentane to give 3.1 g (41%) of **7** as a light yellow, crystalline powder: mp 256–259°; ^{1}H nmr τ 2.16 (1, NH) and 6.88 ppm (singlet, 2, CH_2); ^{19}F nmr 72.6 (septet, 1, J_{FF} = 4.2 Hz, CF_3) and 75.6 ppm (septet, 1, J_{FF} = 4.2 Hz, CF_3).

Anal. Calcd for $C_9H_3F_{12}N_3O$: C, 27.2; H, 0.8; F, 57.4; N, 10.6. Found: C, 27.0; H, 1.1; F, 57.0; N, 10.9.

4-Nitramino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (10) and Its Tetramethylammonium Salt.—Red, fuming nitric acid, 50 ml, was added dropwise to a stirred solution of 7.14 g (0.02 mol) of **1** in 50 ml of 20% fuming sulfuric acid at such a rate that the temperature remained at 100–105°. The addition required *ca.* 10 min. The reaction mixture was cooled and poured over 500 ml of crushed ice. The white solid that formed was collected on a filter, washed with water, and dried in air. Recrystallization from alcohol–water gave 6.8 g (85%) of **10** as colorless needles: mp 176–177° (sealed capillary); ir 6.07 μ (C=N); ^{19}F nmr 72.9 (septet, 1, J_{FF} = 4.5 Hz, CF_3) and 77.0 ppm (septet, 1, J_{FF} = 4.5 Hz, CF_3); ^{1}H nmr τ 0.2 (singlet, 1, NH) and 2.8 ppm (singlet, 1, NH). The compound was acidic, pK_a = 2.78 in water.

Anal. Calcd for $C_7H_2F_{12}N_4O_2$: C, 20.9; H, 0.5; F, 56.7; N, 13.9; neut equiv, 402. Found: C, 21.6; H, 0.6; F, 55.6; N, 14.4; neut equiv, 404.

A solution of 0.5 g of tetramethylammonium chloride in 5 ml of water was mixed with a solution of 0.8 g (0.002 mol) of **10** in 5 ml of 5% aqueous sodium bicarbonate. The reaction mixture was cooled to 0° and the colorless crystals that formed were collected on a filter and washed with water. After drying, there was obtained 0.70 g of the tetramethylammonium salt, mp 207–208°.

Anal. Calcd for $C_{11}H_{13}F_{12}N_5O_2$: C, 27.8; H, 2.8; F, 48.0. Found: C, 28.1; H, 2.8; F, 47.9.

Preparation and Reduction of 4-(Methoxyazoxy)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (12).—A 2% solution of diazomethane in ether was added portionwise to a solution of 40.2 g (0.1 mol) of **10** in 100 ml of ether until a faint yellow color persisted. The ether was evaporated under reduced pressure, and the white residue was recrystallized from pentane to give 40.0 g (96%) of **12** as a white solid: mp 68–73°; ir 6.15 and 6.44 μ; ^{19}F nmr 71.8 (septet, 1, J_{FF} = 4.6 Hz, CF_3) and 76.2 ppm (septet, 1, J_{FF} = 4.6 Hz, CF_3); ^{1}H nmr τ 5.74 (singlet, 3, CH_3) and 3.46 ppm (broad, 1, NH). Both the melting point and nmr spectra indicate that this sample is contaminated with a few per cent another isomer.

Anal. Calcd for $C_8H_4F_{12}N_4O_2$: C, 23.1; H, 1.0; F, 54.8; N, 13.5. Found: C, 23.1; H, 0.9; F, 54.4; N, 12.7.

A solution of 12.48 g (0.03 mol) of **12** in 50 ml of ethanol was shaken with 0.2 g of PtO_2 under 2–3 atm of hydrogen pressure until *ca.* 0.09 mol of hydrogen had been absorbed (4 hr). The reaction mixture was filtered, and the filtrate was mixed with 300 ml of water. The white solid that separated was collected on a filter, washed with water, and dried. There was obtained 8.0 g (75%) of a crystalline, white powder identified as **1** by ir.

1-Methyl-4-nitramino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (11).—To a solution of 6.43 g (0.016 mol) of **10** in 75 ml of dimethyl sulfoxide was added with cooling (20°) 1.78 g (0.033 mol) of sodium methoxide. The almost clear solution was treated with 2.17 g (0.017 mol) of methyl iodide added dropwise at 20° over 5 min. After 10 min, the solution was poured into 450 ml of water. The clear solution was diluted to 600 ml and a 100-ml aliquot was treated with 3.0 g of tetraethylammonium chloride. The resulting precipitate (1.1 g) was recrystallized four times from 25-ml portions of water containing 3 ml of ethanol to give 0.73 g (50%) of the tetraethylammonium salt of **11**: mp 132–133°; ir 6.25 μ (strong); uv $\lambda_{max}^{H_2O}$ 289 mμ (ϵ 11,600).

Anal. Calcd for $C_{16}H_{23}F_{12}N_5O_2$: C, 35.2; H, 4.3; F, 41.8; N, 12.8. Found: C, 35.0; H, 4.2; F, 42.0; N, 12.8.

The remaining 500 ml of solution above was acidified with 2 *N* sulfuric acid, and the crystalline precipitate was collected, washed with water, and dried to give 4.25 g (77%) of crude **11**, mp 104–112°. Four recrystallizations from 50 ml of benzene afforded 2.54 g of an analytical sample: mp 115–116°; ir 2.94 and 3.03 broad, NH), 6.08 (C=N), and 6.49 μ (NO_2); ^{1}H nmr τ 0.61 (broad, 1, exchangeable with D_2O, NH) and 6.85 ppm (septet, 3, J_{HF} = 1.1 Hz, CH_3); ^{19}F nmr 70.6 (1, CF_3) and 75.1 ppm (1, CF_3).

4-Amino-1-methyl-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (8).—The 1-methyl derivative can be synthesized from the pure 1-methylnitramino derivative. In practice the crude material was utilized without purification, as described below.

A stirring solution of 32.6 g (0.081 mol) of **10** in 150 ml of dimethyl sulfoxide was treated with 9.65 g (0.179 mol) of sodium methoxide added in small portions while the temperature was maintained at 20–22° in an ice–water bath. Methyl iodide (17.1 g, excess) was added dropwise over 15 min, while the temperature was still kept down. The resulting slurry was stirred for 15 min and poured into 600 ml of ice–water. The clear solution was acidified with 25 ml of 6 *N* sulfuric acid and the solid was collected and washed with water. The wet crude **11** was dissolved in 375 ml of ethanol and treated with 18 g of zinc dust. To the resulting slurry, stirred while in an ice–water bath, was added 90 ml of concentrated hydrochloric acid. The rate of

addition was such that the temperature was kept below 25° initially and had risen to 40° at the end. The mixture was warmed to 65–70° for 45 min and then filtered. The filtrate was heated to boiling and diluted with water to a cloud point (total volume *ca.* 900 ml). After cooling in an ice bath, the product was collected, washed with water, and air dried to give 24.2 g (81%) of **8** as white needles, mp 168–170°. An analytical sample, mp 170.5–171°, was obtained by two recrystallizations from 50% ethanol, followed by sublimation at 110° (0.1 mm): ir 2.84 and 3.21 (NH_2), 5.93 (C=N), and 6.27 μ (NH_2); ^{1}H nmr τ 2.80 (broad, 2, NH_2) and 7.00 ppm (3, CH_3); ^{19}F nmr 68.7 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 73.8 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_8H_5F_{12}N_3$: C, 25.9; H, 1.4; F, 61.4; N, 11.3; mol wt, 371. Found: C, 25.8; H, 1.3; F, 61.4; N, 11.4; mol wt, 371 (mass spectrum).

4-Amino-1-ethyl-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (9).—To a solution of 10.8 g (0.025 mol) of **10** in 50 ml of excess dimethyl sulfoxide was added with cooling 5.4 g (0.01 mol) of sodium methoxide. The resulting slurry was treated with 15.6 g (0.01 mol) of ethyl iodide added dropwise at 20° over 20 min. After 1 hr, the mixture was poured into ice–water and made strongly acidic with 6 *N* sulfuric acid. The organic product was extracted into ether, washed with water, dried, and concentrated to give 8.9 g of solid. The crude solid was dissolved in 125 ml of ethanol and treated with 6.5 g of zinc dust. To the stirred slurry was added 30 ml of concentrated hydrochloric acid, with warming. After the zinc was consumed (1 hr), water was added to the clear hot solution to the cloud point. After cooling in an ice bath, the crude solid, weighing 2.96 g, was collected and shown to be 90% desired product and 10% unalkylated imidazoline. The experiment was repeated twice and the crude products were combined and recrystallized from 250 ml of 50% aqueous ethanol to give 6.2 g (21%) of **9** as white needles, mp 148–150°. An analytical sample, mp 150–151°, was obtained by two recrystallizations from 50% ethanol followed by sublimation at 110° (0.1 mm): ir 2.86, 3.11, and 3.17 (NH_2), 5.90 (C=N), and 6.21 μ (NH_2); ^{1}H nmr τ 1.87 (broad, 2, NH_2), 6.55 (quartet, 2, J_{HH} = 7.0 Hz, CH_2), and 8.79 ppm (triplet, 3, J_{HH} = 7.0 Hz, CH_3); ^{19}F nmr 68.1 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 73.0 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_9H_7F_{12}N_3$: C, 28.1; H, 1.8; F, 59.2; N, 10.9. Found: C, 27.8; H, 2.4; F, 59.0; N, 10.9.

N-Methylene-2,2,2-trifluoro-1-(trifluoromethyl)-ethylamine (15).—A solution of 60 g (0.34 mol) of N-methylhexafluoroacetone imine (**13**) and 0.6 ml of triethylamine was warmed to reflux (39°). After 35 min the yellow solution was refluxing at 65°. After 1 hr the mixture was distilled through a spinning-band column to give 50.6 g (85%) of **15**: bp 79°; n^{25}D 1.2994; ir 5.97 μ (C=N); ^{1}H nmr (neat) τ 2.45 (singlet, 2, $=CH_2$) and 5.90 ppm (septet, 1, J_{HF} = 6.7 Hz, CH); ^{19}F nmr 71.7 ppm (doublet, J_{HF} = 6.7 Hz, CF_3).

Anal. Calcd for $C_4H_3F_6N$: C, 26.8; H, 1.7; F, 63.7; N, 7.8; mol wt, 179. Found: C, 27.1; H, 1.8; F, 63.7; N, 8.3; mol wt, 179 (mass spectrum).

3,3,3-Trifluoro-2-trifluoromethyl-2-(methylamino)propionitrile (14).—A mixture of 62 g (0.35 mol) of N-methylhexafluoroacetone imine and 16 ml (11.4 g, 0.50 mol) of hydrogen cyanide was cooled to 5° in a 200-ml flask fitted with a thermometer and a wet ice condenser. To it was added 0.05 ml of piperidine with stirring. The clear liquid was allowd to warm to reflux (28°). As the reflux rate diminished or the temperature started to drop, additional 0.05-ml portions of piperidine were added. After four portions of piperidine had been added, the temperature in the flask had risen to 55°. The reaction mixture was then heated to reflux at 90°. After cooling, the clear orange liquid was distilled through a spinning-band column to give 60.7 g (85%) of **14**: bp 63–65° (185 mm); ir 2.94 (NH) and 4.44 μ (C≡N); ^{1}H nmr (neat) τ 7.62 (broad doublet, 3, J_{HH} = 5.2 Hz, CH_3) and 8.00 ppm (broad, 1, NH); ^{19}F nmr 87.1 ppm (quadruplet, J_{HF} = 0.8 Hz, CF_3).

Anal. Calcd for $C_5H_4F_6N_2$: C, 29.1; H, 2.0; F, 55.3; N, 13.6; mol wt, 206. Found: C, 29.4; H, 2.0; F, 55.0; N, 13.5; mol wt, 206 (mass spectrum).

4-[N-(Hydroxymethyl)amino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (21).—A mixture of 10 g (0.008 mol) of **1** and 50 ml of 27% aqueous formaldehyde was heated to boiling. The resulting clear solution was cooled to 0°, diluted with 200 ml of cold water, and made strongly basic with 100 ml of 10% sodium hydroxide. The white precipitate that formed was collected on a filter and recrystallized from ether–pentane (10–90%). There was obtained 6.1 g (56%) of **21** as a white, crystalline powder: mp 90–92°; ir 6.00 (C=N) and 6.44 μ (NH); ^{1}H nmr τ 2.30 (broad, 1, NH), 3.90 (singlet, 1, NH), and 4.97 ppm (doublet superimposed on broader signal, 3, J_{HH} = 5.4 Hz, CH_2OH); ^{19}F nmr 72.1 (septet, 1, J_{FF} = 4.8 Hz, CF_3) and 77.1 ppm (septet, 1, J_{FF} = 4.8 Hz, CF_3).

Anal. Calcd for $C_8H_5F_{12}N_3O$: C, 24.8; H, 1.3; F, 58.9; N, 10.9. Found: C, 25.4; H, 1.5; F, 58.6; N, 11.3.

4-[N-(hydroxymethoxymethyl)amino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (22).—A 10-g sample (0.028 mol) of **1** was dissolved in 50 ml of boiling 37% aqueous formaldehyde. The resulting solution was cooled and diluted with 100 ml of water. The oil that separated was washed with water several times until it solidified. Recrystallization of the solid from ether–pentane gave 8.7 g (74%) of **22** as colorless crystals: mp 106–108°; ir 6.00 (C=N) and 6.44 μ (NH); ^{1}H nmr τ 2.13 (broad, 1, NH), 3.72 (singlet, 1, NH), 4.57 (triplet, 1, J_{HH} = 7.5 Hz, OH), 4.92 (doublet, 2, J_{HH} = 6.0 Hz, NCH_2O), and 5.15 ppm (doublet, 2, J_{HH} = 7.5 Hz, OCH_2O); ^{19}F nmr 72.3 (septet, 1, J_{FF} = 4.8 Hz, CF_3) and 77.2 ppm (septet, 1, J_{FF} = 4.8 Hz, CF_3).

Anal. Calcd for $C_9H_7F_{12}N_3O_2$: C, 25.9; H, 1.7; F, 54.7; N, 10.1. Found: C, 25.9; H, 1.5; F, 54.6; N, 9.9.

4-[N-(Pyrrolidylmethyl)amino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (23).—Pyrrolidine, 10 ml, was added to a hot (90°) solution of 10 g (0.028 mol) of **1** in 50 ml of 37% aqueous formaldehyde. The resulting reaction mixture was cooled, and the solid that precipitated was collected on a filter, washed with water, and dried. Recrystallization from pentane gave 9.6 g (78%) of **23** as colorless needles: mp 127–128°; ^{1}H nmr τ 2.73 (broad, 1, NH), 3.90 (broad, 1, NH), 5.45 (singlet, 2, NCH_2N), 7.3 (multiplet, 4, CH_2), and 8.3 ppm (multiplet, 4, CH_2); ^{19}F nmr 71.0 (septet, 1, J_{FF} = 4.8 Hz, CF_3) and 77.2 ppm (septet, 1, J_{FF} = 4.8 Hz, CF_3).

Anal. Calcd for $C_{12}H_{12}F_{12}N_4$: C, 32.7; H, 2.8; F, 51.8; N, 12.7. Found: C, 32.6; H, 3.0; F, 52.3; N, 12.8.

A solution of 3.0 g of **23** in 50 ml of ether was saturated with dry hyrogen chloride gas. The white precipitate that formed was collected on a filter and washed with ether. There was obtained 3.1 g of the hydrochloride as a white, crystalline powder, mp 123–126°.

Anal. Calcd for $C_{12}H_{13}F_{12}N_4Cl$: Cl, 7.4. Found: Cl, 7.0.

Methyl iodide, 25 ml, was added to a solution of 5.0 g (0.011 mol) of **23** in 25 ml of ether. The solution was allowed to stand for 3 hr at 25°, and the solid that precipitated during this time was then collected on a filter and washed with ether. The solid (5.85 g) was dissolved in acetone and fractionally precipitated by the addition of ether. The first fraction contained no fluorine and was discarded. The methiodide, yield 3.0 g (47%), mp 190–193°, was obtained as the last fraction.

Anal. Calcd for $C_{13}H_{15}F_{12}N_4I$: C, 26.8; H, 2.6; F, 39.2; I, 21.8; N, 9.6. Found: C, 27.0; H, 2.9; F, 38.7; I, 22.1; N, 9.3.

4-[N-(Pyrrolidylmethyl)amino]-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline (24).—A 2.0-g sample (0.0062 mol) of 4-amino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline was dissolved in 5 ml of hot 37% aqueous formaldehyde. The solution was cooled and mixed with 2 ml of pyrrolidine. Water, 100 ml, was added, and the solid that separated was collected on a filter and washed with water. Recrystallization from pentane gave 1.15 g (46%) of **24** as colorless crystals: mp 97–99°; ^{1}H nmr τ 3.06 (broad, 1, NH), 3.54 (triplet, 2, J_{HF} = 54 Hz, CHF_2), 3.95 (singlet, 1, NH), 5.54 (doublet, 2, J_{HH} = 4.5 Hz, NCH_2N), 7.34 (multiplet, 4, CH_2), and 8.31 ppm (multiplet, 4, CH_2); ^{19}F nmr multiplets at 73.9 (3), 77.8 (3), 126.2 (2), and 131.6 ppm (2).

Anal. Calcd for $C_{12}H_{14}F_{10}N_4$: C, 35.7; H, 3.5; F, 47.0; N, 13.9. Found: C, 35.8; H, 3.5; F, 46.9; N, 13.5.

4-Acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (25) and Its Tetrmethylammonium Salt.—A solution of 5.0 g (0.014 mol) of **1** in 25 ml of acetyl chloride was heated at reflux for 20 hr. The reaction mixture was cooled and poured into 300 ml of cold water to decompose the excess acetyl chloride. The solid that formed was collected on a filter and dried in air. There was obtained 5.32 g (95% yield) of crude **25** as a white powder. Recrystallization from alcohol–water gave colorless needles: mp 154–155° (sealed capillary); ir 5.79, 6.00, and 6.61 μ (conjugated amide); uv λ_{max}^{EtOH} 223 mμ (ϵ 13,500) and 265 (sh); ^{1}H nmr τ 0.80 (broad, 1, NH), 3.46 (broad, 1, NH), and 7.63

ppm (singlet, 3, CH_3); ^{19}F nmr 71.7 (septet, 1, J_{FF} = 4.6 Hz, CF_3) and 76.5 ppm (septet, 1, J_{FF} = 4.6 Hz, CF_3).

Anal. Calcd for $C_9H_{15}F_{12}N_3O$: C, 27.1; H, 1.3; F, 57.1; N, 10.5. Found: C, 27.5; H, 1.4; F, 58.1; N, 11.3.

A 10% aqueous sodium hydroxide solution was added dropwise to a suspension of 5.0 g (0.013 mol) of **25** in 25 ml of water until solution was complete. The solution was filtered, and the filtrate was mixed with a solution of 5.0 g of tetramethylammonium chloride in 10 ml of water. The crystalline precipitate that formed upon cooling to 0° was collected on a filter and recrystallized from alcohol–ether. There was obtained 4.1 g (67%) of the tetramethylammonium salt as colorless crystals, mp 225–227°, ir 6.44 μ.

Anal. Calcd for $C_{13}H_{16}F_{12}N_4O$: C, 33.1; H, 3.4; F, 48.3; N, 11.9. Found: C, 33.4; H, 3.7; F, 47.7; N, 11.6.

4-Acetylimino-1-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (26).—A mixture of 3 g (0.008 mol) of **8** and 6 ml of acetyl chloride was heated at reflux for 26 hr. The excess acetyl chloride was evaporated and the residue was sublimed at 80° (0.1 mm) to give 3.29 g (99%) of **26**, mp 159–160°. An analytical sample, mp 159–160°, was obtained by recrystallization from ethanol, followed by sublimation: ir 3.05, 3.09, and 3.17 (NH and CH) and 5.75 and 6.06 μ (C=O and C=N); ^1H nmr τ 0.8 (broad, 1, NH), 6.95 (septet, 3, J_{HF} = 1.1 Hz, NCH_3), and 7.60 ppm (singlet, 3, CH_3CO); ^{19}F nmr 68.4 (septet, 1, CF_3) and 73.4 ppm (septet, 1, CF_3).

Anal. Calcd for $C_{10}H_7F_{12}N_3O$: C, 29.1; H, 1.7; F, 55.2; N, 10.2; mol wt, 413. Found: C, 28.7; H, 2.0; F, 55.2; N, 10.5; mol wt, 413 (mass spectrum).

4-Acetylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (27).—A mixture of 2.0 g (0.0054 mol) of **17** and 5 ml of acetyl chloride was heated at reflux for 30 hr, cooled, and poured over ice. The solid that formed was collected on a filter, washed with water, and recrystallized from alcohol–water. There was obtained 1.85 g (83%) of **27** as colorless crystals: mp 137–139°; ir 5.75 (C=O) and 6.00 μ (C=N); uv λ_{max}^{EtOH} 217 mμ (ϵ 8300); ^1H nmr (CD_3CN) τ 6.98 (septet, 3, J_{HF} = 1.0 Hz, CH_3N), 7.67 (singlet, 1, NH), and 7.83 ppm (singlet, 3, CH_3); ^{19}F nmr 73.1 (septet, 1, J_{FF} = 4.2 Hz, CF_3) and 75.1 ppm (multiplet, 1, CF_3).

Anal. Calcd for $C_{10}H_7F_{12}N_3O$: C, 29.1; H, 1.7; F, 55.2; N, 10.2. Found: C, 29.4; H, 2.0; F, 54.9; N, 10.2.

4-Isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (28) and Its Dimer.—A solution of 30 g (0.084 mol) of **1** in 100 ml of oxalyl chloride was stirred at 25° for 3 days and then distilled. There was obtained 26.05 g (81%) of the isocyanate as a colorless liquid, bp 67–67.5° (49 mm).

The isocyanate can also be prepared in ether solution and used as such or isolated by distillation.

A three-necked flask attached to the bottom of a spinning-band column was equipped with a magnetic stirrer, nitrogen inlet, and dropping funnel. The equipment was flame-dried and cooled and 15 ml of oxalyl chloride and 75 ml of anhydrous ether were introduced into the flask under positive nitrogen pressure. A solution of 30 g (0.084 mol) of **1** dissolved in 100 ml of ether was added over 30 min with vigorous stirring. After an additional 20 min, the mixture was distilled to give 25.7 g (80%) of product isocyanate, bp 78° (75 mm). The isocyanate reacts readily with moist air: ir 4.35 μ (NCO); ^1H nmr (neat) τ 6.4 ppm (broad, NH); ^{19}F nmr 73.3 (septet, 1, J_{FF} = 5.0 Hz, CF_3) and 78.0 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3).

Anal. Calcd for $C_6HF_{12}N_3O$: C, 28.1; H, 0.3; N, 11.0. Found: C, 28.6; H, 0.8; N, 11.5.

The isocyanate dimerized spontaneously at 25° over a period of days. The solid dimer, mp 152–154° dec, no longer has a band for isocyanate in its infrared spectrum: ir 2.89 and 3.02 (NH), 5.51 (small ring C=O), 5.71 (C=O or C=N *exo* to small ring), and 5.95 μ (imidazoline C=N); uv $\lambda_{max}^{CH_3CN}$ 228 mμ (ϵ 2700); ^1H nmr τ 2.35 (1, NH) and 2.90 ppm (1, NH); ^{19}F nmr 70.3 (septet, 1, J_{FF} = 5.0 Hz, CF_3), 72.8 (multiplet, 1, CF_3), 73.3 (multiplet, 1, CF_3), and 75.0 ppm (septet, 1, J_{FF} = 5.0 Hz, CF_3). Pyrolysis to the original isocyanate occurs in high yield above 155°, so that the easily stored dimer can be used as a source of the reactive isocyanate.

Anal. Calcd for $(C_6HF_{12}N_3O)_2$: C, 28.1; H, 0.3; F, 59.5; N, 11.0. Found: C, 25.1; H, 0.5; F, 59.5; N, 11.0.

4-Isocyanato-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (30) and Its Dimer.—A solution of 5.0 g (0.012 mol) of 4-amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline in 20 ml of ether was added dropwise over 30 min to a stirred mixture of 3 ml of oxalyl chloride and 10 ml of ether. The reaction mixture was stirred for 20 min and distilled to give 3.4 g (63%) of **30**: bp 78° (1.5 mm); ir 4.34 μ (NCO); ^1H nmr (CCl_4) τ 5.96 ppm (NH); ^{19}F nmr complex multiplets at 53.0 (1), 53.6 (1), 58.1 (1), and 58.7 ppm (1).

Anal. Calcd for $C_8HCl_4F_8N_3O$: C, 21.9; H, 0.2. Found: C, 21.8; H, 0.7.

The isocyanate solidified on standing for several days. The isocyanate was regenerated when the solid was heated above its apparent melting point, 120–140°: ir isocyanate bands typical of dimer and no isocyanate; uv $\lambda_{max}^{CH_3CN}$ 233 mμ (ϵ 9800); ^1H nmr τ 2.90 (1, NH) and 3.15 ppm (1, NH).

Anal. Calcd for $(C_8HCl_4F_8N_3O)_2$: C, 21.9; H, 0.2; F, 33.9; N, 9.4. Found: C, 21.9; H, 0.6; F, 33.9; N, 9.2.

4-Benzylideneamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (32a).—A 30-g sample (0.078 mol) of the 4-isocyanato derivative was heated at reflux for 0.5 hr under a nitrogen atmosphere with 50 g of benzaldehyde. Distillation gave 28 g (80%) of **32a**: bp 91° (1.0 mm); uv $\lambda_{max}^{CH_3CN}$ 235 mμ (sh, ϵ 5250), 245 (4600), 273 (600), and 280 (600); ^1H nmr τ 3.60 (1, NH) and *ca.* 3.0 ppm (multiplet, 5, aromatic CH); ^{19}F nmr 72.7 (multiplet, 1, CF_3) and 77.9 ppm (multiplet, 1, CF_3). This compound is very easily hydrolyzed to a mixture of **1** and benzaldehyde.

Anal. Calcd for $C_{14}H_7F_{12}N_3$: C, 37.8; H, 1.6; F, 51.2; N, 9.4. Found: C, 36.9; H, 1.6; F, 51.5; N, 9.3.

4-(N,N-Diisopropylureido)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (29e) and Its Diisopropylammonium Salt.—A 1.9-g sample (0.005 mol) of the isocyanate was added in one portion at room temperature to 7.5 g (large excess) of diisopropylamine dissolved in 100 ml of ether. After an exothermic reaction occurred, the ether and excess amine were evaporated, giving 2.6 g (84%) of the diisopropylammonium salt: mp 76–81° dec; ^1H nmr τ 3.30 (singlet, 2, NH_2^+), 4.4 (1, NH), 5.8 (broad, 2, CH), 6.76 (septet, 2, J_{HH} = 13.0 Hz, CH), 8.78 [doublet, 12, J_{HH} = 14.5 Hz, $CH(CH_3)_2$], and 8.82 ppm [septet, 12, J_{HH} = 13.0 Hz, $CH(CH_3)_2$]; ^{19}F nmr 71.8 (septet, 1, J_{FF} = 4.0 Hz, CF_3) and 76.7 ppm (septet, 1, J_{FF} = 4.0 Hz, CF_3). The salt was not stable to storage.

Anal. Calcd for $C_{20}H_{31}F_{12}N_5O$: C, 41.0; H, 5.3; F, 38.9; N, 12.0. Found: C, 40.6; N, 5.2; F, 41.7; N, 11.8.

Acidification of a sample of the above salt with 3 *N* hydrochloric acid–ice gave **29e** a white solid which was isolated by ether extraction: mp 123–126°; uv λ_{max}^{EtOH} 250 mμ (ϵ 8400) and 226 (10,900); ^1H nmr τ 0.3 (broad, 1, NH), 3.3 (broad, 1, NH), 5.77 (septet, 2, J_{HH} = 14.0 Hz, CH), and 8.73 ppm [doublet, 12, J_{HH} = 14.0 Hz, $CH(CH_3)_2$]; ^{19}F nmr 72.7 (septet, 1, CF_3) and 77.8 ppm (septet, 1, CF_3).

Anal. Calcd for $C_{14}H_{16}F_{12}N_4O$: C, 34.7; H, 3.3; F, 47.1; N, 11.6. Found: C, 34.6; H, 3.4; F, 47.2; N, 11.6.

Registry No.—**2**, 23757-54-2; **3**, 14373-01-4; **6a**, 14373-02-5; **6b**, 14372-99-7; **6c**, 14373-00-3; **6d**, 23757-59-7; **7**, 23757-60-0; **8**, 23757-51-9; **9**, 23757-62-2; **10**, 23757-63-3; **10** tetramethylammonium salt, 12408-04-7; **11**, 23757-64-4; **11** tetraethylammonium salt, 12408-05-8; **12**, 23829-38-1; **14**, 23757-65-5; **15**, 23757-66-6; **21**, 14373-03-6; **22**, 14373-04-7; **23**, 14373-05-8; **23** hydrochloride, 14704-55-3; **23** methiodide, 23757-70-2; **24**, 14373-10-5; **25**, 14373-12-7; **26**, 23757-73-5; **27**, 14373-14-9; **28**, 14491-96-4; **29a**, 23757-76-8; **29b**, 23757-77-9; **29c**, 23753-55-1; **29d**, 23757-78-0; **29e**, 23757-79-1; **29e** diisopropylammonium salt, 23829-40-5; **30**, 23757-80-4; **32a**, 23757-81-5; **32b**, 23757-82-6; **32c**, 23757-83-7; **32d**, 23757-84-8; **32e**, 23757-85-9; **25** tetramethylammonium salt, 12408-06-9.

The Periodate Oxidation of Heterocycles. II. 2-Methylindole and 2,3-Diphenylindole[1,2]

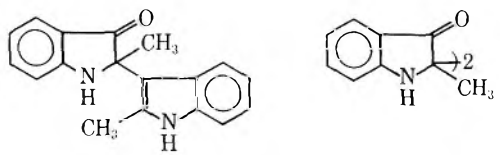
Lloyd J. Dolby[3] and Ralph M. Rodia[4]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received August 14, 1969

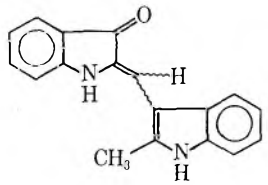
The oxidations of 2-methylindole and 2,3-diphenylindole with sodium periodate in aqueous methanol have been examined. Only the indoxyl dimers 2-methyl-2,3′-(2′-methylindolyl)indoxyl (**1**), 2,2′-dimethyl-3,3′-dioxodiindolinyl-2,2′ (**2**), and 2-[3′-(2′-methylindolyl)methylene]indoxyl (**3**) are isolated from the treatment of 2-methylindole. The products from the oxidation of 2,3-diphenylindole include 2,2-diphenylindoxyl, *o*-benzamidobenzophenone, and the reaction intermediate 3-hydroxy-2,3-diphenylindolenine.

In an earlier study of the oxidation of indoles by periodate species, it was found that 2,3-disubstituted indoles suffered cleavage of the 2,3 double bond or conversion into 2-acylindoles.[2] This work has been extended to new examples. The action of sodium periodate on 2-methylindole has been examined to determine the course of the reaction with indoles unsubstituted in the 3 position. It was found that the reaction mixture contained at least four products by tlc. However, one of these materials was consumed during isolation and a new compound was formed. Three crystalline compounds (**1**–**3**) were isolated and identified.



1

2



3

Compound **1**, obtained in 39% yield, was identified as 2-methyl-2,3′-(2′-methylindolyl)indoxyl[5] by comparison with an authentic sample. This compound is the major product isolated from the treatment of 2-methylindole with a variety of oxidizing agents, including oxygen,[6] hydrogen peroxide,[5] and peracetic acid.[7]

When **1** was exposed to the reaction conditions, **2** was obtained in 62% yield. However, **1** is not necessarily an intermediate in the formation of **2**, since **1** fragments under a variety of conditions to 2-methylindole and 2-methylindolone.[8]

Compound **2**, obtained in 33% yield, shows absorption maxima in its infrared (1700 and 1623 cm^{-1}) and ultraviolet–visible (387 mμ) spectra which have been described[9] as typical for indoxyls. The nuclear magnetic resonance spectrum indicated the presence of two equivalent methyl groups. On this basis, **2** was assigned the structure of 2,2′-dimethyl-3,3′-dioxodiindolinyl-2,2′.[10] This assignment was confirmed by synthesis.

Compound **3**, corresponding to the product appearing in the reaction mixture after work-up, was isolated in 4% yield. This material gave spectra consistent with the following structural elements: normal indole (271, 281, and 288 mμ), isatin-like chromophore (392 and 492 mμ), α,β-unsaturated carbonyl (1655 cm^{-1}), and conjugated double bond (1625 cm^{-1}). The nmr spectrum (dimethyl sulfoxide-d_6) indicated a singlet methyl group at δ 2.57. In comparison, the methyl group of 2-methylindole appears at δ 2.18 and the 2′ methyl group in compound **1** is found at δ 2.51. The mass spectrum indicated a molecular weight of 274 and molecular formula of $C_{18}H_{14}N_2O$. These data suggested structure **3**, 2-[3′-(2′-methylindolyl)methylene]-indoxyl. The structural assignment for compound **3** was verified by an independent synthesis[11] from indoxyl[12] and 2-methylindole-3-aldehyde.[13]

It is possible for the indogenide **3** to occur as two geometric isomers. However, we found only one isomer, whose geometry was not established.

The second indole chosen for study was 2,3-diphenylindole. Three products were obtained from 2,3-diphenylindole by oxidation with sodium periodate. Two of the three compounds were shown by melting point and spectral comparisons to be 2,2-diphenylindoxyl[14] and *o*-benzamidobenzophenone.[15] These compounds were obtained in yields of 8 and 42%, respectively. The third product was identified as 3-hydroxy-2,3-diphenylindolenine (**4**). Combustion analysis of **4** indicates the formula $C_{20}H_{15}NO$. The infrared spectrum shows no carbonyl absorption but peaks at 3600 and 1540 cm^{-1}. Catalytic hydrogenation of **4** gives a quantitative yield of 2,3-diphenylindole. That **4** is not an N-hydroxyindole was shown by a negative ferric

(1) This work was supported by the National Institutes of Health (Grant HE 09521) and a Public Health Service career program award 1-K3-NB-28,105 from the National Institute of Neurological Diseases and Blindness.

(2) Part I: Lloyd J. Dolby and David L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).

(3) Alfred P. Sloan Research Fellow, 1965–1967.

(4) National Defense Education Act Predoctoral Fellow, 1964–1967.

(5) G. Plancher and U. Colacicchi, *Atti. Accad. Naz. Lincei, Rend., Cl. Sci. Fis. Met. Nat.*, **20**, (1), 453 (1911); *Chem. Abstr.*, **5**, 3403 (1911).

(6) B. Oddo, *Gazz. Chim. Ital.*, **46** (I), 323 (1916); *Chem. Abstr.*, **11**, 1143 (1917).

(7) B. Witkop, *Justus Liebigs Ann. Chem.*, **556**, 98 (1947).

(8) C. Toffoli, *Rend. Ist. Santa Publica*, **2**, 565 (1939); *Chem. Abstr.*, **34**, 4733[9] (1940).

(9) B. Witkop and J. P. Patrick, *J. Amer. Chem. Soc.*, **73**, 713 (1951).

(10) J. Van Alphen, *Rec. Trav. Chim. Pays-Bas*, **61**, 888 (1942).

(11) (a) A. Baeyer, *Chem. Ber.*, **16**, 2188 (1883); (b) for a general discussion of this topic, see R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1952, p 200.

(12) D. Vorlander and B. Dreshler, *Chem. Ber.*, **35**, 1701 (1902).

(13) G. Plancher and U. Ponti, *Atti accad. Naz. Lincei, Rend., Cl. Sci. Fis. Mat. Nat.*, **16**, 130 (1908); *Chem. Abstr.*, **2**, 1147 (1908).

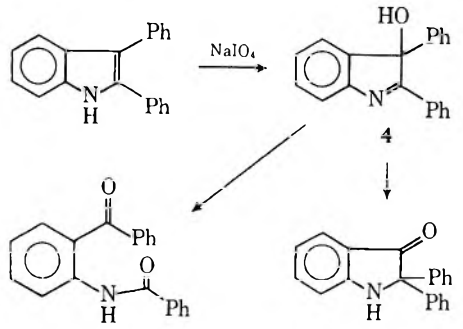
(14) S. Sarel and J. T. Klug, *Israel J. Chem.*, **2**, 143 (1964).

(15) P. Grammaticakus, *Bull. Soc. Chim. Fr.*, 86 (1953).

chloride test and the lack of a bathochromic shift in the ultraviolet spectrum in alkaline solution.[16]

Compound **4** was readily reduced with sodium borohydride to compound **5**, which was transformed by a trace of acid or merely on standing to 2,3-diphenylindole. The infrared spectrum for compound **5** showed NH absorption at 3450 cm^{-1}, an OH band at 3650 cm^{-1}, the loss of $N{=}CR_2$ absorption at 1540 cm^{-1}, and the appearance of the typical $C_6H_5NCR_3$ band at 1620 cm^{-1}. The ultraviolet spectrum showed no absorption above 260 mμ. The nmr spectrum consisted of an aromatic multiplet centered at δ 7.02, a singlet for the tertiary benzylic proton at δ 4.92, and a broad peak consisting of the NH and OH protons at δ 3.17. All of the above data is consistent with formulation of **5** as 3-hydroxy-2,3-diphenylindoline. Previously, Witkop and Patrick obtained 11-hydroxy-1,2,3,4,10,11-hexahydrocarbazole by sodium borohydride reduction of the corresponding indolenine.[17] These authors also noted that the hydrated indole was stable only in the absence of any trace of acid. The facile dehydration of **5** is another example of this sensitivity toward acid.

It was of interest to determine if **4** could act as an intermediate in the periodate oxidation of 2,3-diphenylindole. Indeed, treatment of **4** with sodium periodate yielded *o*-benzamidobenzophenone and 2,2-diphenylindoxyl. This transformation was complete in much less time (12 hr *vs.* 48 hr) than the corresponding partial conversion of 2,3-diphenylindole into the same products. We suggest the following reaction sequence for the periodate oxidation of 2,3-diphenylindole.



This suggestion is in accord with the previous results on indole oxidation.[18-20] All of the products which have been obtained from the oxidation of indoles by sodium periodate are readily rationalized on the basis of a β-hydroxyindolenine intermediate. However, the oxidation of 2,3-disubstituted indoles by methanolic periodic acid gives 2-acylindoles,[2] and we find that β-hydroxyindolenines are not converted into 2-acylindoles by methanolic periodic acid. It appears that the corresponding β-methoxindolenine is the intermediate in this case, since the oxidation of tetrahydrocarbazole by methanolic periodic acid yields 11-methoxytetrahydrocarbazolenine, which is further converted into 1-oxotetrahydrocarbazole under the reaction conditions.[21]

(16) (a) J. D. Loudon and I. Wellings, *J. Amer. Chem. Soc.*, **82**, 3462 (1960); (b) M. Kawana, M. Yoshioka, H. Katanka, Y. Omote, and N. Sugiyama, *Nippon Kagaku Zasshi*, **86**, 526 (1965); *Chem. Abstr.*, **63**, 11479 (1966).

(17) B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, **73**, 2188 (1951).

(18) B. Witkop and J. B. Patrick, *ibid.*, **73**, 2196 (1951).

(19) B. Witkop and J. B. Patrick, *ibid.*, **74**, 3856 (1952).

(20) W. I. Taylor, *Proc. Chem. Soc.*, 247 (1962).

(21) Unpublished results of S. R. Twedt, deceased.

Experimental Section[22]

2-Methylindole was prepared by modification of the procedure of Allen and Van Allen.[23] Acetyl-*o*-toluidine[24,25] (100 g) and sodium amide[26] (64 g) were mixed in a 1-l., three-necked, round-bottom flask equipped with a nitrogen atmosphere and a syringe cap through which passed a spatula. Dry ether (50 ml) was added to the mixture and with a steady current of nitrogen passing above it, and the mixture was heated rapidly to 240–260° (external measurement) and held there for 10 min by means of a silicone oil heating bath. The spatula was used to press the tan crust into the molten mass during the heating period.

Ethanol (50 ml) followed by warm water (250 ml) was added to the cooled reaction mixture. The flask was heated until any remaining ethanol had been driven off, all solid had dissolved, and two distinct layers had formed. While still hot the two layers were separated, and upon cooling the upper layer completely solidified. The solidified material and a small amount of material, extracted from the water layer, were subjected to molecular distillation at 80° (0.03 mm) in a large sublimation apparatus to give 2-methylindole, yield 71.2 g (81%), mp 57–58° (lit.[27] mp 50°).

Treatment of 2-Methylindole with Sodium Periodate.—A sample of 2-methyindole (0.23 g, 0.00175 mol) was dissolved in methanol (15 ml) and water (5 ml). To this, under nitrogen, was added dropwise 0.488 *M* sodium periodate (7 ml), methanol (8 ml), and water (5 ml). After 1 hr the yellow solution containing solid sodium iodate showed on tlc (8:1 chloroform–ethyl acetate) four substances in addition to starting material.

After 3 hr the dark orange mixture was filtered and extracted with dichloromethane, the extract was dried, and the solvent was removed to give a dark brown, tarry mass. Thin layer chromatography of this mass indicated the presence of a new material, red-orange in color, near the origin and the loss of one of the materials noted prior to the work-up.

The brown material was dissolved in dichloromethane, placed on a column of silica gel (50 g), and eluted with 4:1 chloroform–hexane to give three crystalline materials.

A. 2,2′-Dimethyl-3,3′-dioxodiindolinyl-2,2′ (2).—The first material eluted was crystallized from methanol to give 0.10 g (39%) of 2,2′-dimethyl-3,3′-dioxodiindolinyl-2,2′ (**2**), mp 174–176° dec (lit.[10] mp 174° dec). This material was shown to be identical (uv, ir, nmr, and mixture melting point) with authentic material prepared as described below.

B. 2-Methyl-2,3′-(2′-methylindolyl)indoxyl (1).—The second product, yield 0.082 g (33%), mp 209–211° dec (lit.[28] mp 212° dec), which was obtained as yellow to pale orange crystals (from methanol), was identified as 2-methyl-2,3′-(2′-methylindolyl)-indoxyl (**1**). The structural assignment was based on comparison (uv, ir, nmr, tlc, and mixture melting point) with authentic material prepared as described below.

C. 2-[3′-(2′-Methylindolyl)methylene]indoxyl (3).—The third product, yield 0.010 g (4%), was identified as 2-[3′-(2′-methylindolyl)methylene]indoxyl (**3**). It was identical in all respects (uv, ir, nmr, tlc, and mixture melting point) with authentic indogenide prepared as described below, from indoxyl and 2-methylindole-3-aldehyde.

(22) Melting points and boiling points are uncorrected. Anhydrous magnesium sulfate was used to dry solutions unless otherwise noted. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., Berkeley Analytical Laboratories, Berkeley, Calif., or Alfred Bernhardt Mickroanalytisches Laboratorium, Mülheim (Ruhr), West Germany. Infrared spectra were determined with a Beckman IR-5 or IR-7 infrared spectrophotometer using chloroform as solvent. Ultraviolet–visible spectra were determined on a Cary Model 15 spectrophotometer. A Varian Associates A-60 instrument was used to record the nmr spectra. Unless otherwise noted, deuteriochloroform was used as solvent and tetramethylsilane was the internal standard. The mass spectrum was determined by the Morgan–Schaffer Corp., Quebec, Canada. Baker silica gel was used for column chromatography and the column was continuously eluted with the indicated solvent. Silica gel G (according to Stahl) was used for thin layer chromatography and 8:2 chloroform–ethyl acetate was used as eluent. The spots were visualized using iodine or a 3% ceric sulfate–10% sulfuric acid solution.

(23) C. F. H. Allen and J. Van Allen, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 597.

(24) F. Beilstein and A. Kuhlberg, *Justus Liebigs Ann. Chem.*, **156**, 72 (1870).

(25) Prepared in 85% yield by the method of I. S. Ioffe, *J. Gen. Chem. USSR*, **14**, 812 (1944); *Chem. Abstr.*, **39**, 3786[3] (1945).

(26) The amide was used as received without additional grinding.

(27) H. Fischer, *Justus Liebigs Ann. Chem.*, **236**, 116 (1886).

(28) B. Witkop, *ibid.*, **558**, 98 (1947).

A mass spectrum of this compound showed the parent peak at *m/e* 274 and a peak at *m/e* 257 which was ascribed to the loss of hydroxyl. Calculations using the percentages of the M, M + 1, and M + 2 peaks gave the molecular formula $C_{18}H_{14}N_2O$.

N,O-Diacetyl-2-methylindoxyl was prepared in 24% yield from 1-(2′-carboxyphenyl)aminopropionic acid[29] following the procedure of Van Alphen.[10] It had the following properties: mp 132–133° (lit.[10] mp 134°); ir max ($CHCl_3$) 1758 and 1770 cm^{-1}; nmr δ 2.33, 2.41, and 2.58 (s, CH_3-2) and 1- and 3-acetyl CH_3), 7.32 (m, 4–6-Ar H), and 8.08 (m, 7-Ar H).

2,2′-Dimethyl-3,3′-dioxodiindolinyl-2,2′ (2).—A mixture of N,O-diacetyl-2-methylindoxyl (0.351 g, 0.0015 mol), dioxane (10 ml), and 2 *N* aqueous sodium hydroxide (40 ml) was allowed to stir uncovered for a period of 72 hr. The product did not precipitate as described by Van Alphen.[10] The mixture was acidified with glacial acetic acid to pH 5.5 and extracted first with dichloromethane and then with ether. The solvent was partially removed and the extract was chromatographed to give 0.406 g (16%) of the 2,2′-diindoxyl **2**: mp 173–174° dec (from methanol) [lit.[10] mp 174° dec (from benzene)]; $\lambda_{max}^{CHCl_3}$ 245 mμ (ε 35,600), 255 (s, 15, 000), and 387 (6600); nmr δ 1.14 (s, CH_3-2 and-2′), 6.13 (br s, NH-1 and -1′), and 6.87 and 7.50 (m, 10-Ar H).

2-Methyl-2,3′-(2′-methylindolyl)indoxyl (1) was prepared in 45–52% yield as yellow to orange crystals (from methanol), mp 210–211° (lit.[28] mp 212°), by treating 2-methylindole with 40% hydrogen peroxide in glacial acetic acid according to the method of Witkop.[28] The hydrogen peroxide must be added dropwise with stirring and the temperature kept below 80°, or only a dark red, tarry material results.

In one experiment the residue, after removal of the 2,3′-indolylindoxyl, was column chromatographed to give an additional amount of the dimer and a small amount of red-orange solid, which was shown (tlc, uv) to be identical with the indogenide **3** isolated from the sodium periodate oxidation of 2-methylindole.

2-Methyl-2,3′-(2′-methylindolyl)indoxyl (1) possessed the following spectra properties:[30] nmr (acetone-d_6) δ 1.58 and 2.51 (s, CH_3-2 and -2′) and 6.98 and 7.58 (m, 9-Ar H and NH-1).

N,O-Diacetylindoxyl was prepared in 6% yield from phenylglycine-*o*-carboxylic acid[31] by the method of Friedlander and Kunz.[32] When the phenylglycine-*o*-carboxylic acid was added in small portions to the boiling solution of acetic anhydride and sodium acetate, there was considerable foaming. The acid could be added without difficulty to the cool solution. After complete addition of the acid and boiling for 10 min, the product was isolated by extraction with dichloromethane and crystallization from very dilute alcohol.

In another experiment, a mixture of the acid, sodium acetate, and acetic anhydride was boiled for 10 min. In this case, although there was no foaming, the yield of N,O-diacetylindoxyl, after isolation as described above, was only 3%.

The product had the following spectral properties: ir max ($CHCl_3$) 1755 and 1780 cm^{-1} (C=O); nmr δ 2.32 and 2.53 (s, 1- and 3-acetyl CH_3), 7.35 (m, 4–6-Ar H), 7.67 (s, 2-Ar H), and 8.44 (m, 7-Ar H).

2-Methylindole-3-aldehyde.—When 2-methylindole (11.14 g, 0.085 mol) was treated with phosphorus oxychloride and dimethylformamide according to the procedure of James and Snyder,[33] there resulted 13.0 g (96%) of 2-methyl-indole-3-aldehyde: mp 197–200° (from water) (lit.[13] mp 193°); ir max ($CHCl_3$) 3480 (NH) and 1650 cm^{-1} (C=O); λ_{max}^{EtOH} 246 mμ (ε 13,300), 367 (10,100) and 303 (11,500); nmr (acetone-d_6) δ 2.74 (s, CH_3-2), 3.01 (br m, NH), 7.20 (m, 4–6-Ar H), 8.14 (m, 7-Ar H), and 12.18 (s, 3-aldehyde H).

2-[3′-(2′-Methylindolyl)methylene]indoxyl (3).—To a stirring mixture of N,O-diacetylindoxyl (0.956 g, 0.0044 mol) in methanol (40 ml), under nitrogen, was added a solution of potassium hydroxide (2.5 g) in water (10 ml). The mixture became cherry red in color and after 3 hr, concentrated hydrochloric acid (3 ml) was added to give a green-red solution of indoxyl. A sample of 2-methylindole-3-aldehyde (0.676 g, 0.0043 mol) dissolved in methanol (30 ml) was added to the acidified solution over a period of 6 hr.

Water (*ca.* 40 ml) was added to dissolve the precipitated potassium chloride and to cause precipitation of the indogenide **3** as it formed.

After the solution had been stirred for 18 hr, **3** (0.366 g crude) was filtered off and crystallized from acetone–hexane to give 0.263 g of red-orange microcrystals. Extraction of the mother liquor provided 0.143 g of aldehyde and a small amount of indigo. The yield of **3** was 29% based upon unrecovered aldehyde. The product had the following characteristics: mp 263–264° dec; ir max (KBr) 1650 (C=O) and 1617 cm^{-1} (C=C); λ_{max}^{EtOH} 231 mμ (ε 22,000), 271 (15,500), 279 (s, 14,900), 288 (s, 10,900), 392 (8930), and 492 (20,500); nmr (dimethyl sulfoxide-d_6) δ 2.57 (s, CH_3-2), 7.5 (br m, 8-Ar H and 1-vinyl H), and 9.12 and 11.83 (br s, NH-2).

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.15; N, 10.21. Found: C, 79.07; H, 5.30; N, 10.51.

Treatment of 2-Methyl-2,3′-(2′-methylindolyl)indoxyl (1) with Sodium Periodate.—A sample of 2-methyl-2,3′-(2′-methylindolyl)indoxyl (1, 0.029 g, 1.05×10^{-4} mol) was dissolved in a mixture of methanol (3 ml), water (1 ml), and 0.488 *M* sodium periodate (1.5 ml) and stirred for 4 hr. After filtration and treatment in the usual way, the residue was column chromatographed to give 2,2′-dimethyl-3,3′-dioxodiindolinyl-2,2′ (**2**, 0.019 g, 62%) and a small amount of green oil.

2,3-Diphenylindole.—A mixture of benzoin (64 g, 0.3 mol), aniline (96 g, 1.0 mol), and aniline hydrochloride (40 g, 0.3 mol) were refluxed and then treated according to the procedure of Fennel[34] to give 64 g (79%) of the title compound: mp 226–227° (lit.[34] mp 227–228°); λ_{max}^{EtOH} 205 mμ (ε 35,100), 225 (24,600), 247 (21,600), and 307 (16,800); nmr δ 7.12 (br m, 13-Ar H and NH) and 7.67 (m, 7-Ar H).

Treatment of 2,3-Diphenylindole with Sodium Periodate.—A sample of 2,3-diphenylindole (0.47 g, 1.75×10^{-3} mol) was stirred for 36 hr and then refluxed for 48 hr in 0.488 *M* sodium periodate (7 ml), methanol (23 ml), and water (10 ml). Although tlc (8:1 chloroform–ethyl acetate on silica gel) showed the presence of starting material, the reaction mixture was treated in the usual way and chromatographed over silica gel (50 g) using 4:1 chloroform–hexane as an eluent to give 0.050 g of starting material plus three other compounds.

A. 2,2-Diphenylindoxyl.—The first compound (0.042 g, 8%), which crystallized as yellow-green needles from methanol, mp 184–186° (lit.[14] mp 185–186°), was shown to be 2,2-diphenylindoxyl by comparison of ir, uv, and nmr spectra with those reported[14] for this compound.

B. *o*-Benzamidobenzophenone.—The second compound, initially obtained as a pale yellow oil, crystallized upon standing. This material (0.220 g, 42%), mp 90–91° (lit.[15] mp 91°), was *o*-benzamidobenzophenone. The ultraviolet spectrum and melting point were consistent with those reported for this compound.[15] The compound had the following infrared spectral characteristics: ir max ($CHCl_3$) 3330 (NH), 1675 (ketone C=O), and 1625 cm^{-1} (amide C=O).

C. 3-Hydroxy-2,3-diphenylindolenine.—The last material from the column was crystallized from petroleum ether (bp 30–60°) to give 0.060 g (12%) of the title compound as white needles: mp 191–193°; ir max ($CHCl_3$) 3600 (OH) and 1540 cm^{-1} (C=N); λ_{max}^{EtOH} 245 mμ (ε 14,100) and 317 (12,200) and the same spectrum with base, but with acid λ_{max} 248 mμ (ε 8900) and 338 (12,600); nmr (DMSO-d_6) δ 6.94 (s, 3-hydroxyl H), 7.27 (br m, 13-Ar H), and 8.14 (m, 7-Ar H).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.07; H, 5.27; N, 5.08.

Reduction of 2-Hydroxy-2,3-diphenylindolenine. A. By Catalytic Hydrogenation.—A mixture of 3-hydroxy-2,3-diphenylindolenine (0.03 g, 1×10^{-4} mol), 10% palladium on carbon (0.03 g), and absolute ethanol (15 ml) containing triethylamine (3 drops) was stirred at 25° for 8 hr in the presence of hydrogen (1 atm). The mixture was filtered and the filtrate was concentrated to dryness. Comparison (ir, uv, nmr, and tlc) with authentic material showed it to be 2,3-diphenylindole.

B. By Sodium Borohydride.—A stirring mixture of 3-hydroxy-2,3-diphenylindolenine (0.029 g, 1×10^{-4} mol) in methanol (10 ml) was treated with excess sodium borohydride for 1 hr. Water (10 ml) and then saturated sodium carbonate solution (5 ml) were added to the mixture, and then it was extracted with dichloromethane. The extract was dried over sodium sulfate and

(29) Prepared in 66% yield by the method cited in A. I. Vogel, "Practical Organic Chemistry," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1962, p 980.

(30) For infrared and ultraviolet spectra, see ref 9.

(31) Prepared in 62% yield by the method cited in ref 29.

(32) P. Friedlander and J. Kunz, *Chem. Ber.*, **55**, 1600 (1922).

(33) P. N. James and H. R. Snyder in "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 539.

(34) R. C. G. Fennel, *J. Amer. Chem. Soc.*, **54**, 2872 (1932).

the solvent was removed to give 0.025 g (87%) of 3-hydroxy-2,3-diphenylindoline: ir max ($CHCl_3$) 3650 (OH), 3450 (NH), and 1620 cm^{-1} ($PhNCR_3$); λ_{max}^{EtOH} 242 and 305 mμ; nmr δ 3.17 (br s, NH-1 OH-1), 4.92 (s, 2-benzylic H), and 7.02 (br m, 14-Ar H).

This compound dehydrated very rapidly upon standing or during attempted crystallization from ethanol–water. Treatment with warm acetic acid caused complete dehydration, giving 2,3-diphenylindole. The ultraviolet spectrum and tlc of the dehydrated product were identical with those of authentic material.

Treatment of 3-Hydroxy-2,3-diphenylindolenine with Sodium Periodate.—A sample of 3-hydroxy-2,3-diphenylindolenine (0.005 g, 1.75×10^{-5} mol) was dissolved in methanol (4.5 ml), water (1.5 ml), and 0.488 *M* sodium periodate (0.5 ml) and refluxed for 12 hr. After cooling the mixture was treated in the usual manner to provide nearly white solid (0.005 g, 95%).

Comparison (ir, tlc) with authentic material demonstrated that this material was *o*-benzamidobenzophenone containing a little 2,2-diphenylindoxyl.

Registry No.—**1**, 23740-95-6; **2**, 23740-96-7; **3**, 23740-97-8; **4**, 23740-98-9; 2-methylindole, 95-20-5; N,O-diacetyl-2-methylindoxyl, 23741-00-6; N,O-diacetylindoxyl, 16800-67-2; 2-methylindole-3-aldehyde, 5416-80-8; 2,3-diphenylindole, 3469-20-3; 3-hydroxy-2,3-diphenylindoline, 23829-47-2.

Stereochemistry at Trivalent Nitrogen. VIII. Steric and Solvent Effects on Slow Nitrogen Inversion in an Isoxazolidine[1a]

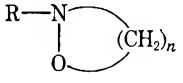
MORTON RABAN, FREEMAN B. JONES, JR.,[1b] ERIC H. CARLSON, EUGENE BANUCCI, AND NORMAN A. LEBEL

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received June 27, 1969

Chemical-shift nonequivalence arising from slow nitrogen inversion in *cis*-1,8-dimethyl-2-oxa-1-azabicyclo[3.3.0]octane (**2**) was observed. An assignment of the configurations at nitrogen in the two diastereomers observed in low-temperature nmr spectra can be made on the basis of steric and solvent effects on the equilibrium constant, and on the effect of the orientation of the lone pair of electrons on chemical shifts. The nitrogen inversion barrier was determined using complete line-shape methods, and its dependence on solvent and steric factors is discussed.

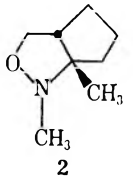
Numerous reports have appeared in recent years describing temperature dependence in the nmr spectra of amine derivatives which have a heteroatom (especially nitrogen, oxygen, or sulfur) directly bonded to the nitrogen atom. This behavior results from conformational interchange which is slow on the nmr time scale. Two classes of compounds which have received considerable attention in this respect are the cyclic and acyclic trialkylhydroxylamines. Although earlier papers[2,3] postulated a substantial barrier to inversion of the nitrogen pyramid as the origin of chemical-shift nonequivalence of diastereotopic nuclei in acyclic trialkylhydroxylamines, more recent work has indicated that the results observed more probably reflect the existence of a substantial barrier to torsion about the N–O bond.[4] By contrast to the acyclic compounds, chemical-shift nonequivalence in the cyclic systems **1** can be unequivocally ascribed to slow nitrogen inversion when the size of the heterocyclic ring is small enough to eliminate ring inversion as a possible process. When this work was begun, reports of



1, n = 1, 2, 3, 4

slow nitrogen inversion had appeared for oxaziridines[5–7] (**1**, n = 1) and a substituted 1,2-oxazetidine[8] (a derivative of **1**, n = 2) in which the heteroatoms are part of strained rings. However, a dihydro-1,2-oxazine (an unsaturated derivative of **1**, n = 4) was reported to exhibit chemical-shift equivalence resulting from more rapid nitrogen inversion.[8] Hence, it was of interest to determine whether the presence of a strained ring was a requirement for the observation of slow nitrogen inversion or whether the presence of the oxygen atom would slow nitrogen inversion in isoxazolidines (**1**, n = 3) so that chemical-shift nonequivalence could be observed. Most recently, chemical-shift nonequivalence in isoxazolidines (**1**, n = 3) and tetrahydro-1,2-oxazines (**1**, n = 4) has been described[9,10] indicating that a strained ring is not a prerequisite for a measurable nitrogen inversion barrier.

The bicyclic isoxazolidine **2** represents an additional example of a molecule which exhibits chemical-shift



2

nonequivalence due to hindered stereomutation at nitrogen. Comparison of the barrier to nitrogen inversion in **2** with those in other examples of the isoxazolidine system indicates that a significant steric effect on the inversion rate obtains.

(1) (a) Part VII: E. Carlson, F. B. Jones, Jr., and M. Raban, *Chem. Commun.*, 1235 (1969). (b) University Fellow, 1969–1970.

(2) D. L. Griffith and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 4089 (1965).

(3) R. E. Banks, M. G. Barlow, R. N. Haszeldine, and M. K. McCreath, *J. Chem. Soc.*, 7203 (1965).

(4) M. Raban and G. W. J. Kenney, Jr., *Tetrahedron Lett.*, 1295 (1969).

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

(6) S. J. Brois, *ibid.*, **90**, 506 (1968).

(7) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1694 (1968).

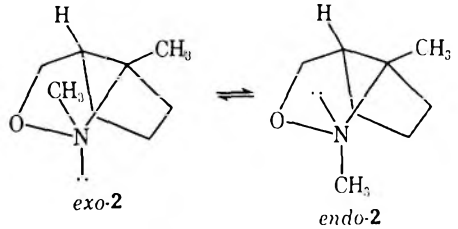
(8) J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **61**, 2342 (1965).

(9) (a) F. G. Riddell, J. M. Lehn, and J. Wagner, *Chem. Commun.*, 1403 (1968); (b) D. L. Griffith and B. L. Olson, *ibid.*, 1682 (1968).

Results and Discussion

The internal 1,3-dipolar addition of the nitrone dipole to a double bond provides a convenient entry into the isoxazolidine ring system.[10] Thus, condensation of N-methylhydroxylamine with 6-hepten-2-one followed by *in situ* 1,3-dipolar cyclization of the resulting nitrone affords **2** in high yield.

The room-temperature nmr spectrum of **2** in toluene-d_8 (Figure 1A) is consistent with the occurrence of rapid stereomutation at nitrogen. Chemical-shift nonequivalence is observed for the diastereotopic methylene protons in the heterocyclic ring which appear as two multiplets at δ 3.25 and 3.83.[11] However, this nonequivalence is not a consequence of slow nitrogen inversion but rather may be ascribed to the adjacent asymmetric carbon atoms. By contrast, the low-temperature nmr spectrum (Figure 1B) provides evidence of the existence of the nitrogen invertomers, *exo*-**2** and *endo*-**2**. Thus, two singlets at δ 0.90 and 1.00 are observed for the C-methyl groups in the two epimers since the two groups are diastereotopic by external comparison.[12] On the other hand, the diastereotopic N-methyl groups exhibit apparent chemical-shift equivalence and a sharp singlet is observed at δ 2.45 in the low-temperature spectrum as well as in the room-temperature spectrum. This event is understandable upon detailed examination of the difference in the environments of the diastereotopic methyl groups in the two epimers. The environments of the two C-methyl groups differ considerably; in *endo*-**2** the C-methyl group is *cis* to the nitrogen lone pair of electrons, while in *exo*-**2** it is *cis* to the N-methyl group. The N-methyl group, on the other hand, is *cis* to



exo-**2** *endo*-**2**

either a methyl group (in *exo*-**2**) or to a methylene group (in *endo*-**2**), and apparently this less significant difference in environments is not sufficient to make the chemical-shift difference large enough to be observable.

When the temperature is raised, the C-methyl signals broaden, coalesce ($T_c = -24°$), and collapse to a sharp singlet as stereomutation at the conformationally labile chiral center becomes rapid on the nmr time scale. Since the bulk composition of the sample does not change as inversion of the nitrogen pyramid becomes rapid, the epimerization is, in a sense, degenerate.

We assign the less intense low-field C-methyl singlet to the less abundant *endo*-**2** on the basis of relative

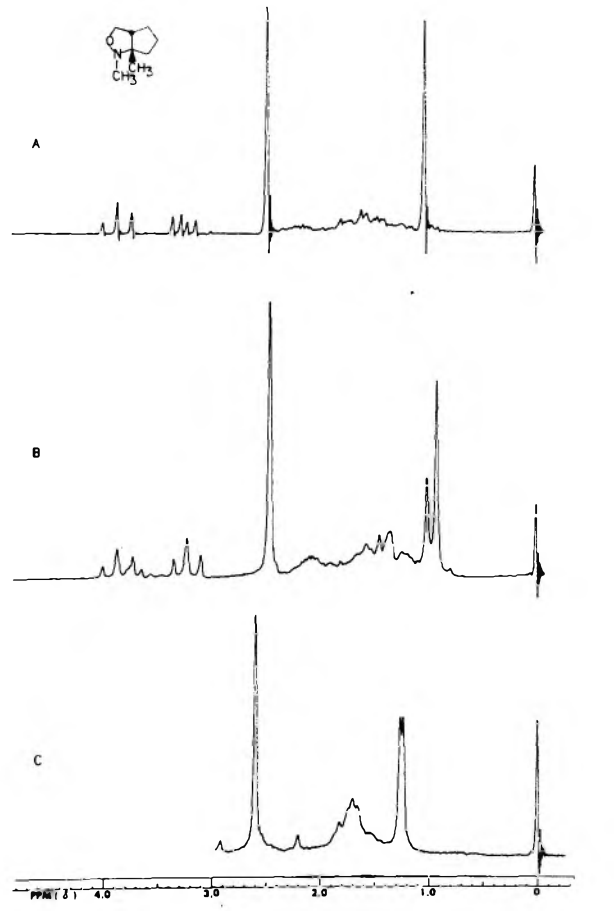


Figure 1.—Nmr spectra of isoxazolidine **2**: (A) toluene-d_8, room temperature; (B) toluene-d_8, $-50°$; (C) methanol–water (4:1), $-40°$.

chemical shifts, the equilibrium constant, and the effect of hydrogen-bonding solvents on the equilibrium constant.

Although the question of the "size"[13,14] of the lone pair of electrons remains a topic of lively controversy, most authors agree that the conformational preference of a methyl group for a less hindered environment is greater than that of the lone pair.[14] Thus, we may assign the more intense signal to *exo*-**2** where the methyl group is in the less congested *exo* position and the lone pair is in the more congested *endo* region. Additional evidence of the correctness of this assignment is based on the proposition that the effect of hydrogen-bonding solvents on the equilibrium between the two invertomers will be to stabilize the isomer in which hydrogen bonding can occur more readily, *viz.*, *endo*-**2**. Examination of the low-temperature nmr spectrum in methanol–water (Figure 1 C) indicates that the low-field signal is augmented and hence must arise from *endo*-**2**.

Alternatively, we might express this result by noting that the conformational preference of the methyl group is greatly diminished in hydrogen-bonding solvents since the solvation shell of the lone pair of electrons effectively increases its steric bulk until it is

(10) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, **86**, 3759 (1964).

(11) The two multiplets represent the M and A portions of an AMX spin system since both H_A and H_M are coupled to the methine proton. First-order analysis gave $J_{AX} = 8$ Hz, $J_{MX} = 5$ Hz, and $J_{AM} = 8$ Hz. On this basis we assign the high field multiplet (H_M) to the *exo* proton since it has the lower vicinal coupling constant and must be *cis* to the methine proton.

(12) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1967, Chapter 1.

(13) We use this term as a convenient means of describing the conformational preference of the lone pair and without prejudice concerning the detailed reasons for this conformational preference.

(14) (a) F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967); (b) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967); (c) J. B. Lambert, R. G. Keske, R. E. Cathcart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967); (d) M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968); (e) R. W. Baldock and A. R. Katritzky, *ibid.*, 1159 (1968).

TABLE I
SOLVENT EFFECTS ON INVERTOMER EQUILIBRIUM CONSTANT AND NITROGEN INVERSION BARRIER IN 2

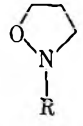
Solvent	$\Delta\nu$,[a] Hz	T_c, °C	K[b]	k_c (approx)[c]	k_c (cls)[d]	ΔG_c^* (approx),[c] kcal/mol	ΔG_c^* (cls),[d] kcal/mol
Neat	3.0	−32	0.6	6.7	4.6	13.1	13.3
Toluene-d_8	5.5	−24	0.4	12	9.5	13.3	13.4
Carbon disulfide	2.7	−32	0.4	5.9	4.3	13.2	13.3
Chloroform-d	3.0	−21	0.5	6.7	4.5	13.7	13.9
Methylene chloride	2.6	−25	0.4	5.8	4.2	13.6	13.7
Acetone-d_6	3.1	−28	0.4	6.8	4.6	13.3	13.5
Methanol–water (4:1)	1.6	−18	1.0	3.6	2.5	14.2	14.4
Acetic acid–acetone (1:1)	5.3	−5	1.4	12	10	14.3	14.4

[a] Chemical-shift difference for C-methyl protons. [b] Ratio of intensities of low-field to high-field C-methyl signals determined at low temperature. [c] Approximate rate and free energy of activation at T_c calculated using the equation $k_c = \pi\Delta\nu/\sqrt{2}$. [d] Rate and free energy of activation for conversion of less stable to more stable isomer obtained using complete line shape.

comparable in size with a methyl group.[15] Finally, we can assign configuration based on the deshielding of spatially contiguous nonvicinal protons by the lone pair of electrons on nitrogen. This effect has been noted in bicyclic piperidines and in related compounds.[14d] Our assignment, on this basis, that the low-field singlet arises from *endo*-**2** in which the lone pair is *cis* to the C-methyl group is in accord with the judgment above made on the basis of steric considerations and the effect of hydrogen-bonding solvents.

The rates of conformational interchange (k_c) and the free energies of activation (ΔG_c^*) at the coalescence temperatures in a variety of solvents were calculated using the expression[16a] $k_c = \pi\Delta\nu/\sqrt{2}$ and are given in Table I. Although this approximate expression is based on the equally populated, two-site, AB spin system, it has been widely used in cases, like the present example, where the assumptions made in its derivation are not valid. Recently, this approach has been severely criticized as unreliable and inaccurate, and the exclusive use of complete line-shape analysis has been recommended.[16b] In order to evaluate the validity of this expression, we have used a complete line-shape analysis spectrum simulator program (CLASS) to determine k_c for a range of values of $\Delta\nu$ (1–40 Hz) and K (0.33–3.0).[16c] We used a reasonable value of T_2 of 0.4 sec corresponding to a half band width ($W_{1/2}$) of 0.8 Hz for these calculations. These values of k_c were compared with those obtained using the approximate equation. The discrepancy between the two results varied. In general, the approximate equation resulted in larger errors for very small values of $\Delta\nu$, because of overlap due to natural broadness of peaks and magnet inhomogeneity and for values of K markedly different from unity. However, if a discrepancy of *ca.* 100% in k_c corresponding to a difference of only *ca.* 0.3 kcal/mol in ΔG_c^* is considered tolerable, the approximate equation gives acceptable results when $\Delta\nu$ is larger than 2 Hz, K lies between 1 and 3, and T_2 is not markedly different from 0.4. To exemplify our findings, we have included the results of both the approximate equation and the complete line-shape method for **2** in Table I. As is evident, the error introduced by using the approximate expression is relatively small in comparison with experimental errors.

Comparison of the barriers to conformational interchange in **2** with those in isoxazolidines previously reported allows a judgment concerning the effect of



3a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = CH_2OCH_3

steric bulk on the free energy of activation for inversion of the nitrogen pyramid. Isoxazolidines **3a**, **3b**, and **2** form a series with groups of increasing bulk attached to the nitrogen atom; the most bulky substituent is primary in **3a**, secondary in **3b**, and tertiary in **2**. As the data in Table II indicates, the increase in steric bulk results in a decrease in coalescence temperature (T_c) and free energies of activation. The decrease in the barrier to pyramidal inversion is the result of greater steric destabilization in the ground state where the CNC angles are *ca.* 109°, than in the transition state where the CNC angles are *ca.* 120°. Such steric acceleration of pyramidal inversion has been previously described for aziridines[17,18] and oxazetidines.[8]

TABLE II
STERIC DEPENDENCE OF THE BARRIER TO NITROGEN INVERSION IN ISOXAZOLIDINES

Compound	Solvent	T_c, °C	ΔG_c^*, kcal/mol	Ref
3a[a]	Chloroform-d	+42	15.6	9a
3b[a]	Methylene chloride	+5	14.8	9b
3c[a]	Methylene chloride	−74	10.3	9b
2[b]	Methylene chloride	−25	13.7	

[a] ΔG_c^* calculated using the expression $k_c = \pi\Delta\nu/\sqrt{2}$. [b] ΔG_c^* obtained using complete line shape.

(15) K. Brown, A. R. Katritzky, and A. J. Warring, *Proc. Chem. Soc.*, 257 (1964).

(16) (a) 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; (b) G. Binsch, "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1967, Chapter 2; (c) A Similar treatment has been reported: A. Jaeschke, H. Muensch, H. G. Schmid, H. Friebolin, and A. Mannschreck, *J. Mol. Spectrosc.*, **31**, 14 (1969).

(17) S. J. Brois, *J. Amer. Chem. Soc.*, **89**, 4242 (1967).

(18) R. G. Kostyanovsky, Z. E. Samojlova, and I. I. Tchervia, *Tetrahedron Lett.*, 3025 (1968); V. F. Bystrov, R. G. Kostyanovskii, O. A. Panshin, A. U. Stepanyants, and O. A. Iuzhakova, *Opt. Spectrosc.*, **19**, 122 (1965).

We note that the substantially lower barrier of **3c**, with respect to **3b**, does not arise from steric factors. Presumably, the presence of the electronegative oxygen atom is responsible.[18]

Although solvent dielectric constant does not appear to exert a significant influence on the free-energy barrier, hydrogen bonding by solvent results in an increase in the barrier.[19] The change in the free energy of activation accompanying change of solvent from chloroform to methanol–water for **2** ($\Delta\Delta G_c^* = 0.4$ kcal/mol) is in the same direction but smaller than that reported for the monocyclic analog **3a** ($\Delta\Delta G_c^* = 1.3$ kcal/mol).[9a] When acetic acid–acetone (1:1) is used, the increase in ΔG_c^* is comparable. Inspection of Table I suggests that some hydrogen bonding may be occurring even in chloroform and methylene chloride.

The steric acceleration in the rate of stereomutation observed in cyclic hydroxylamines may be compared with the behavior of acyclic amines bearing heteroatoms attached to nitrogen for which steric deceleration has been observed and torsional barriers about the nitrogen heteroatom postulated.[20-23]

Although the attachment of an atom with nonbonded electrons can augment the barrier to nitrogen inversion in cyclic hydroxylamines, this does not necessarily account for chemical-shift nonequivalence in acyclic compounds. It is possible that the CNXC (X = heteroatom) dihedral angle must be small in order for electron repulsion between the nitrogen lone pair and that on the heteroatom to be significant enough to cause the maximum increase in the inversion barrier. The ground-state geometry in acyclic compounds is one of minimum interaction with a large dihedral angle, and, in this geometry, torsional barriers appear to be more substantial than those to inversion of the nitrogen pyramid.[20-23]

(19) The increase in the free energy of activation upon dissolution in hydrogen bonding solvents observed in **2** and **3a** is not observed for acyclic hydroxylamines, a further reflection of the difference in the mechanism of stereomutation (unpublished result).

(20) A. H. Cowley, M. J. S. Dewar, and W. R. Jackson, *J. Amer. Chem. Soc.*, **90**, 4185 (1968).

(21) J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968).

(22) M. Raban, F. B. Jones, Jr., and G. W. J. Kenney, Jr., *Tetrahedron Lett.*, 5055 (1968); M. Raban, G. W. J. Kenney, Jr., and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 6677 (1969).

(23) J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 706 (1969).

Experimental Section

Variable-temperature nmr spectroscopy was performed on a Varian A-60A spectrometer equipped with a Varian variable-temperature probe using *ca.* 20% solutions. Temperatures were determined using methanol spectra as described in the Varian Manual. Each coalescence temperature was measured three to five times and the results were averaged. In general, duplicate measurements were within ±2°.

Theoretical spectra were generated by an IBM 360/65 computer and plotted on a Calcomp plotter using a program based on the solution to the exchange-modified Block equations.[16a] The rate at coalescence (k_c) was assigned to the lowest rate at which the minimum between two resonances disappeared, *i.e.*, became a saddle point or maximum. Plots of k_c as a function of $\Delta\nu$ and K were constructed from which k_c could be determined for intermediate values of $\Delta\nu$ and K. The value of T_2 chosen was based on the observed width at half-height at the slow exchange limit, and tetramethylsilane was used as a standard for magnet inhomogeneity as well as chemical shift.

cis-1,8-Dimethyl-2-oxa-1-azabicyclo[3.3.0]octane.—A solution of 5.52 g (0.05 mol) of 6-hepten-2-one[10] in 200 ml of toluene was heated to reflux in a flask to which was attached a Stark water separator. A solution of 5.0 g (0.1 mol) of N-methylhydroxylamine in 50 ml of toluene and 10 ml of absolute methanol was added dropwise over a period of 2 hr. The theoretical amount of water was collected and the mixture was heated under reflux for an additional 16 hr. The cooled solution was extracted with six 35-ml portions of 10% hydrochloric acid. The acid extract was washed with ether and then basified with 20% sodium hydroxide solution; the organic product was extracted with ether. The combined ether extract was washed with water, dried, and concentrated. Distillation gave 5.58 g (80%) of the isoxazolidine **2**, bp 87–88° (40 mm), $n^{25}D$ 1.4627. Gas chromatography showed one component.

Registry No.—**2** (*exo*), 23884-98-2; **2** (*endo*), 23884-99-3.

Acknowledgment.—This work was supported by the U. S. Public Health Service (Grant No. GM16600-01 to M. R.) and the National Science Foundation (Grant No. GP-6393 to N. A. L.).

Reaction of Grignard Reagents with Tetramethylthiuram Disulfide[1]

JOHN R. GRUNWELL

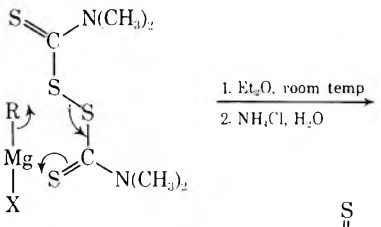
Department of Chemistry, Miami University, Oxford, Ohio 45056

Received September 22, 1969

Alkyl, alkenyl, and aryl Grignard reagents react with tetramethylthiuram disulfide to produce the corresponding dimethyldithiocarbamate esters. The spectral properties of the esters are discussed.

The object of this research was to find an alternative synthesis of dithiocarbamate esters. Since tetramethylthiuram disulfide (TMTD) suffers a displacement reaction at sulfur when it is treated with nucleophiles, such as cyanide ion[2] or amines,[3] the reaction between TMTD and Grignard reagents was investigated.

A general, preparatively useful reaction was discovered. Primary, secondary, and tertiary alkyl, alkenyl, and aryl Grignard reagents react with TMTD to form the corresponding dithiocarbamate esters **1** (eq 1). The synthetic advantages of this reaction are



$$(CH_3)_2NCSR + (CH_3)_2NCSMgX \quad (1)$$

1 **2**

X	I	Br	Br	Cl	Br	Br
R	CH_3	C_2H_5	*i*-C_3H_7	*t*-C_4H_9	C_6H_5	*trans*-$C_6H_5CH{=}CH$
Yield, % 1	33	38	75	71	26	51

clear. It represents the most convenient and least hazardous procedure for preparing *t*-alkyl, alkenyl, and aryl esters. For example, phenyl dimethyldithiocarbamate was previously prepared by the reaction between phenyldiazonium ion and dimethyldithiocarbamate ion,[4] while vinyl diethyldithiocarbamate was synthesized by the high-pressure reaction of diethylamine, carbon disulfide, and acetylene.[5]

Reaction 1 is carried out by adding solid TMTD to an ethereal solution of the Grignard reagent. The mechanism of this exothermic reaction probably involves a displacement reaction at sulfur, and apparently the driving force is the formation and precipitation of the magnesium dithiocarbamate salt **2**.

The esters were identified by their spectral properties. The infrared spectra showed a strong 1500-cm^{-1} band, which is consistent with the N—C=S group frequency.[6] The mass spectra reveal the esters as having intense molecular ions and a base peak at *m/e* 88, which corresponds to the structure $(CH_3)_2N^+{=}$C=S.[7] The nuclear magnetic resonance spectra are consistent with all proposed structures. The assignment of *trans* isomerism for styryl dimethyldithiocarbamate rests on the coupling constant (J = 16 Hz) for the vinyl hydrogens. The methyl groups substituted on nitrogen are equivalent for each ester. However, the spectrum of dimethylthiobenzamide displays nonequivalent methyl groups at the same temperature. Evidently the electron-donating ability of the thiol sulfur atom of dithiocarbamates serves to decrease the amount of double-bond character of the carbon–nitrogen bond relative to that of the thioamide and thus decreases the rotational barrier about the bond. This behavior is consistent with that observed for dialkylcarbamates and amides.[8]

Experimental Section[9]

Methyl Dimethyldithiocarbamate.[10]—Methylmagnesium iodide (0.20 mol) was prepared from 4.92 g (0.20 g-atom) of magnesium metal and 30.14 g (0.21 mol) of iodomethane in 250 ml of dry ether. By means of Gooch tubing 24.06 g (0.10 mol) of TMTD was added slowly. The reaction mixture was stirred for 1 hr and then was poured into 500 ml of a cold aqueous saturated solution of NH_4Cl. The ether was separated, dried ($MgSO_4$), and evaporated. The crude white crystals were chromatographed on 200 g of Merck acid-washed aluminum oxide and eluted with hexane and then with benzene. This gave 4.5 g (33%) of the dithiocarbamate, mp 45–47° (lit.[10] mp 45–46°). An analytical sample was prepared by sublimation at 25° (0.02 mm): uv max (95% EtOH) 221 mμ (ε 10,800), 247 (9240), 273 (11,780), and 318 (584); ir ($CHCl_3$) 2980, 2925, 1500, 1380, 1260, 1150, 1060, 1010, 990, 965, and 570 cm^{-1}; nmr ($CDCl_3$) δ 2.72 (s, 3) and 3.58 (s, 6); mass spectrum (80 eV), *m/e* (relative intensity), 120 (2), 91 (15), 88 (100), 73 (22), 47 (7), 45 (18), 44 (29), and 42 (27). *Anal.* Calcd for $C_4H_9NS_2$: C, 35.52; H, 6.71; N, 10.35; S, 47.42. Found: C, 35.38; H, 6.68; N, 10.39; S, 47.21.

Ethyl Dimethyldithiocarbamate.[11]—Ethylmagnesium bromide (0.25 mol) was treated with 24.11 g (0.10 mol) of tetramethylthiuram disulfide as described above. After addition of aqueous NH_4Cl solution, the mixture was filtered and the precipitate was washed with ether. The ether was evaporated giving a crude brown oil, which was distilled giving 5.7 g (38%) of the dithiocarbamate: bp 55–57° (0.05 mm); mp +2.0° (lit.[11] mp +2.0°); uv max (95% EtOH) 222 mμ (ε 9920), 248 (9010), and 277 (10,450); ir ($CHCl_3$) 2980, 2940, 3880, 1500, 1390, 1280, 1260, 1150, 1060, 990, 880, and 570 cm^{-1}; nmr ($CDCl_3$) δ 1.38 (t, 3, J = 7.5 Hz), 3.48 (q, 2, J = 7.5 Hz), and 3.55 (s, 6); mass

(1) Abstracted from the Ph.D. Thesis of J. R. Grunwell. Massachusetts Institute of Technology, 1968.

(2) (a) J. C. D. Brand and J. R. Davidson, *J. Chem. Soc.*, 15 (1956); (b) R. E. Davis and A. Cohen, *J. Amer. Chem. Soc.*, **86**, 440 (1964).

(3) M. Delepine, *Bull. Soc. Chim. Fr.*, **7**, 988 (1910).

(4) A. M. Clifford and J. G. Lichty, *J. Amer. Chem. Soc.*, **54**, 1163 (1932).

(5) J. C. Sauer, *J. Org. Chem.*, **24**, 1592 (1959).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., 1958, p 350.

(7) (a) J. B. Thompson, P. Brown, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 4049 (1966); (b) J. P. Madsen, S. O. Lawesson, A. M. Duffield, and C. Djerassi, *J. Org. Chem.*, **32**, 2054 (1967).

(8) R. A. Bauman, *ibid.*, **32**, 4129 (1967).

(9) All melting points and boiling points are uncorrected. Ultraviolet spectra were taken on a Cary Model 14 scanning spectrophotometer. Infrared spectra were run on a Perkin-Elmer 337 spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as internal reference. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. TMTD can be obtained from Aldrich Chemical Co. and was used without further purification. Microanalyses were performed by Scandinavian Microanalytical Laboratories and Galbraith Laboratories, Inc.

(10) A. D. Ainley, W. H. Davies, H. Gudgeon, J. C. Harland, and W. A. Sexton, *J. Chem. Soc.*, 151 (1944).

(11) M. Delepine, *Bull. Soc. Chim. Fr.*, **27**, 591 (1902).

spectrum (80 eV), *m/e* (relative intensity) 149 (33), 134 (3), 121 (16), 120 (15), 106 (30), 105 (35), 91 (56), 88 (100), 77 (22), 73 (18), 57 (52), 55 (36), 44 (27), 43 (74), 42 (45), 41 (76), and 39 (60).

Isopropyl Dimethyldithiocarbamate.[12]—Isopropylmagnesium bromide (0.20 mol) was treated with 24.14 g (0.10 mol) of tetramethylthiuram disulfide. After addition of aqueous NH_4Cl, the ether solution was filtered, dried ($MgSO_4$), and evaporated to give 12.3 g (75%) of a light brown oil, which distilled to give the colorless dithiocarbamate: bp 67–69° (0.08 mm) (lit.[13] 126° (12 mm)); uv max (95% EtOH) 223 mμ (ε 12,830), 248 (11,620), and 277 (13,220); ir ($CHCl_3$) 2975, 2940, 2880, 1500, 1380, 1265, 1153, 1065, 990, 880, 753, and 580 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (d, 6, J = 7.5 Hz), 4.05 (septet, 1, J = 7.5 Hz) and 3.57 (s, 6); mass spectrum (80 eV), *m/e* (relative intensity) 163 (52), 121 (31), 120 (11), 88 (100), 73 (13), 44 (15), 43 (18), and 41 (22).

***t*-Butyl Dimethyldithiocarbamate.**—*t*-Butylmagnesium chloride (0.21 mol) was treated with 17.11 g (0.07 mol) of tetramethylthiuram disulfide. After hydrolysis the mass was filtered and the precipitate was washed with ether. The ether was dried ($MgSO_4$) and evaporated giving 13.5 g of a crude black oil, which was distilled giving 8.2 g (71%) of the yellow dithiocarbamate, bp 60–64° (0.08 mm). When the product was cooled in a Dry Ice–acetone bath, colorless crystals formed. It slowly decomposed to tetramethylthiuram disulfide at room temperature. Therefore a good analysis could not be obtained: uv max (95% EtOH) 222 mμ (ε 8600), 250 (8450), and 280 (9550); ir ($CHCl_3$) 2975, 2930, 2865, 1500, 1460, 1375, 1260, 1160, 1140, 1060, 995, 870, 595, and 570 cm^{-1}; nmr ($CDCl_3$) δ 1.65 (s, 9), and 3.40 (s, 6); mass spectrum (80 eV), *m/e* (relative intensity) 166 (12), 121 (27), 88 (95), 73 (18), 57 (56), 44 (31), 42 (50), 41 (100), and 39 (58). *Anal.* Calcd for $C_7H_{15}NS_2$: C, 47.35; H, 8.53; N, 7.96; S, 36.16. Found: C, 48.13; H, 8.64; N, 8.09; S, 35.28.

(12) M. J. Janssen, A. Balasubramanian, and C. N. R. Rao, *J. Sci. Ind. Res.*, **20B**, 349 (1961).

(13) C. W. Pluijgers, "Direct and Systematic Antifungal Action of Dithiocarbamate Acid Derivatives," Thesis, Utrecht, 1959.

Phenyl Dimethyldithiocarbamate.[4]—Phenylmagnesium bromide (0.20 mol) was treated with 0.10 mol of tetramethylthiuram disulfide. After hydrolysis the ether was separated, washed, dried ($MgSO_4$), and evaporated to give a semisolid red oil. Crystallization from cyclohexane gave 5.2 g (26%) of the dithiocarbamate: mp 94–95°; uv max (95% EtOH) 215 mμ (ε 19,600), 243 (12,700), 248 (12,400), and 270 (9200); ir ($CHCl_3$) 2990, 2940, 1510, 1480, 1450, 1390, 1260, 1150, 990, 870, 690, 570, and 510 cm^{-1}; nmr ($CDCl_3$) δ 3.45 (s, 6) and 7.41 (s, 5); mass spectrum (80 eV), *m/e* (relative intensity) 197 (49), 109 (7), 88 (100), 77 (10), 73 (18), and 42 (11). *Anal.* Calcd for $C_9H_{11}NS_2$: C, 54.78; H, 5.57; N, 7.10; S, 32.51. Found: C, 54.77; H, 5.69; N, 7.06, S, 32.61.

***trans*-Styryl Dimethyldithiocarbamate.**—To *trans*-styrylmagnesium bromide from 0.30 mol of *trans*-β-bromostyrene was added 0.10 mol of tetramethylthiuram disulfide. After the usual work-up the ether solution was evaporated to a semisolid, which was crystallized from benzene–hexane to give 11.0 g (51%) of the dithiocarbamate. An analytical sample was obtained from further recrystallization: mp 93–94°; uv max (95% EtOH) 217 mμ (ε 18,950), 275 (25,100), and 302 (17,420); ir ($CHCl_3$) 2990, 2940, 2860, 1610, 1550, 1450, 1390, 1260, 1155, 990, 950, 880, 690, 590, and 570 cm^{-1}; nmr ($CDCl_3$) δ 3.45 (s, 6), 6.75 (d, 1, J = 16 Hz), 7.37 (m, 5), and 7.50 (d, 1, J = 16 Hz); mass spectrum (80 eV), *m/e* (relative intensity), 223 (20), 88 (100), 73 (4), and 42 (3). *Anal.* Calcd for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.86; N, 6.27; S, 28.72. Found: C, 59.26; H, 6.00; N, 6.36; S, 28.15.

Registry No.—Methyl dimethyldithiocarbamate, 3735-92-0; ethyl dimethyldithiocarbamate, 617-38-9; isopropyl dimethyldithiocarbamate, 23885-26-9; *t*-butyl dimethyldithiocarbamate, 23885-27-0; phenyl dimethyldithiocarbamate, 16906-70-0; *trans*-styryl dimethyldithiocarbamate, 23846-99-3; TMTD, 137-26-8.

Acknowledgment.—The author wishes to thank Professor Glenn A. Berchtold for his helpful advice.

Isolation of an Unstable Intermediate in the Reaction of Tetramethyl-3-thio-1,3-cyclobutanedione with Diazomethane

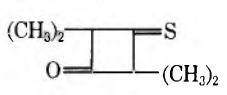
C. E. DIEBERT

Research Laboratories, Tennessee Eastman Company, Division of Eastman Kodak Company, Kingsport, Tennessee 37662

Received November 6, 1969

The reaction of tetramethyl-3-thio-1,3-cyclobutanedione (1) with diazomethane gave 4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexan-5-one (9). An unstable intermediate isolated from this reaction was tentatively assigned the structure of 3,4-diaza-6,6,8,8-tetramethyl-7-oxo-1-thiaspiro[4.3]oct-3-ene (8a) on the basis of infrared and nmr spectra. The thiirane ring of 9 was found to be surprisingly unreactive toward nucleophilic and electrophilic reagents, although it could be desulfurized with triphenylphosphine to give 2,2,4,4-tetramethyl-3-methylenecyclobutanone (17) or with Raney nickel to yield 2,2,3,4,4-pentamethylcyclobutanone as the major product. Reduction of 9 with lithium aluminum hydride or sodium borohydride gave a mixture of isomeric alcohols 12, leaving the thiirane ring unattacked.

The synthesis of tetramethyl-3-thio-1,3-cyclobutanedione (1) was recently reported.[1,2] This compound is



1

one of the few stable aliphatic thio ketones known. It has no tendency to polymerize or dimerize, in contrast to most aliphatic thio ketones.[3,4] The ready availability of 1 allowed studies of the chemistry of an aliphatic thione group without the complications of dimerization, enolization, etc. This account will be limited primarily to a discussion of the reaction of the thione group with diazomethane and to a discussion of the chemistry of the resulting products.

The first report of the reaction between a diazoalkane and a thio ketone was that of Staudinger and Siegwart,[5] who investigated the reaction between diphenyldiazomethane and various diaryl thio ketones (Scheme I). The reaction resulted in the formation of tetrasubstituted thiiranes, which lost sulfur upon heating to give the corresponding ethylenes. Staudinger and Siegwart postulated the formation of an unstable Δ^2-1,2,3-

(1) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967).

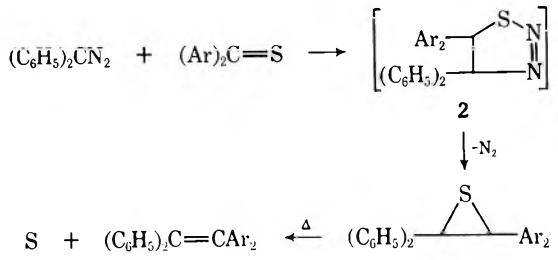
(2) R. D. Lipscomb (to E. I. du Pont de Nemours and Co., Inc.), U. S. Patent 3,297,765 (Jan 10, 1967).

(3) R. Mayer, J. Morgenstern, and I. Fabian, *Angew. Chem.*, **76**, 157 (1964).

(4) E. Campaigne in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1966, p 917.

(5) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920).

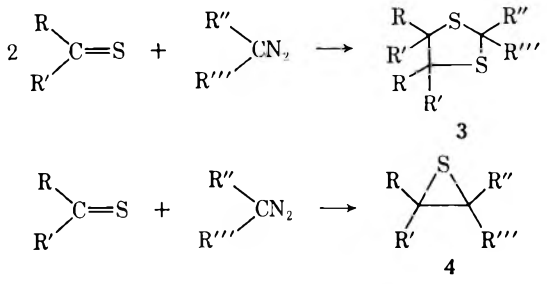
SCHEME I



thiadiazoline intermediate **2**, but they were not able to isolate it or provide any evidence for its existence.

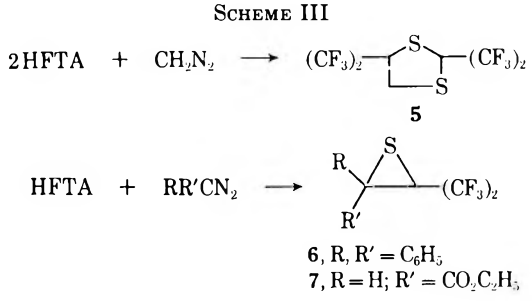
Since 1930 Schönberg and coworkers have described, in an extensive series of papers, similar reactions between diazoalkanes and various diaryl thio ketones.[6] They isolated either a 1,3-dithiolane **3** or a thiirane **4** but they never found both in the same reaction (Scheme II).

SCHEME II



The reactions of hexafluorothioacetone (HFTA) with diazomethane, diphenyldiazomethane, and ethyl diazoacetate have been reported.[7] HFTA with diazomethane yields the unsymmetrical product, 2,2,5,5-tetrakis(trifluoromethyl)-1,3-dithiolane (**5**). With diphenyldiazomethane or ethyl diazoacetate, HFTA gives the normal thiirane derivative (**6** or **7**, Scheme III).

SCHEME III



Results and Discussion

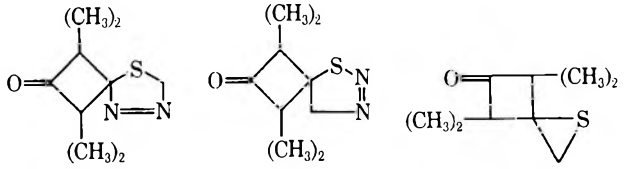
Reaction of Tetramethyl-3-thio-1,3-cyclobutanedione (1) with Diazomethane.—When an ether solution of the monothione **1** was treated with an ether solution of diazomethane, the initial red color disappeared as the diazomethane was added and no nitrogen was evolved. When the ether was removed at 0° or below, a white solid A was obtained; this solid spontaneously lost nitrogen when allowed to warm to room temperature or when refluxed in ether–pentane to give a new white solid **9**.

(6) A. Schönberg, B. Konig, and E. Singer, *Chem. Ber.*, **100**, 767 (1967), and references therein.

(7) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

The spectral data obtained from **9** established its structure as that of 4,4,6,6-tetramethyl-1-thiaspiro-[2.3]hexan-5-one.[8]

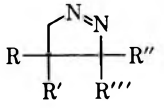
The infrared spectrum of A displayed strong bands at 1780 (cyclobutanone carbonyl) and at 1565 cm^{-1} (–N=N–). No absorption due to the RN_2^+ group was observed in the region of 2100 cm^{-1}. The nmr spectrum showed absorptions at 1.17 and 1.25 (each singlets with combined area of 12, CH_3) and at 5.70 ppm (singlet with area of 2, CH_2). From the spectral data, it appears that there are two reasonable structures for A: a Δ^3-1,3,4-thiadiazoline (**8a**) or a Δ^2-1,2,3-thiadiazoline (**8b**). These are the products from the two possible modes of addition of diazomethane to the



8a **8b** **9**

thiocarbonyl group. Although the infrared spectrum is compatible with both structures, the nmr spectrum suggests that **8a** is the more probable structure on the basis of the low field position of the methylene protons. No nmr data were found for the chemical shift of a methylene group in a Δ^2-1,2,3-thiadiazoline or a Δ^3-1,3,4-thiadiazoline.

The most nearly analogous compounds for which nmr data were found were 1-pyrazolines (**10a–10d**), which were prepared by the reaction of diazomethane with electron-deficient olefins.[9,10] In these compounds the methylene protons showed a chemical shift in the range of δ 4.20–4.81 ppm. On this basis, A was assigned



10a–10d

10a, R and R′ = CH_3; R″ = CN; R‴ = CO_2CH_3
b, R and R′ = CH_3CH_2; R″ = CN; R‴ = CO_2CH_3
c, R = CH_3; R′ = CH_3CH_2; R″ = CN; R‴ = CO_2CH_3
d, R and R′ = CH_3; R″ and R‴ = CN

the structure of 3,4-diaza-6,6,8,8-tetramethyl-7-oxo-1-thiaspiro[4.3]oct-3-ene (**8a**)[11] to account for the downfield shift of the methylene protons (~1 ppm) relative to the 1-pyrazolines. Structure **8a** is assumed to be correct for the unstable intermediate in discussions in the text, although it is recognized that structure **8b** cannot be discarded since the nmr evidence is not entirely definitive.

Thermal Decomposition of the Thiadiazoline 8a.—The rate of decomposition of **8a** in carbon tetrachloride at 49 ± 2° was followed by integrating the areas of the

(8) The photochemistry of 4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexan-5-one was described in a recent communication: J. G. Pacifici and C. E. Diebert, *J. Amer. Chem. Soc.*, **91**, 4595 (1969).

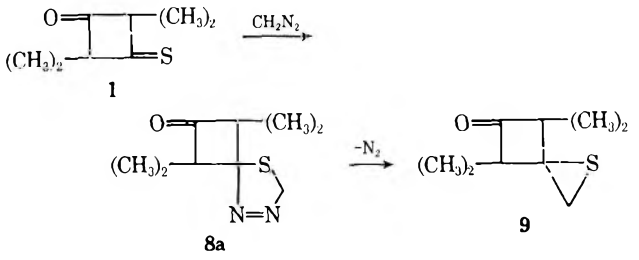
(9) J. Bus, H. Steinberg, and Th. J. de Boer, *Monatsh. Chem.*, **44**, 675 (1967).

(10) D. E. McGreer, R. S. McDaniel, and M. J. Vinjé, *Can. J. Chem.*, **43**, 1389 (1965).

(11) During the preparation of this paper, an isolable intermediate was reported in the reaction of hexafluorothioacetone with bis(trifluoromethyl)-diazomethane. The intermediate was shown to have a structure analogous to **8a** on the basis of its ^{19}F nmr spectrum: W. J. Middleton, *J. Org. Chem.*, **34**, 3201 (1969).

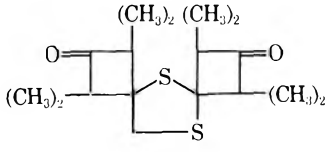
two different methylene resonances as the decomposition proceeded. The decomposition followed first-order kinetics, with $k = 5.2(10^{-4})$ sec^{-1}. The only product found from the decomposition was the thiirane **9**. The reaction sequence is shown in Scheme IV.

SCHEME IV



This report appears to be the first to describe the actual isolation and spectral characterization of an intermediate in the reaction of unsubstituted diazoalkanes with a thio ketone.[11]

Decomposition of the Thiadiazoline 8a in Excess Monothione 1.—When **8a** was decomposed in the presence of excess monothione **1**, a new product was obtained in addition to the thiirane **9**. This new compound showed infrared absorption at 1765 cm^{-1} (cyclobutanone carbonyl). A high-resolution mass spectrum of the compound gave the molecular weight as 326.1371. The molecular weight calculated for the molecular formula $C_{17}H_{26}O_2S_2$ is 326.1374. Therefore, the compound was an adduct containing two molecules of monothione **1** and one methylene group. The nmr spectrum of the compound in deuteriochloroform displayed four singlets at δ 1.28, 1.38, 1.43, and 3.18 ppm in the area ratio of 6:3:3:1. Addition of a small amount of benzene to the deuteriochloroform solution caused the singlet at δ 1.28 ppm to split into two singlets; no other new peaks were observed. On the basis of the spectral data, this compound was assigned structure **11**, which is analogous to the HFTA–diazomethane adduct **5**.



Reactions of Thiirane 9.—The reactions of **9** which were investigated are summarized in Scheme V.

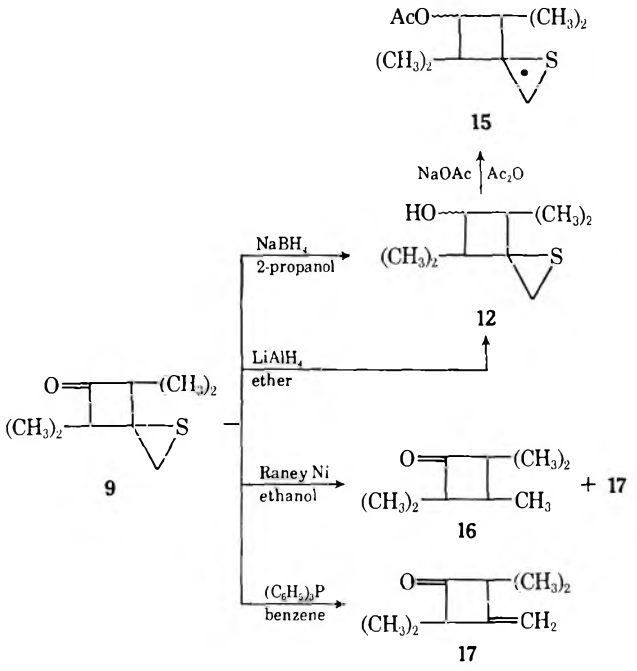
Ring-opening reactions of thiiranes with both electrophilic and nucleophilic reagents are usually facile.[12,13] Polymerization of the thiirane is often an important competing reaction. Surprisingly, **9** failed to react with copper bronze in refluxing xylene for 3.5 hr, with morpholine at 100° for 24 hr, with acetyl chloride at reflux for 3.5 hr, or with 0.1 *N* sodium methoxide in methanol at reflux for 1.5 hr.

Reduction of **9** with sodium borohydride or lithium aluminum hydride gave a mixture of *cis*- and *trans*-4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexan-5-ols (**12**).

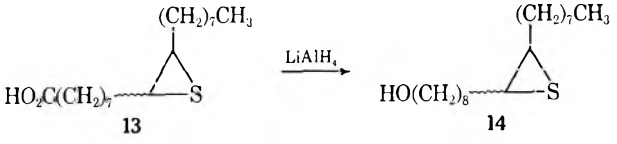
(12) M. Sander, *Chem. Rev.*, **66**, 297 (1966).

(13) D. D. Reynolds and D. L. Fields in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Vol. 19, Part 1, Interscience Publishers, Inc., New York, N. Y., 1964, p 602.

SCHEME V



There was no evidence for reduction of the thiirane ring. These reactions further demonstrate the unreactive nature of the thiirane ring in episulfide **9**, since reduction of thiiranes with lithium aluminum hydride usually gives mercaptans resulting from attack of the hydride at the least substituted carbon of the thiirane ring.[14,15] However, the *cis* and *trans* thiiranes **13** are known to react with lithium aluminum hydride to yield the *cis* and *trans* alcohols **14** without opening of the thiirane ring.[16]



The mixture of alcohols **12** reacted with acetic anhydride in the presence of sodium acetate to give a mixture of *cis* and *trans* acetates **15**. No ring-opened product from this reaction was found.

Thiirane **9** was desulfurized with Raney nickel in ethyl alcohol to give 2,2,3,4,4-pentamethylcyclobutanone (**16**) and 2,2,4,4-tetramethyl-3-methylenecyclobutanone (**17**).

When **9** was heated with triphenylphosphine in refluxing benzene, it reacted slowly to give only one product, 2,2,4,4-tetramethyl-3-methylenecyclobutanone (**17**). The physical constants of **16** and **17** were in good agreement with reported values, thus providing further confirmation of the structure of **9**.

Owing to the proximity of the methylene and carbonyl groups, it was thought that the ultraviolet spectrum of **17**[17] should display 1,3-π interaction similar to that postulated for the homologous compound, 3-methy-

(14) F. G. Bordwell, H. M. Andersen, and B. M. Pitt, *J. Amer. Chem. Soc.*, **76**, 1082 (1954).

(15) R. L. Jacobs and R. D. Schuetz, *J. Org. Chem.*, **26**, 3472 (1961).

(16) J. F. McGhie, W. A. Ross, F. J. Julietti, B. E. Grimwood, G. Usher, and N. M. Waldron, *Chem. Ind.* (London), 1980 (1962).

(17) The synthesis of **17** was reported by D. P. Hamon, *J. Amer. Chem. Soc.*, **90**, 4513 (1968), and its ultraviolet spectrum was recorded. This author did not discuss its ultraviolet spectrum.

lenecyclobutanone.[18,19] Thus, the ultraviolet spectrum of **17** was examined. The methylenecyclobutanone **17** showed the following absorptions in the ultraviolet: λ_{max}^{hexane} 211 nm (ϵ 1800), 313 (22). The pentamethylcyclobutanone[20] **16** showed the following absorption: λ_{max}^{hexane} 311 nm (ϵ 23), none in the 200-nm region. The bands at ~310 nm in **16** and **17** can be attributed to an $n\rightarrow\pi^*$ absorption of the carbonyl group. The band at 211 nm in **17** is at a longer wavelength than would be expected for the $\pi\rightarrow\pi^*$ absorption of a nonconjugated ethylene group and presumably is not due to a $\pi\rightarrow\pi^*$ absorption of the carbonyl group, since **16** shows no absorption in the 200-nm region. Thus, it appears that the 211-nm absorption in **17** is most reasonably attributed to a $\pi\rightarrow\pi^*$ charge-transfer band resulting from overlap of the π orbitals of the ketone and double bond.[19,21]

Experimental Section[22]

Materials.—Diazomethane was generated from N,N′-dimethyl-N,N′-dinitrosoterephthalamide (Aldrich Chemical Co.).[23] The tetramethyl-3-thio-1,3-cyclobutanedione[1] used in these studies was ≥95% pure by glpc.

4,4,6,6-Tetramethyl-1-thiaspiro[2.3]hexan-5-one (9).—Tetramethyl-3-thio-1,3-cyclobutanedione (15.6 g, 0.1 mol) was dissolved in *ca.* 100 ml of dry ether and cooled to 0° while the solution was stirred by means of a magnetic stirrer. Diazomethane was generated and slowly distilled into the ether solution until the initial deep red color of the solution had changed to a faint yellow. No nitrogen was evolved during addition of the diazomethane. The ether was then removed below 20° by means of a rotary evaporator. The residual mixture of solid and oil began to evolve nitrogen upon warming to room temperature. The mixture was dissolved in boiling pentane and filtered to remove traces of suspended matter. During the filtration, evolution of gas was vigorous. The pentane filtrate was cooled in Dry Ice and filtered to yield 11.4 g (67%) of a white solid, mp 77.5–81°. Recrystallization of the solid from pentane yielded an analytical sample of **9**, mp 80–82°.

The following spectral data were obtained on **9**: ir (KBr) 2960, 1785, 1445, 1375, 1360, 1005, 815, and 665 cm^{-1}; nmr ($CDCl_3$) δ 2.55 (singlet, area 2, CH_2), 1.18 and 1.12 ppm (both singlets with combined area of 12, CH_3); uv λ_{max}^{hexane} 209 nm (ϵ 610), 225 (190), 265 (62), and 313 (21). The mass spectrum of **9** showed the mass of the parent ion to be 170.

Anal. Calcd for $C_9H_{14}OS$: C, 63.48; H, 8.29; S, 18.83. Found: C, 63.36; H, 8.36; S, 18.50.

Isolation of the Unstable Intermediate 8a.—An aliquot of the cold ether solution of intermediate **8a**, prepared as described above, was transferred to a Schlenk tube, and the ether was pumped off while the solution was maintained at 0° or below. After the ether was completely removed, a white solid remained. The sample was stored at −60°, the Schlenk tube was opened under nitrogen, and the sample was dissolved in carbon tetrachloride. The temperature of the nmr probe was adjusted to 49 ± 2°, and a nmr spectrum was obtained on the freshly prepared sample. The intermediate showed absorptions at δ 5.70 (singlet, area 2, CH_2) and 1.25 and 1.17 ppm (both singlets with combined area of 12, CH_3). As the decomposition of **8a** proceeded, new absorptions at δ 2.55 (singlet), 1.18 (singlet), and 1.12 ppm (singlet) appeared. No absorption due to other decomposition products was observed. The rate of decomposition of **8a** was obtained by integrating the areas of the methylene proton signals at δ 5.70 and 2.55 ppm. The decomposition was found to obey first-order kinetics, with $k = 5.2(10^{-4})$ sec^{-1}.

The infrared spectrum (CCl_4) of **8a** displayed strong absorption at 2930, 1780, 1565, 1450, 1375, 1360, and 1025 cm^{-1}.

Decomposition of the Intermediate 8a in the Presence of Excess Monothione 1.—Monothione **1** (1.56 g, 10 mmol) was dissolved in 10 ml of anhydrous ether, the solution was cooled to 0°, and diazomethane (25 ml of 0.33 *M* solution, 8.3 mmol) was added dropwise. After the addition of diazomethane was completed, the ether was removed by means of rotary evaporator to give a red, semisolid product. About 5 ml of hexane was added to the reaction product, and the solution was warmed on a steam bath. The solution was cooled and then filtered to yield 0.50 g (31% based on **1**) of the 2:1 adduct **11**, mp 162–164°. Glpc analysis of the filtrate showed the presence of unchanged monothione **1** as well as thiirane **9**.

The following spectral data were obtained on **11**: ir (KBr) 2960, 1765, 1450, 1372, 1352, and 1020 cm^{-1}; nmr ($CDCl_3$) δ 3.18 (singlet, area 2, CH_2), 1.43 (singlet, area 6, CH_3), 1.38 (singlet, area 6, CH_3), and 1.28 ppm (singlet, area 12, CH_3); nmr ($CDCl_3$–benzene) δ 2.88 (singlet area 2, CH_2) and 1.33, 1.28, 1.23, and 1.08 ppm (all singlets, combined area 24, CH_3). A high-resolution mass spectrum of **11** gave the mass of the parent ion as 326.1371; the calculated mass for the molecular formula $C_{17}H_{26}O_2S_2$ is 326.1374.

4,4,6,6-Tetramethyl-1-thiaspiro[2.3]hexan-5-ol (12). A. From Reduction with Sodium Borohydride.—Thiirane **9** (1.70 g, 10 mmol) was dissolved in 15 ml of dry 2-propanol. Sodium borohydride (0.76 g, 20 mmol) dissolved in 10 ml of dry 2-propanol was added dropwise to the stirred reaction mixture. The mixture was stirred at room temperature for 17 hr, and excess borohydride was then destroyed by addition of 2% hydrochloric acid. The aqueous solution (pH 2) was saturated with sodium chloride, 20 ml of ether was added, and the ether phase was then washed with two 20-ml portions of saturated sodium chloride solution. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and evaporated to give 1.7 g (99%) of a mixture of *cis* and *trans* alcohols **12**, mp 45–53°. The alcohol mixture was recrystallized from 30–60° petroleum ether to give an analytical sample, mp 57–59°.

The infrared spectrum (CCl_4) showed absorption at 3600, 3450, 2940, 1465, 1375, 1365, and 1075 cm^{-1}. The nmr spectrum ($CDCl_3$) indicated that the sample was a 30:70 mixture of isomeric alcohols. The major isomer showed absorption at δ 3.76 (–O–C(H)–), 2.44 (CH_2), 2.14 (OH), 1.13 (CH_3), and 0.98 ppm (CH_3); the other isomer showed corresponding absorption at δ 3.88, 2.38, 2.14, 1.10, and 1.01 ppm. All absorptions were singlets. Since suitable model compounds were not available, assignment of absorptions to the appropriate isomer was not possible. The ultraviolet spectrum of the mixture of isomers showed absorption at λ_{max}^{hexane} 208 nm (ϵ 730) and 261 (44). The mass spectrum of the mixture showed the mass of the parent ion to be 172.

Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36; S, 18.61. Found: C, 62.87; H, 9.02; S, 18.61.

B. From Reduction with Lithium Aluminum Hydride.—Lithium aluminum hydride (0.40 g, 10 mmol) was suspended in 20 ml of anhydrous ether. Thiirane **9** (1.70 g, 10 mmol) was dissolved in 15 ml of ether and added dropwise to the stirred suspension. The mixture was then refluxed for 2 hr. The reaction mixture was cooled to *ca.* 5°, and water (0.4 ml), 15% sodium hydroxide (0.4 ml), and water (1.2 ml) were added successively. The resulting fine, granular precipitate was collected on a filter and washed with a small amount of ether. The ether filtrate was then dried over anhydrous sodium sulfate. The ether solution was filtered, and the filtrate was then evaporated to give 1.4 g (82%) of **12**, mp 55–58°.

The infrared and nmr spectra of the mixture of alcohols were identical with the spectra reported under A. The nmr spectrum indicated the sample to be a 25:75 mixture.

(18) F. F. Caserio and J. D. Roberts, *J. Amer. Chem. Soc.*, **80**, 5837 (1958).
(19) P. Dowd and K. Sachdev, *ibid.*, **89**, 714 (1967).
(20) J-M. Conia and J. Gore, *Bull. Soc. Chim. Fr.*, 1968 (1964).
(21) S. Winstein, L. de Vries, and R. Orloski, *J. Amer. Chem. Soc.*, **83**, 2020 (1961).
(22) Melting points were obtained with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were obtained with a Varian A-60 spectrometer equipped with a variable-temperature probe and a Varian HA-100 spectrometer. Chemical shifts are expressed in δ values (parts per million) from tetramethylsilane as internal standard; coupling constants are expressed in cycles per seconds. Mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110B mass spectrometer operated at an ionizing voltage of 70 eV. Infrared spectra were obtained with a Perkin-Elmer Infracord and a Perkin-Elmer Model 421 spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14-MS and a Perkin-Elmer Hitachi Model 123 spectrophotometer. Glpc analyses were done with an F & M Model 810 chromatograph using a 20% silicone QF-1 on Chromosorb P (1/8 in. × 6 ft) column. Elemental analyses were performed by the Analytical Services Laboratory of Tennessee Eastman Research Laboratories.
(23) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

2,2,4,4-Tetramethyl-3-methylenecyclobutanone (17).—A mixture of 9 (1.70 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in 20 ml of dry benzene was refluxed for 38 hr. The reaction mixture was periodically examined by glpc. The reaction was found to be about 50% complete after 3 hr and about 90% complete after 38 hr. The reaction proceeded cleanly to give only triphenylphosphine sulfide and **17**; no other products were found by glpc.

Samples of **17** (mp 42.5–44°) were collected from an analytical chromatograph in capillary tubes. The following spectral data[24] were obtained: ir (CCl_4) 3050, 2940, 1790, 1675, 1460, 1000, and 890 cm^{-1}; uv λ_{max}^{hexane} 211 nm (ϵ 1800) and 313 (22); nmr (CCl_4) δ 5.03 (singlet) and 1.22 ppm (singlet) with area ratio 1:6. The mass spectrum showed the mass of the parent ion to be 138.

A 2,4-dinitrophenylhydrazone of **17** was prepared, mp 145–147°; uv $\lambda_{max}^{abs\ EtOH}$ 212 nm (ϵ 6510), 230 (6360), and 355 (10,300).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.81; H, 5.73; N, 17.58.

4,4,6,6-Tetramethyl-1-thiaspiro[2.3]hexan-5-yl Acetate (15).—The mixture of *cis* and *trans* alcohols **12** (0.5 g, 2.9 mmol) was heated with 0.5 g of sodium acetate and 5 ml of acetic anhydride on a steam bath for 2 hr. The solution was then poured into 30 ml of cold water. The mixture was allowed to stand, with occasional stirring, for 30 min. The aqueous mixture was extracted with three 20-ml portions of ether, and the combined ether extracts were washed with cold 15% sodium carbonate. The ether layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give 0.54 g (87%) of a white solid. The mixture of *cis* and *trans* acetates was recrystallized from 30–60° petroleum ether, mp 35–37.5°.

The following spectral data were obtained for **15**: ir (KBr) 2960, 1740, 1460, 1450, 1365, 1230, and 1050 cm^{-1}; the nmr ($CDCl_3$) of the major isomer showed absorption at δ 4.60 (AcOCH), 2.46 (CH_2), 2.10 (CH_3CO_2), 1.12 (CH_3), and 1.07 ppm (CH_3); the minor isomer displayed corresponding absorptions at δ 4.74, 2.40, 2.10, 1.18, and 0.98 ppm. All peaks in the nmr spectrum were singlets, and the spectrum showed that the sample was a 30:70 mixture. A high-resolution mass spectrum of the mixture gave the measured mass of the parent ion as 214.1032, which corresponds to the molecular formula $C_{11}H_{18}O_2S$ (calcd for $C_{11}H_{18}O_2S$: 214.1027).

(24) The spectral data agree favorably with those reported by Hamon.[17]

Reaction of Thiirane 9 with Raney Nickel.—Thiirane **9** (1.0 g, 5.9 mmol) was dissolved in 25 ml of ethyl alcohol and Raney nickel catalyst (~10 g) was added. The reaction mixture became warm. The mixture was refluxed under nitrogen for 3 hr and then filtered through Celite filter aid.

The filtrate was examined by glpc. A major product and a minor product were found. These two products were collected from the analytical glpc in capillary tubes. The minor product was shown to have structure **17** by comparison of its infrared spectrum with that of an authentic sample.

The major product, 2,2,3,4,4-pentamethylcyclobutanone (**16**), was isolated as a colorlessl iquid. The following spectral data were obtained for **16**: ir (neat) 2950, 1785, 1580, 1380, 1 365, and 1040 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (quartet, $CHCH_3$, J = 7 cps), 1.17 (singlet, CH_3), 1.06 (singlet, CH_3), and 1.03 ppm (doublet, $CHCH_3$, J = 7 cps) [lit.[25] nmr (CCl_4) δ 1.91, 1.15, 1.06, and 1.06 ppm]; uv λ_{max}^{hexane} 311 nm (ϵ 23), [lit.[20] uv λ_{max}^{hexane} 311 nmr (ϵ 22)]. The mass spectrum of **16** showed the mass of the parent ion to be 140.

A 2,4-dinitrophenylhydrazone of **16** was prepared, mp 144–145° (lit.[20] mp 145°).

Registry No.—**8a**, 23604-61-7; **9**, 23604-62-8; **11**, 23604-63-9; *cis*-**12**, 23601-92-5; *trans*-**12**, 23601-93-6; *cis*-**15**, 23601-94-7; *trans*-**15**, 23601-95-8; **17**, 20019-11-8; 2,4-dinitrophenylhydrazone of **17**, 23604-65-1.

Acknowledgment.—The author is grateful to Dr. V. W. Goodlett and Mr. H. D. Kinder, Research Laboratories, Tennessee Eastman Co., for helpful discussions of the nmr spectra.

(25) B. Braillon, J. Salaun, J. Gore, and J-M. Conia, *Bull. Soc. Chim. Fr.* 1981 (1964).

The Facilitation of Sodium Borohydride Reduction of Esters of Phenols and of Acidic Alcohols

SHO TAKAHASHI[1] AND LOUIS A. COHEN

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received June 6, 1969

The reduction of esters (RCOOR′) by sodium borohydride is facilitated by use of R′ groups more electronegative than methyl, rate enhancements of at least 300-fold having been demonstrated. The rates of reduction of substituted phenyl esters correlate linearly with the pK_a values of the corresponding phenols (ρ = 2.6), a separate correlation being obtained for alcohols. In 1,2-dimethoxyethane as solvent, esters of acidic alcohols are 10–50 times as reactive toward borohydride as are those of phenols of comparable pK_a, the difference being ascribed to conformational or steric obstruction by the aromatic ring; furthermore, reduction is significantly faster in media containing water. By use of an appropriate alcohol for esterification, carboxyl groups can be reduced selectively to primary alcohols in the presence of functional groups which are reactive toward more powerful reducing agents.

Esters of simple carboxylic acids are normally resistant to reduction by sodium borohydride.[2] However, reduction can sometimes be effected by activation of the reagent, *e.g.*, by its conversion, *in situ*, into lithium or magnesium borohydride,[3] or to a more reactive alkoxyborohydride.[4]

In connection with studies on the selective modification of proteins,[5] we encountered the problem of effecting the specific reduction of esters under the mildest possible conditions. Since lithium borohydride[6a] and diborane[5,6b] are known to reduce amides as well as esters, and since the solubility and stability properties of proteins restrict the use of the methods cited above, an alternative mode of reduction was sought.

In a number of instances, sodium borohydride has been effective in reducing esters of carboxylic acids con-

(1) Associate in the Visiting Program, National Institutes of Health, 1967–1969.

(2) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 2.

(3) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **77**, 6209 (1955).

(4) (a) H. C. Brown and E. J. Mead, *ibid.*, **75**, 6263 (1953); (b) H. C. Brown, E. J. Mead, and C. J. Shoaf, *ibid.*, **78**, 3616 (1956); (c) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(5) See, *e.g.*, S. Takahashi and L. A. Cohen, *Biochemistry*, **8**, 864 (1969).

(6) (a) A. C. Chinbnall and M. W. Rees, *Biochem. J.*, **68**, 105 (1958); (b) O. Yonemitsu T. Hamada, and Y. Kanaoka, *Tetrahedron Lett.*, 3575 (1968).

TABLE I

ESTERS OF 3-PHENYLPROPIONIC ACID[a]

Ester	Registry no.	Mp or bp, °C (mm)	Ester	Registry no.	Mp or bp, °C
Methyl	103-25-3	75 (1)	*p*-Fluorophenyl (B)	23522-72-7	29–34
Propargyl	23522-64-7	120 (2)	*p*-Chlorophenyl (D)	23522-73-8	48–49
Trichloroethyl	23522-65-8	138–140 (1.5)	*m*-Chlorophenyl (B)	23522-74-9	34
Trifluoroethyl	23522-66-9	69–72 (1)	Pentachlorophenyl (E)	23522-75-0	106–107
Hexafluoroisopropyl	23522-67-0	61–62 (1)	*p*-Bromophenyl (C)	23522-76-1	54–55
3,5-Dinitrobenzyl (A)[b]	23568-84-5	83–84	*p*-Iodophenyl (C)	23522-77-2	64–67
Phenyl	726-26-1	147 (1)	*p*-Nitrophenyl (E)	17895-71-5	94–95
p-Methylphenyl (B)	22020-95-7	35–36	*m*-Nitrophenyl (C)	23522-79-4	63–64
p-*t*-Butylphenyl (B)	23522-70-5	49–50	2,4-Dinitrophenyl (C)	23522-80-7	54–55
p-Methoxyphenyl (C)	23522-71-6	40			

[a] All compounds provided acceptable elemental analyses. [b] Solvents for recrystallization: A, chloroform; B, petroleum ether; C, ethyl acetate–petroleum ether; D, cyclohexane; E, ethyl acetate.

taining electron-withdrawing substituents α to the carbonyl group.[7] Indeed, a correlation of the rate of ester reduction with the electron-withdrawing power of the substituent has been demonstrated,[7e] although intramolecular complexing with the reagent may become an accessory factor.[7c] Such observations led us to consider an alternative route to activating the carbonyl group, *i.e.*, by utilizing the esters of phenols and of alcohols more acidic than methanol. Although thiol esters[8a] and carbonic anhydrides[8b] are reduced readily by sodium borohydride, the meager data available provide little basis for estimating the dependence of reduction rate of an ester on the acidity of the corresponding alcohol or phenol. We have, therefore, determined the rates of reduction of a series of esters of 3-phenylpropionic acid and have found a linear variation of the logarithm of the rate with the pK_a of alcohol or phenol. Furthermore, esters of alcohols are significantly more reactive toward borohydride than are those of phenols of comparable pK_a. Rates of reduction greater than 300 times that of the methyl ester have been observed.

Results

Esters of 3-phenylpropionic acid were chosen for the present study because of their ease of purification and because the reduction product, 3-phenyl-1-propanol, is readily separated from other components by gas–liquid chromatography. Since the pK_a value of 3-phenylpropionic acid (4.66)[9] is similar to those of simple aliphatic carboxylic acids, the observed rates of reduction are probably applicable to the corresponding esters of a variety of carboxylic acids. Initially, attempts were made to utilize esters of cinnamic acid, since rates of reduction could be followed spectrophotometrically. However, saturation of the double bond appeared to be competitive with ester reduction for such compounds.[4c]

The phenols and alcohols used in this study were chosen to provide as wide a range of pK_a values as possible. However, for phenols having pK_a values below 9, rates of reduction were too fast to provide reliable data. The esters of 3-phenylpropionic acid (Table I) were obtained in yields of 60–90% by coupling the acid and the hydroxyl compound by means of trifluoroacetic anhydride.[10] In order to avoid wide alterations in the nature of the reagent, 1,2-dimethoxyethane was used as solvent at 40°. At this temperature, a solution saturated with sodium borohydride was found to be 0.11 *M* (manometric assay). The amount of sodium borohydride added in each run corresponded to a 10–20 molar excess of reagent, a portion remaining undissolved.

Reaction rates were obtained by assay of the 3-phenyl-1-propanol content of aliquots on a glpc column. For all esters studied, pseudo-first-order kinetics were observed up to 50–80% reaction (Table II). Some representative results are shown in Figure 1. In a few cases, small deviations occurred beyond 50% conversion. Fivefold variations in the initial concentration of ester or in the ester/borohydride ratio had no signifi-

TABLE II

RATES OF BOROHYDRIDE REDUCTION OF ESTERS OF 3-PHENYLPROPIONIC ACID (RCOOR′)

R′	pK_a(R′OH)[a]	σ[b]	$k' \times 10^4$, min^{-1}
m-Chlorophenyl	9.02[c]	0.40	500
p-Iodophenyl	9.30	0.28	230
p-Bromophenyl	9.36	0.25	200
p-Chlorophenyl	9.42	0.22	162
p-Fluorophenyl	9.91	0.01	48.0
Phenyl	9.99	0	39.8
p-*t*-Butylphenyl	10.23[d]	−0.14	20.8
p-Methylphenyl	10.26	−0.15	17.4
p-Methoxyphenyl	10.21	−0.13	7.85
Hexafluoroisopropyl	9.30[e]		(1070)[f]
Trifluoroethyl	12.37[g]		35.6
Trichloroethyl	12.70[h]		13.6
Propargyl	13.55[g]		9.40
Methyl	15.09[i]		1.52

[a] Unless indicated otherwise, pK_a values are taken from A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [b] Values based on the ionization of phenols, calculated from the equation $pK_a = 9.919 - 2.229\sigma$ (A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [c] C. M. Judson and M. Kilpatrick, *J. Amer. Chem. Soc.*, **71**, 3110 (1949). [d] L. A. Cohen and W. M. Jones, *ibid.*, **85**, 3397 (1963). [e] B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965). [f] Extrapolated from Figure 2, using the pK_a value of 9.30. [g] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960). [h] S. Takahashi and L. A. Cohen, manuscript in preparation. [i] J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964).

(7) (a) E. Schenker, *Angew. Chem.*, **73**, 81 (1961); (b) V. Boekelheide and R. J. Windgassen, Jr., *J. Amer. Chem. Soc.*, **81**, 1456 (1959); (c) J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963); (d) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965); (e) H. Seki, K. Koga, and S. Yamada, *ibid.*, **15**, 1948 (1967).

(8) (a) E. J. Barron and L. A. Mooney, *Anal. Chem.*, **40**, 1742 (1968); (b) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

(9) J. F. J. Dippy, *Chem. Rev.*, **25**, 151 (1939).

(10) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).

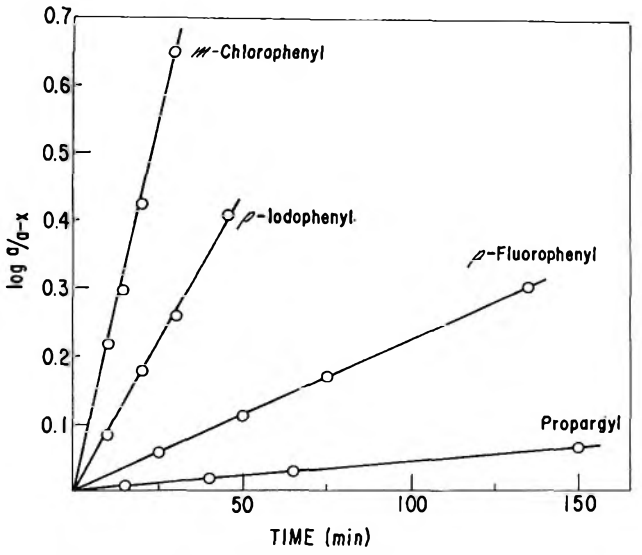


Figure 1.—Representative pseudo-first-order plots of the reduction of esters of 3-phenylpropionic acid with sodium borohydride in 1,2-dimethoxyethane at 40°.

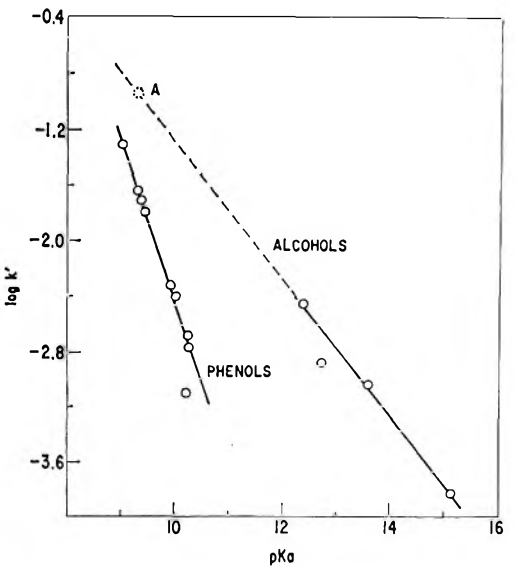


Figure 2.—Plots of log k' (borohydride reduction of esters) *vs.* pK_a of phenol or alcohol component of ester: A, extrapolated rate for hexafluoroisopropyl ester, based on pK_a of 9.30.

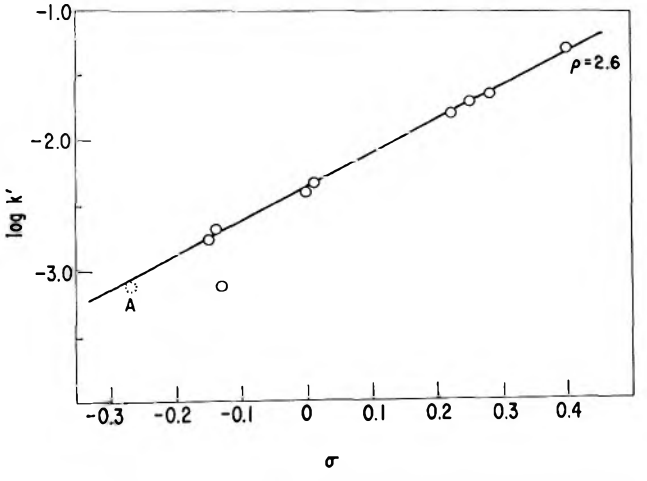


Figure 3.—Plot of log k' (borohydride reduction of esters) *vs.* σ values of aryl substituents: A, correlation of *p*-methoxy substituent, using a σ value of −0.27.

cant effect on values of k'. In the cases of *p*-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl, and hexafluoroisopropyl esters, reduction was too rapid to obtain reliable kinetic data by this technique, even at temperatures below 40°. Thin layer chromatography was used to demonstrate the complete conversion of these esters into 3-phenyl-1-propanol within 5 min of mixing. Reduction of the 3,5-dinitrobenzyl ester was complicated by the formation of intensely colored complexes with sodium borohydride, probably owing to proton abstraction from the benzene ring. Similarly colored species are formed by the addition of sodium borohydride or of strong nonreducing bases to solutions of *m*-dinitrobenzene.

Solvent effects were examined briefly by comparing the rates of reduction of the phenyl ester at 0° in 1,2-dimethoxyethane ($k' = 0.53 \times 10^{-3}$ min^{-1}) and in dimethoxyethane–water (7:3, v/v) ($k' = 4.10 \times 10^{-3}$ min^{-1}). Thus reduction is 7.5 times as rapid in the presence of water, at least for the one case examined.[11] Satisfactory comparisons could not be made for the more reactive esters because of the rapidity of reduction and the competitive alkaline hydrolysis of such esters.

As is evident from Figure 2, log k' varies linearly with the pK_a of the phenol component of the phenyl ester (log $k' = -1.15pK_a + 9.05$). A similar plot of log k' *vs.* σ (Figure 3) provides a ρ value of 2.6. The reason for the deviation of the *p*-methoxyphenyl ester is not immediately obvious, being well beyond the limits of experimental error. It is interesting, although probably fortuitous, that a correlation with the Hammett plot of Figure 3 can be obtained by use of the σ value (−0.27) based on ionization of *p*-anisic acid rather than that for ionization of *p*-methoxyphenol (−0.13).

Studies with esters of alcohols were limited by the unavailability of sufficiently acidic alcohols. Thus a wide gap exists between trifluoroethanol (pK_a 12.37) and hexafluoro-2-propanol (pK_a 9.3). From the limited data obtained, it would appear that a linear relationship does, in fact, exist between the logarithm of the rate of ester reduction and the pK_a of the corresponding alcohol. From three points, the equation log $k' = -0.50pK_a + 3.73$ may be derived. Despite the use of a revised value for the pK_a of trichloroethanol,[12] the rate of reduction of the trichloroethyl ester was less than that required for linear correlation, possibly owing to steric interaction between the substituent and the borohydride–carbonyl complex.[12]

Discussion

The inductive effect of a substituent on the β carbon of ethyl alcohol influences the acidity of the alcohol in a predictable manner, which can be related to the Taft constant for that substituent.[13a] It is reasonable to expect the inductive effect to be relayed to the adjacent

(11) The enhanced reactivity of sodium borohydride, or of its hydrolysis products, in aqueous media has been noted previously: H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **83**, 4372 (1961); see also ref 7e.

(12) S. Takahashi and L. A. Cohen, manuscript in preparation. Although partial dehalogenation of the trichloromethyl substituent by borohydride was considered, glc demonstrated the absence of any abnormal reduction products.

(13) (a) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960); (b) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).

carbonyl carbon in the corresponding ester, thus determining its relative electrophilicity toward borohydride. Similarly, the combined inductive and resonance effects of a substituent on the benzene ring, acting on the phenolic oxygen, should be transmitted to the adjacent carbonyl group as a net inductive effect.[13b] The correlation of reduction rate with pK_a, in both series, is in accord with such considerations. On the other hand, esters of 3-phenylpropionic acid with alcohols are reduced significantly faster than are those with phenols of comparable acidity. Whereas the ester of *p*-iodophenol (pK_a 9.3) shows $t_{1/2}$ = 30 min, $t_{1/2}$ for the ester of hexafluoro-2-propanol (pK_a 9.3) is probably less than 3 min. Furthermore, the trifluoroethyl ester was reduced at approximately the same rate as the phenyl ester, despite a pK_a difference of 2.4 units.

In earlier studies on alkaline hydrolysis,[13b] esters of phenols have been found, invariably, to be more reactive than those of alcohols of comparable pK_a, phenyl acetate hydrolyzing six times as rapidly as trifluoroethyl acetate. Such results are in accord with electronic considerations. Furthermore, the rates of alkaline hydrolysis of both types of esters can be correlated with the pK_a of the leaving group on a single plot.[13b] Since attack of hydride or of borohydride ion on the ester carbonyl may be viewed as another example of a nucleophilic reaction, it is doubtful whether the present results can be explained on the basis of electronic factors alone. Inspection of molecular models reveals that phenyl esters cannot achieve the *trans* conformation of simple aliphatic esters. Indeed, it has been concluded from molecular polarizability measurements that the carbonyl group of a phenyl ester is perpendicular to the aromatic plane.[14] Such a difference in conformation may force the borohydride ion to approach the carbonyl group of a phenyl ester from a less favorable direction than is possible for an aliphatic ester. Alternatively, the bulk of the aromatic ring may present a steric obstacle to the formation either of the borohydride–carbonyl complex or of the tetrahedral alkoxyborohydride intermediate. The importance of such factors is difficult to evaluate, since the electronic and steric components are not readily separated. We studied the reduction of the hexafluoroisopropyl ester, as the closest aliphatic approximation to a phenyl ester, both in steric and in electronic properties. As previously noted, the rate proved to be too fast to be measured accurately.

The rates of borohydride reduction of substituted phenyl esters are considerably more sensitive to the nature of the substituent (ρ = 2.6) than are those for alkaline hydrolysis of phenyl acetates (ρ = 0.8).[15] Because of the sizable differences in sensitivity to substitution, both in alcohols and in phenols, rough comparisons reveal that $k_2^{OH^-}/k^{BH_4^-}$ = *ca.* 1000 for the trifluoroethyl ester, 100 for the phenyl ester, and only 3 for the *p*-nitrophenyl ester. Therefore, in the application of borohydride reduction of activated esters in aqueous media, it is desirable to employ high concentrations of reducing agent at as low an alkaline pH as is practical.

Thus it is evident that sodium borohydride reduction of simple carboxylic acids can be achieved under mild conditions by prior esterification with an appropriate partner. The rate data, considered together with stability of the ester in mildly alkaline media,[13b] suggest the choice of the trifluoroethyl ester, particularly for the carboxyl groups of peptides and proteins. Its candidacy is supported by the relative ease of esterification of carboxylic acids with trifluorodiazoethane.[16]

Experimental Section[17]

Preparation of Esters of 3-Phenylpropionic Acid.—To a solution of 0.02 mol of 3-phenylpropionic acid in an equimolar amount of trifluoroacetic anhydride was added 0.02 mol of alcohol or phenol, and the reaction mixture was stored at ambient temperature for 3 hr.[10] In several instances, the product separated as a solid during the reaction. In the case of 2,4-dinitrophenol, esterification was performed at 40° for 3 hr, and in that of pentachlorophenol, at 40° for 5 hr. The reaction mixture was poured into aqueous sodium bicarbonate with vigorous stirring and cooling. Solid esters were collected by filtration, washed with water, and dried over KOH *in vacuo;* solvents for recrystallization are listed in Table I. Liquid esters were extracted with ether, and the extracts were washed with 3% sodium bicarbonate, dried (Na_2SO_4), and evaporated. The residual oils were purified by distillation at reduced pressure. Alternatively, the esters were distilled directly from the esterification reaction mixture. The purified esters were obtained in yields of 60–90%. Physical and analytical data are summarized in Table I.

Kinetic Measurements.—A solution of ester in 1,2-dimethoxyethane (30–40 ml, 0.1–0.02 *M*) was placed in a jacketed test tube maintained at 40 ± 0.1° with a circulating water bath. Solid sodium borohydride (1–2 g) was added in one portion and the reaction mixture was stirred vigorously with a magnetic stirrer. At appropriate time intervals, 5-ml aliquots were removed for assay of 3-phenyl-1-propanol. To each aliquot was added, with cooling, 1.5 ml of 6 *N* hydrochloric acid to destroy excess borohydride. After 30 min, the solution was made alkaline with 2.5 ml of 6 *N* sodium hydroxide and the phases were then separated. The aqueous phase was extracted with three portions of 4 ml of ethyl acetate and the combined organic extracts were evaporated to dryness. The residue was diluted to 0.5 or 1 ml with ethyl acetate and a measured amount of 1-decanol was added to serve as an internal standard for gas chromatography. Analyses were performed on a Glowall, Unilab Model 400, gas chromatograph using a column of Gas-Chrom P (HMDS) coated with 20% Reoplex 400 (Applied Science Labs, Inc.). At a column temperature of 175° and a flash temperature of 220°, 3-phenyl-1-propanol emerged at 9–10 min, well separated from other reaction components. Peak areas were integrated and compared with a standard calibration curve. Conversion yields used for rate calculations were the averages of at least three glpc determinations, maximum deviations falling within 5%. When the identical manipulations were performed on control samples of 3-phenyl-1-propanol, recoveries of 96–100% were obtained. The retention times of *p*-fluorophenol and of *p*-cresol were sufficiently close to that of 3-phenyl-1-propanol to cause peak distortion. Since the corresponding anisoles did not interfere in the gas chromatographic analysis, the reaction mixtures containing these phenols were treated with a large excess of ethereal diazomethane for 24 hr prior to analysis; under these conditions, methylation of the phenols appeared to be complete.

Registry No.—Sodium borohydride, 16940-66-2.

(14) M. Aroney, R. J. W. Le Fèvre, and S. Chang, *J. Chem. Soc.*, 3173 (1960).

(15) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964).

(16) B. L. Dyatkin and E. P. Mochalina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1225 (1964).

(17) Melting points and boiling points are uncorrected. Microanalyses were performed by Dr. W. C. Alford and his associates of this Institute.

Stereospecific Syntheses of Deuterated Clovane and Caryolane Derivatives Related to the Cyclization of Caryophyllene[1a]

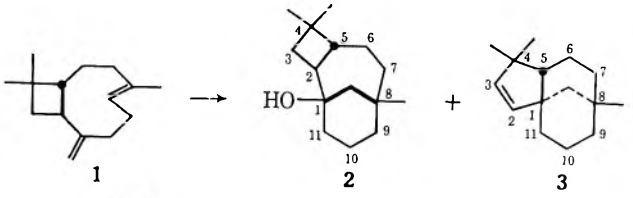
FRED Y. EDAMURA[1b] AND ALEX NICKON[1c]

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

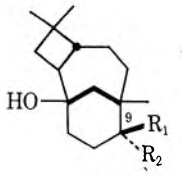
Received October 6, 1969

Stereospecific syntheses of four deuterium-labeled compounds related to the cyclization of caryophyllene are described. The routes may be generally useful for introduction of deuterium at hindered sites. Caryolan-1-ol-9-one was converted by a series of reactions into caryol-9-en-1-ol (**7**) and caryol-9-en-1-ol-9-*d* (**8**). Caryolan-1-ol-9β-*d* (**2b**) and -9α-*d* (**2a**) were prepared by respective deuterioboration of **7** and hydroboration of **8**, as their trimethylsilyl ethers, followed by removal of the C-10 hydroxyl group. Clovane-2β-ol-9-one was converted into clov-9-en-2β-ol (**19**) and into clov-9-en-2β-ol-9-*d* (**20**). Clovenic anhydride-6α-*d* (**4a**) and -6β-*d* (**4b**) were prepared by respective deuterioboration of **19** and hydroboration of **20**, as their trimethylsilyl ethers, followed by removal of the C-10 function and oxidation of the five-membered ring. The reduction of ketone tosylhydrazones with lithium aluminum hydride followed by D_2O work-up was found to provide an effective route to monodeuterated olefins.

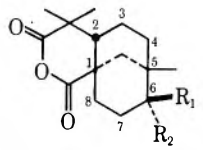
Caryophyllene (**1**) undergoes acid-catalyzed cyclization to give (among other products) caryolan-1-ol (**2**) and clov-2-ene (**3**).[2] Cyclization with D_2SO_4 leads to monodeuterated **2** and **3**,[3] whose deuterium configurations are pertinent for mechanistic understanding of the



1 **2** **3**



2a, $R_1 = H$; $R_2 = D$
b, $R_1 = D$; $R_2 = H$



4a, $R_1 = H$; $R_2 = D$
b, $R_1 = D$; $R_2 = H$

cyclizations. To permit a rigorous assignment of deuterium configurations in the cyclization products, we synthesized the following authentic deuterated compounds by stereospecific routes: caryolan-1-ol-9-α-*d* (2a) and -9β-*d* (**2b**) and clovenic anhydride-6α-*d* (**4a**) and -6β-*d* (**4b**).[4]

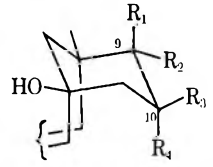
Attempts were initially made to prepare the desired deuterated compounds by direct deuteride displacements on appropriately functionalized C-9 derivatives of caryolane and clovane. However, such a route was vitiated by eliminations and molecular rearrangements, which are characteristic of nucleophilic substitutions at neopentyl positions.[5] Incorporation of deuterium of known configuration at the C-9 position in the caryolane and clovane systems was accomplished by deuterioboration[6] of olefins **7a** and **19a**, and by hydroboration[7] of deuterated olefins **8a** and **20a**. The known *cis* mechanism of hydroboration was used to determine deuterium configuration.

Caryolane System.—The preparation of caryolan-1-ol-9α-*d* (**2a**) and -9β-*d* (**2b**) is outlined in Scheme I.

SCHEME I

5, R = O
6, R = NNHTs

7, $R_1 = R_2 = H$
7a, $R_1 = Me_3Si$; $R_2 = H$
8, $R_1 = H$; $R_2 = D$
8a, $R_1 = Me_3Si$; $R_2 = D$



9, $R_1 = OH$; $R_2 = R_3 = R_4 = H$
10, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
11, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
12, $R_1 = R_2 = R_3 = H$; $R_4 = OH$
13, $R_1 = OH$; $R_2 = R_4 = H$; $R_3 = D$
14, $R_1 = D$; $R_2 = R_4 = H$; $R_3 = OH$
15, $R_1 = OH$; $R_2 = D$; $R_3 = R_4 = H$
16, $R_1 = R_4 = H$; $R_2 = D$; $R_3 = OH$

11 → C-10 tosylate **11a** → **2**
14 → C-10 tosylate **14a** → **2b**
16 → C-10 tosylate **16a** → **2a**

(1) (a) Support by the National Institutes of Health (Grant GM 06304), and by an Esso Education Foundation Fellowship to F. Y. E., is gratefully acknowledged; (b) taken from the Ph.D. dissertation of F. Y. E., Johns Hopkins University, 1965; (c) to whom inquiries should be sent.

(2) (a) A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J. Chem. Soc.*, 3124 (1953); (b) A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey, *ibid.*, 4659 (1954); (c) A. Nickon, *Perfumery Essent. Oil Record*, **45**, 149 (1954); (d) W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Lett.*, 2313 (1965).

(3) A. Nickon, F. Y. Edamura, T. Iwadare, K. Matsuo, F. J. McGuire, and J. S. Roberts, *J. Amer. Chem. Soc.*, **90**, 4196 (1968).

(4) Because clovene is a liquid, its solid anhydride **4**, obtainable by oxidation of **3**, was chosen as the compound for comparison. Note that the C-6 position in **4** corresponds to the C-9 position in **3**.

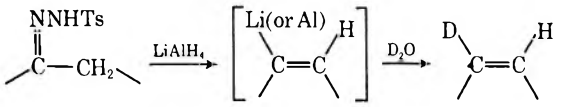
(5) E. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p 277.

(6) H. C. Brown and K. J. Murray, *J. Org. Chem.*, **26**, 631 (1961).

(7) (a) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962; (b) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

Caryolan-1-ol-9-one (**5**)[8] was converted into its tosylhydrazone derivative **6**. Caryol-9-en-1-ol (**7**) was obtained when **6** was treated with sodium methoxide in diethyl Carbitol (Bamford–Stevens[9] reaction under aprotic conditions[10-12]). Olefin **7** was also obtained when **6** was treated with lithium aluminum hydride (Caglioti[13] reaction). The structure of **7** was established by its infrared and nuclear magnetic resonance spectra, and by hydrogenation to the known alcohol **2**. The position of the double bond was verified by hydroboration experiments (described below), which gave C-9 and C-10 alcohols.

Deuterium incorporation was achieved by treatment of **6** with lithium aluminum hydride followed by work-up in D_2O, which gave caryol-9-en-1-ol-9-*d* (**8**, 6% d_0, 94% d_1). The nmr spectrum of **8** showed a one-proton triplet (J = 3.5 Hz) at δ 5.55 attributed to the C-10 proton.[14] The deuterium must therefore be located at C-9. Treatment of **6** with lithium aluminum deuteride, followed by H_2O work-up, gave **7** (96% d_0, 4% d_1); furthermore, deuterium was not incorporated into **7** when it was treated with $LiAlH_4$ followed by D_2O work-up. These results demonstrate that deuterium does not come from the reducing agent but rather by deuterolysis of some intermediate (eq 1) during work-up, and the method appears attractive for the preparation of monolabeled olefins.[16]



(1)

Hydroboration of hydroxy olefin caryol-9-en-1-ol (**7**) gave a mixture of all four possible diols (analyzed as their bistrimethylsilyl ethers[17] by gas chromatography): caryolane-1,9β-diol (**9**),[18] -1,9α-diol (**10**),[2b] -1,10β-diol (**11**), and -1,10α-diol (**12**). Attempts were made to optimize the formation of diol **11**. No reaction occurred when the more selective reagent disiamylborane[19] was tried. The best results were obtained when the trimethylsilyl ether of caryol-9-en-1-ol (**7a**) was treated with externally generated[7b] diborane: 49% of a mixture[20] of **9** and **10**, 37% **11**, and 7% **12**.

Diol **11** was isolated as its bistrimethylsilyl ether. The nmr of **11** and of its C-10 tosylate **11a** showed symmetrical seven-line multiplets centered at δ 4.10 and 4.80, respectively, for the carbinyl proton at C-10. The relative band intensities were 1:2:3:4:3:2:1, with band separations of 5.5 Hz. The pattern results from two diaxial splittings of 11 Hz and two axial–equatorial splittings of 5.5 Hz. The carbinyl-proton must therefore be at C-10 and have axial character (hence equatorial hydroxyl group). Similar spectra have been reported for steroidal[21a] and bicyclo[3.3.1]nonane[22,23] systems. The β assignment for the C-10 OH in **11** is based on the predominant β attack in hydroboration.[20] Our results thus show that the six-membered ring in **11** exists in a chairlike conformation.[24]

Similarly, caryolane-1,10β-diol-9β-*d* (**14**, 10–23% d_0, 76–84% d_1, 0–8% d_2) was prepared by deuterioboration of **7a**.[25] The nmr of **14** and of its C-10 tosylate **14a** showed symmetrical five-line multiplets with relative band intensities of 1:2:2:2:1 and band separations of 5.5 Hz. This pattern arises from one diaxial and two axial–equatorial splittings and is consistent with the assigned structure for **14** (equatorial OH at C-10 and axial deuterium at C-9). Caryolane-1,10β-diol-9α-*d* (**16**, >90% d_1) was prepared by hydroboration of deuteriоolefin **8a**.[26] The nmr of **16** and of its C-10 tosylate **16a** showed symmetrical six-line multiplets with relative band intensities of 1:1:2:2:1:1 and band separations of 5.5 Hz. This pattern results from two diaxial and one axial–equatorial splittings, and is consistent with structure **16** (equatorial OH at C-10 and equatorial deuterium at C-9). A similar splitting pattern has been reported for a steroidal alcohol in the same sort of environment.[21b] The C–D stretching frequencies[27] in diols **14** (2145 cm^{-1}, axial D) and **16** (2158 cm^{-1}, equatorial D) substantiated the nmr assignments, although by itself the infrared criterion is not unequivocal.

Removal of the C-10 hydroxyl group in diols **11**, **14**, and **16** was accomplished by conversion into the corresponding tosylates **11a**, **14a**, and **16a**, respectively, followed by displacement with lithium aluminum hydride. Thus **14** was converted into caryolan-1-ol-9β-*d* (**2b**, 98% pure, 20% d_0, 73% d_1, 7% d_2), and **16** was converted into caryolan-1-ol-9α-*d* (**2a**, 98% pure, 16% d_0, 84% d_1). Infrared spectra indicated that the deuterium retained its axial character in the conversion of **14** into **2b** (2142 cm^{-1}), and its equatorial character

(8) D. H. R. Barton, T. Bruun, and A. S. Lindsey, *J. Chem. Soc.*, 2210 (1952).

(9) W. R. Bamford and T. S. Stevens, *ibid.*, 4735 (1952).

(10) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

(11) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959).

(12) Rearranged olefins resulted when protic solvents were used. Tosylhydrazone decompositions in protic media involve cationic intermediates, whereas under aprotic conditions carbenes are produced.[10,11]

(13) R. Caglioti and M. Magi, *Tetrahedron Lett.*, 1261 (1962); *Tetrahedron*, **19**, 1127 (1963).

(14) The nmr signal is assigned to the C-10 proton on the basis of the observed coupling constant, which is appropriate for vicinal but not for allylic coupling.[15]

(15) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, London, 1959, p 85.

(16) After completion of our experiments, similar conclusions were drawn about the Caglioti reaction in steroid systems: M. Fisher, Z. Pelah, D. H. Williams, and C. Djerassi, *Chem. Ber.*, **98**, 3236 (1965).

(17) (a) R. Martin, *J. Amer. Chem. Soc.*, **74**, 3024 (1952); (b) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *ibid.*, **85**, 2497 (1963).

(18) W. Treibs, *Chem. Ber.*, **80**, 56 (1947).

(19) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 3222 (1960); **83**, 1241, (1961).

(20) (a) Although our glpc was known not to resolve **9** and **10**, the product after isolation of this peak by preparative glpc was **9**. Therefore, hydroboration of **7a** occurs with predominant β attack at C-9 and at C-10. (b) This result agrees with reports that *exo* alcohols are obtained in hydroborations of bicyclo[3.3.1]non-2-ene[23] and of 1,5-dimethylbicyclo[3.3.1]non-2-ene.[22] (c) For references and stereochemical aspects of related ring systems, see E. Marvel and coworkers, *J. Org. Chem.*, **35**, 388, 391 396 (1970).

(21) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 80, 180; (b) p 82.

(22) W. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, **30**, 2859 (1965).

(23) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(24) An "equatorial" C-10 hydroxyl group would have the α configuration if the ring were in the boat conformation.

(25) Caryolane-1,9β-diol-10β-*d* (**13**) was also isolated (18%) in this reaction.

(26) Caryolane-1,9β-diol-9α-*d* (**15**) was also isolated (14%).

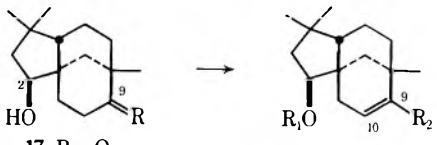
(27) E. J. Corey, M. Howell, A. Boston, R. Young, and R. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

in the conversion of **16** into **2a** (2155 cm^{-1}). Thus the six-membered ring very likely adopts the chairlike shape in all four compounds.[28]

A graded series of ten mixtures of caryolan-1-ol-9α-*d* (**2a**) and -9β-*d* (**2b**) were prepared and their infrared spectra were recorded for comparison with that of caryolan-1-ol obtained from D_2SO_4 cyclization of caryophyllene. On the basis of characteristic peaks in the fingerprint region, these mixtures showed that as little as 3% of **2a** could be detected when mixed with **2b**, whereas the lower limit of detection of **2b** is 10–15% when mixed with **2a**.

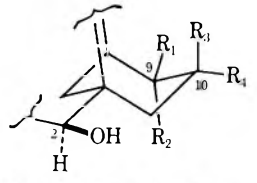
Clovane System.—Our preparation of clovenic anhydride-6α-*d* (**4a**) and -6β-*d* (**4b**) is outlined in Scheme II. A series of reactions analogous to that described

SCHEME II



17, R = O
18, R = NNHTs

19, $R_1 = R_2 = H$
19a, $R_1 = Me_3Si$; $R_2 = H$
20, $R_1 = H$; $R_2 = D$
20a, $R_1 = Me_3Si$; $R_2 = D$



21, $R_1 = OH$; $R_2 = R_3 = R_4 = H$
22, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
23, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
24, $R_1 = R_2 = R_3 = H$; $R_4 = OH$
25, $R_1 = R_3 = H$; $R_2 = OH$; $R_4 = D$
26, $R_1 = R_3 = H$; $R_2 = D$; $R_4 = OH$
27, $R_1 = D$; $R_2 = OH$; $R_3 = R_4 = H$
28, $R_1 = D$; $R_2 = R_3 = H$; $R_4 = OH$

24 ⟶ dibrosylate **24a** $\xrightarrow[2.\ CrO_3]{1.\ LiAlH_4}$ **4**

26 ⟶ dibrosylate **26a** $\xrightarrow[2.\ CrO_3]{1.\ LiAlH_4}$ **4a**

28 ⟶ dibrosylate **28a** $\xrightarrow[2.\ CrO_3]{1.\ LiAlH_4}$ **4b**

earlier for the caryolane system was used. Clov-9-en-2β-ol (**19**) was obtained by treatment of tosylhydrazone **18** (derived from clovan-2β-ol-9-one, **17**[29]) with sodium methoxide in diethyl Carbitol.[12] Olefin **19** was also obtained *via* the Caglioti reaction. The structure of **19** was established by spectral data, by hydrogenation to the known clovan-2β-ol,[29] and by the hydroboration results described below. The deuterioolefin **20** (8% d_0, 92% d_1) was obtained from **18** by lithium aluminum hydride reduction with D_2O work-up. The nmr spectrum of olefin **19** showed the C-9 proton as a six-line multiplet at δ 5.17 consisting of a doublet (J = 10 Hz) of triplets (J = 2 Hz), and the C-10 proton as an eight-line multiplet at δ 5.68 consisting of a doublet (J = 10 Hz) further split into a doublet (J = 4.5 Hz) of doublets (J = 3 Hz). The nmr spectrum of **20** showed only a triplet (J = 3.5 Hz) at δ 5.68, assigned to the C-10 proton.[14]

Hydroboration of **19** gave a mixture of all four possible diols (analyzed as their bistrimethylsilyl ethers by gas chromatography): clovane-2β,9β-diol (**21**), -2β,9α-diol (**22**), -2β,10β-diol (**23**), and -2β,10α-diol (**24**). The C-9 epimers are known compounds.[2] No reaction occurred when disiamylborane[19] was tried in an attempt at greater selectivity. Hydroboration of the trimethylsilyl ether **19a** gave a mixture (1% **21**, 25% **22**, 2% **23**, and 61% **24**), from which pure diol **24** was obtained by preparative gas chromatography of the bistrimethylsilyl ether. The nmr spectra of diol **24** and of its dibrosylate derivative **24a** showed symmetrical seven-line multiplets (similar to those described earlier for caryolane derivatives **11** and **11a**) at δ 4.02 and 4.92, respectively, for the C-10 proton. Therefore, the C-10 hydroxyl in **24** has equatorial character. The results of hydroboration (predominant α attack)[20b,c] indicate that the C-10 hydroxyl also has the α configuration, and thus the six-membered ring containing C-10 exists in a chairlike conformation.

Clovane-2β,10α-diol-9α-*d* (**26**, 10% d_0, 89% d_1, 1% d_2) was prepared by deuterioboration of **19a**.[30] The nmr spectrum of **26** and of its dibrosylate **26a** showed symmetrical five-line multiplets (similar to those described for caryolane derivatives **14** and **14a**) for the C-10 proton, a result consistent with an axial α deuterium at C-9. Clovane-2β,10α-diol-9β-*d* (**28**, 6% d_0, 94% d_1) was obtained by hydroboration of the deuterioolefin trimethylsilyl ether **20a**.[31] The nmr spectrum of **28** and of its dibrosylate **28a** showed symmetrical six-line multiplets (similar to those discussed earlier for caryolane derivatives **16** and **16a**) for the C-10 proton, a result consistent with an equatorial β deuterium at C-9.

Diol **24** was converted into the dibrosylate **24a**, which in turn was reduced with lithium aluminum hydride to a mixture that contained 23% clovene (**3**) and 31% clovan-2β-ol. Oxidative cleavage of the mixture with CrO_3 followed by pyrolysis of the dicarboxylic acid clovenic acid gave clovenic anhydride (**4**). Similarly, diol **26** was converted into clovenic anhydride-6α-*d* (**4a**, 99.3% pure, 3% d_0, 97% d_1) and diol **28** was converted into clovenic anhydride-6β-*d* (**4b**, 98.4% pure, 4% d_0, 96% d_1). Infrared spectra substantiated the axial character of the deuterium in **4a** (2142 cm^{-1}) as well as in **26** (2140 cm^{-1}), and the equatorial character of the deuterium in **4b** (2162 cm^{-1}) as well as in **28** (2152 cm^{-1}). The spectral results are therefore consistent with a chairlike conformation for all four compounds.[32]

Infrared spectra of a graded series of ten mixtures of clovenic anhydride-6α-*d* (**4a**) and -6β-*d* (**4b**) were recorded. Inspection of characteristic fingerprint bands revealed that as little as 3% of **4a** could be detected when mixed with **4b**; and as little as 4% of **4b** could be detected in a mixture with **4a**.

(28) The chairlike geometry for the cyclohexane ring in the caryolane skeleton is supported by X-ray studies on 1-chlorocaryolane: J. M. Robertson and G. Todd, *Chem. Ind.* (London), 437 (1953).

(29) D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 4665 (1954).

(30) Clovane-2β,9α-diol-10α-*d* (**25**) was also obtained (15%).

(31) A 9% yield of clovane-2β,9α-diol-9β-*d* (**27**) was also obtained.

(32) In bicyclo[3.3.1]nonane, the double chair (slightly flattened) is the preferred conformation: W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); see also ref 20c.

Experimental Section[33]

Caryolan-1-ol-9-one *p*-Toluenesulfonylhydrazone (6).—Caryolan-1-ol-9-one[8] (5.00 g, 21.2 mmol) and *p*-toluenesulfonylhydrazine (4.72 g, 25.4 mmol) in methanol (50 ml) were refluxed overnight. Water (100 ml) was then added and the product was extracted with ether. Crystallization from ether–hexane afforded 7.37 g (86%) of **6** as white crystals, mp 145–152° dec. Two recrystallizations from ether–hexane gave a sample: mp 147–152° dec;[36] ir ($CHCl_3$) 3595 (OH), 3290 (NH), 1630 (C=N), 1600 (aromatic C=C), and 1325 and 1164 cm^{-1} (SO_2).

Anal. Calcd for $C_{22}H_{32}N_2O_3S$ (mol wt, 404.57): C, 65.31; H, 7.97. Found: C, 65.51; H, 8.15.

Caryol-9-en-1-ol (7). A. From the Aprotic Bamford–Stevens Reaction.—The general procedure of Friedman and Shechter[11] was used. Tosylhydrazone **6** (3.00 g, 7.4 mmol) was treated with sodium methoxide (3.0 g) in dry diethyl Carbitol (125 ml) for 2.5 hr under reflux. The cooled reaction mixture was diluted with water and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated. Two recrystallizations from ethanol–water and sublimation afforded 1.13 g (69%) of **7** as white needles: mp 102–102.5°; ir (CS_2) 3600 (OH), 3010 (olefinic CH), and 737 and 725 cm^{-1} (*cis*-disubstituted olefin); nmr (CCl_4) δ 5.28–5.71 (m, 2, olefinic H).

Anal. Calcd for $C_{15}H_{24}O$ (mol wt, 220.34): C, 81.76; H, 10.98. Found: C, 81.60; H, 10.86.

The 3,5-dinitrobenzoate of **7** was recrystallized from ethanol–water: mp 92.5–94°; ir (KBr) 3100 (aromatic CH), 3015 (olefinic CH), 1725 (C=O), and 1550 and 1350 cm^{-1} (NO_2).

Anal. Calcd for $C_{22}H_{26}N_2O_6$ (mol wt, 414.44): C, 63.75; H, 6.32. Found: C, 63.79; H, 6.38.

Hydrogenation of **7** (0.062 g) with platinum oxide in ethyl acetate gave 0.058 g (93%) of caryolan-1-ol (**2**), mp 92.5–93.5°, identical with authentic **2** (lit.[8] mp 93–94°) by mixture melting point (93–94°) and infrared spectrum.

B. From the Caglioti Reaction.—The general procedure of Caglioti and Magi[13] was followed. Tosylhydrazone **6** (0.50 g, 1.24 mmol) was added to a slurry of lithium aluminum hydride (0.50 g, 13.2 mmol) in dry tetrahydrofuran (12 ml) under nitrogen. The mixture was refluxed for 21 hr, and then carefully treated successively with water (0.5 ml), 15% sodium hydroxide (0.5 ml), and water (1.5 ml). The mixture was stirred for 1.5 hr and filtered, and the precipitate was washed with warm ether (three 10-ml portions). The combined portions of ether and tetrahydrofuran were washed with water, dried, and evaporated to give a pale yellow solid (0.22 g, 81%). Infrared (CCl_4) indicated that this product consisted mainly of hydroxyolefin **7**. Gas chromatography showed 80% **7**, 2% caryolan-1-ol (**2**), 3% caryolan-1-ol-9-one, and 15% caryolane-1,9α-diol and caryolane-1,9β-diol. Sublimation of the crude solid followed by recrystallization from ethanol–water gave white, crystalline product (0.11 g, 40%), mp 101–101.5°, identical by glpc and infrared spectrum with **7** obtained from the aprotic Bamford–Stevens reaction.

Caryol-9-en-1-ol-9-*d* (8).—Treatment of tosylhydrazone **6** (1.00 g, 2.47 mmol) with lithium aluminum hydride (1.00 g, 23.8 mmol) as described above, but with work-up with D_2O (1.0 ml, 99.5% isotopic purity), 15% sodium deuterioxide (1.0 ml), and D_2O (3.0 ml), successively, afforded 0.19 g (35%) of deuterioolefin **8** after sublimation and recrystallization from ethanol–water: mp 101–101-5°; identical with **7** by glpc; ir (CS_2) 3600 (OH), 3024 (olefinic CH), 2230 (olefinic CD), and 681 cm^{-1} (*cis*-disubstituted olefin); nmr (CCl_4) δ 5.55 (t, 1, J = 3.5 Hz, olefinic H at C-10); 5–8% d_0, 92–95% d_1.

Treatment of tosylhydrazone **6** with lithium aluminum deuteride (Metal Hydrides, 99% minimum isotopic purity), followed by work-up in aqueous medium as above, gave in 26% yield a mixture of 96% **7** and 4% **8**, as determined by mass spectral analysis (96% d_0 and 4% d_1) and by the relative intensities of infrared bands at 737 and 681 cm^{-1}. No detectable amount of deuterium (<3%) was observed (absence of infrared band at 681 cm^{-1}) when pure hydroxyolefin **7** was treated with lithium aluminum hydride and then with D_2O under the conditions of the Caglioti reaction.

Caryol-9-en-1-ol Trimethylsilyl Ether (7a).—The general procedure of Martin was followed.[17a] Freshly distilled trimethylsilyl chloride (2.00 ml, 1.68 g, 15.5 mmol) was added over a period of 5 min to **7** (0.800 g, 3.63 mmol) in dry pyridine (5 ml). After 5 hr at room temperature, the excess of trimethylsilyl chloride and most of the pyridine were removed *in vacuo*. Then dry benzene (30 ml) was added, the precipitated pyridine hydrochloride was filtered, and the solution was concentrated to give 1.09 g (100%) of **7a** as a pale yellow oil: ir (CS_2) 3010 (olefinic CH), 1248 and 838 [$Si(CH_3)_3$], and 1120 cm^{-1} (SiO). Hydroxyolefin **7** was readily recovered by hydrolysis of **7a** with 50% aqueous methanol for 2 hr at reflux.[37]

Caryol-9-en-1-ol-9-*d* Trimethylsilyl Ether (8a).—In a similar manner deuterioolefin **8** was converted into its trimethylsilyl ether **8a**: ir (CS_2) 3028 (olefinic CH), 2230 (olefinic CD), 1248 and 829 [$Si(CH_3)_3$], and 681 cm^{-1} (*cis*-disubstituted olefin).

Caryolane-1,10β-diol (11). Hydroboration of 7a.—Diborane was generated[7b] by the addition (over a 1-hr period) of 1 *M* sodium borohydride in diglyme (18 ml, 18 mmol) to a stirred solution of freshly distilled boron trifluoride etherate (4.6 ml, 5.2 g, 37 mmol) in dry diglyme (4 ml). The gas was bubbled through a solution of sodium borohydride in diglyme to remove traces of boron trifluoride and then transferred with a slight flow of dry nitrogen into a separate vessel containing **7a** (1.06 g, 3.63 mmol) in dry tetrahydrofuran (15 ml) at 25°. The generator was then heated at 60–70° for 1 hr to drive over all the diborane. The reaction mixture was carefully treated with water, and then with 3 *N* sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) for 2 hr. The product after work-up (0.86 g, 100%) was converted into a mixture of trimethylsilyl ethers by treatment with dry pyridine (10 ml) and trimethylsilyl chloride (3.0 ml) for 3.5 hr. Glpc analysis showed the trimethylsilyl ethers of the following diols: 37% **11**, 7% **12**, and 49% of a mixture[20a] of **10** and **9** (listed in order of increasing retention time). The two major components were isolated by preparative glpc.

Collection and hydrolysis (2-hr reflux with 50% aqueous methanol) of the first major component afforded 0.14 g (16%) of diol **11** after recrystallization from ether–hexane: mp 159–159.5°; ir ($CHCl_3$) 3600 (OH), 1095 (CO), and 1005 cm^{-1}; nmr ($CDCl_3$) δ 4.10 (seven-line multiplet, 1, H-10α, see discussion for interpretation). Four recrystallizations from ether–hexane gave the analytical sample, mp 160–160.5°.

Anal. Calcd for $C_{15}H_{26}O_2$ (mol wt, 238.36): C, 75.58; H, 11.00. Found: C, 75.58; H, 10.83.

Collection and hydrolysis of the second major component gave 0.25 g (29%) of caryolane-1,9β-diol (**9**) after recrystallization from ether–hexane: mp 105–106° (lit.[8,18] mp 106–107°); nmr ($CDCl_3$) δ 3.37 (poorly resolved triplet, 1, J = 2.5 Hz, H-9α); ir (CCl_4) 3625 and 3600 (OH), 1093 (CO), 1057, 1025, and 964 cm^{-1}, identical with ir spectrum of authentic **9**.

Caryolane-1,10β-diol-9β-*d* (14). Deuterioboration of 7a.—In an analogous manner, **7a** (1.06 g, 3.63 mmol) was treated with deuteriodiborane [generated from sodium borodeuteride (Metal Hydrides, 99.5% minimum isotopic purity) and boron trifluoride etherate] to give a mixture of deuterated diols after peroxide

(33) Melting points are corrected. Unless otherwise specified, sublimations were carried out at 40–60° (*ca.* 0.1–0.4 mm). Infrared spectra were recorded on Perkin-Elmer Models 21, 337, and 521 spectrophotometers. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 spectrometer in deuteriochloroform (unless otherwise specified) with tetramethylsilane as the internal standard. Analysis by gas–liquid partition chromatography (glpc) was carried out with a Perkin-Elmer Model 226 chromatograph, with 0.02-in. Golay capillary or 0.125-in. packed columns (SE-30 silicone gum rubber) operated at *ca.* 230°. Preparative glpc separations were performed with an Aerograph Autoprep Model A-700 instrument (Wilkins Instrument and Research, Inc.) with a 0.375 in. × 20 ft column packed with 30% SE-30 on Chromosorb P, operated at *ca.* 230°. Mass spectra were recorded with Consolidated Electrodynamics Corp. Model 21-103C, Associated Electrical Industries MS-9, and Hitachi Perkin-Elmer RMU-6D mass spectrometers. Isotopic distributions were calculated as described by Biemann.[34,35] Elemental analyses were performed by Mr. J. Walter at the Johns Hopkins University. Benzene was dried by distillation over sodium; pyridine was distilled over barium oxide. Ether, diglyme, tetrahydrofuran, and diethyl Carbitol were dried by distillation over lithium aluminum hydride.

(34) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 204 ff.

(35) Wherever possible, molecular ion peaks and several fragment ion peaks were used as the bases for these calculations. The ranges of calculated values are reported in the Experimental Section, but the values judged to be most reliable are reported in the discussion. Details are available in ref 1b.

(36) Earlier preparations gave a low-melting form of **6**, mp 93–98° dec after recrystallization, which was identical (by ir spectrum, elemental analysis, and reactivity in the Bamford–Stevens reaction) with the higher melting form. Perhaps we are dealing with *syn* and *anti* isomers.

(37) A. Waiss, R. Lundin, and D. Stern, *Tetrahedron Lett.*, 513 (1964).

oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, afforded 0.10 g (12%) of deuterated diol **14**: mp 159–159.5°; ir ($CHCl_3$) 3600 (OH), 2145 (axial CD), 1091 (CO), 1026, and 1008 cm^{-1}; nmr ($CDCl_3$) δ 4.10 (five-line multiplet, 1, H-10α, see discussion for interpretation); 10–23% d_0, 76–84% d_1, 0–8% d_2.

Collection and hydrolysis of the second major component gave 0.15 g (18%) of caryolane-1,9β-diol-10β-*d* (**13**) after recrystallization from ether–hexane: mp 107.5–108.5°; ir (CCl_4) 3624 and 3600 (OH), 2160 (equatorial CD) 1090 (CO), 1042, 1032, and 965 cm^{-1}; nmr ($CDCl_3$) δ 3.38 (d, 1, J = 2.5 Hz, H-9α).

Caryolane-1,10β-diol-9α-*d* (16). Hydroboration of 8a.—In a similar manner deuterioolefin **8a** (1.30 g, 4.42 mol) was treated with diborane to give a mixture of deuterated diols after peroxide oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, gave 0.10 g (10%) of deuterated diol **16**: mp 159–159.5°; ir ($CHCl_3$) 3600 (OH), 2158 (equatorial CD), 1092 (CO), and 997 cm^{-1}; nmr ($CDCl_3$) δ 4.10 (six-line multiplet, 1, H-10α, see discussion for interpretation); 0–10% d_0, 90–100% d_1.

Collection and hydrolysis of the second major component gave 0.14 g (14%) of caryolane-1,9β-diol-9α-*d* (**15**) after recrystallization from ether–hexane: mp 106–107°; ir (CCl_4) 3623 and 3600 (OH), 2100 (broad, CD), 1091 (CO), and 1053 cm^{-1}; nmr ($CDCl_3$) no signal at δ 3.37.

Caryolane-1,10β-diol 10-Tosylate (11a).—Diol **11** (0.018 g, 0.076 mmol) was treated with a large excess of *p*-toluenesulfonyl chloride (0.073 g, 0.38 mmol) in pyridine (0.5 ml) for 42 hr at room temperature to give after work-up 0.029 g (97%) of **11a** as a colorless oil: ir (CCl_4) 3600 (OH) and 1189 and 1178 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.45 (s, 3, aromatic CH_3), 4.80 (seven-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, J = 8 Hz, aromatic H), and 7.80 (d, 2, J = 8 Hz, aromatic H).

Caryolan-1-ol (2) by Lithium Aluminum Reduction of 11a.—Crude tosylate **11a** (0.029 g) was dissolved in dry tetrahydrofuran (5 ml) and treated with lithium aluminum hydride (0.055 g, 1.4 mmol) for 52 hr at reflux. The product after work-up was sublimed to give oily crystals (0.009 g) shown by ir and glpc to consist of 78% caryolan-1-ol (**2**) and 22% caryol-9-en-1-ol (**7**).

Caryolane-1,10β-diol-9β-*d* 10-Tosylate (14a).—Diol **14** (0.10 g, 0.43 mmol) was converted in 87% yield into tosylate **14a**: ir (CCl_4) 3600 (OH) 1189 and 1178 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.45 (s, 3, aromatic CH_3), 4.80 (five-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, J = 8 Hz, aromatic H), and 7.79 (d, 2, J = 8 Hz, aromatic H).

Caryolan-1-ol-9β-*d* (2b).—Crude tosylate **14a** (0.146 g) in dry tetrahydrofuran (15 ml) was treated with lithium aluminum hydride (0.28 g, 7.4 mmol) for 52 hr at room temperature. The product after work-up was sublimed to give 0.062 g of a mixture of **2b** plus olefinic material. The product was dissolved in carbon tetrachloride and treated with 0.35 *M* bromine in carbon tetrachloride (0.75 ml). Evaporation of excess bromine and solvent, followed by five fractional sublimations, gave 0.007 g (7% yield from the diol) of **2b**: mp 89.5–91.5°; 98% pure by glpc; ir (CCl_4) 3608 (OH), 2142 (axial CD), 1092 (CO), 1058, 1043, and 1020 cm^{-1}; 15–22% d_0, 73–78% d_1, 6–8% d_2

Caryolane-1,10β-diol-9α-*d* 10-Tosylate (16a).—Diol **16** (0.094 g, 0.39 mmol) was converted in 91% yield into tosylate **16a**: ir (CCl_4) 3600 (OH) and 1189 and 1178 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.45 (s, 3, aromatic CH_3), 4.79 (six-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, J = 8 Hz, aromatic H), and 7.79 (d, 2, J = 8 Hz, aromatic H).

Caryolan-1-ol-9α-*d* (2a).—Crude tosylate **16a** (0.135 g) in dry tetrahydrofuran (15 ml) was treated with lithium aluminum hydride (0.26 g, 6.9 mmol) for 60 hr at reflux. The product after work-up was sublimed to give 0.050 g of a mixture of **2a** plus olefinic material. After purification by bromination and repeated sublimations we obtained 0.012 g (14% yield from the diol) of **2a**: mp 93–94°; 98% pure by glpc; ir (CCl_4) 3608 (OH), 2155 (equatorial CD), 1091 (CO), 1063, and 1031 cm^{-1}; 12–17% d_0, 83–88% d_1, 0–1% d_2.

Infrared Spectra of Mixtures of 2a and 2b.—A graded series of ten mixtures ranging from pure **2a** to pure **2b** were prepared and their infrared spectra were recorded in CCl_4 solution with a Perkin-Elmer Model 521 grating spectrophotometer. The CD stretch and fingerprint regions were scale expanded (both ordinate and abscissa) to allow more detailed comparisons.[38] The 9α-*d* epimer **2a** has a medium-intensity characteristic fingerprint band at 1031 cm^{-1} where the 9β-*d* epimer **2b** has a minimum; **2b** has weak, but characteristic, bands at 1043 and 1020 cm^{-1} where **2a** has only very weak absorption. The lower limits of detectability (see discussion) were determined from the mixtures on the basis of these bands.

Clovan-2β-ol-9-one *p*-Toluenesulfonylhydrazone (18).—The reaction of clovan-2β-ol-9-one[29] (12.6 g, 53.2 mmol) and tosylhydrazine (11.9 g, 63.9 mmol) in refluxing methanol (100 ml) gave, after crystallization from methanol–water, 18.4 g (86%) of tosylhydrazone **18**: mp 146–152° dec; ir (KBr) 3480 (broad, bonded OH), 3100 (broad, bonded NH and aromatic CH), 1630 (CN), 1600 (aromatic C=C), 1322 and 1163 (SO_2), and 819 cm^{-1} (aromatic CH).

Anal. Calcd for $C_{22}H_{32}N_2O_3S$ (mol wt, 404.57: C, 65.31; H, 7.97. Found: C, 65.51; H, 7.77.

Clov-9-en-2β-ol (19). A. By the Aprotic Bamford–Stevens Reaction.—Tosylhydrazone **18** (3.20 g, 7.92 mmol) and sodium methoxide (3.00 g, 55.5 mmol) were heated in refluxing dry diethyl Carbitol (85 ml) for 2.5 hr under nitrogen. The product after work-up was an amorphous solid (1.91 g) which could not be crystallized from any of a number of solvents, but was sublimed to give 1.50 g (86%) of **19** as white crystals: mp 50–54°; 94% pure by glpc; ir (CS_2) 3615 (OH), 3010 (olefinic CH), 1645 (C=C), and 710 cm^{-1} (*cis*-disubstituted olefin); nmr (CCl_4) δ 3.62 (doublet of doublets, 1, J = 5 and 2 Hz, H-2α), 5.17 (doublet of triplets, 1, J = 10 and 2 Hz, H-9), 5.68 (pair of doublets of doublets, 1, J = 10, 4.5 and 3 Hz, H-10). Purification by regeneration from the 3,5-dinitrobenzoate, followed by two sublimations, gave pure **19**, mp 55.5–58.5°.

Anal. Calcd for $C_{15}H_{24}O$ (mol wt, 220.34): C, 81.76; H, 10.98. Found: C, 81.88; H, 10.89.

The 3,5-dinitrobenzoate of **19** was recrystallized from hexane: mp 177–175.5°; ir (KBr) 3106 (aromatic CH), 3012 (olefinic CH), 1720 (C=C), and 1550 and 1348 cm^{-1} (NO_2).

Anal. Calcd for $C_{22}H_{26}N_2O_6$ (mol wt, 414.44): C, 63.75; H, 6.32. Found: C, 63.97; H, 6.41.

Hydrogenation of **19** (0.18 g, 0.82 mmol) with platinum oxide in ethyl acetate gave 0.15 g (84%) of clovan-2β-ol after recrystallization from ethanol–water and sublimation: mp 93.5–94.5° (lit.[29] mp 95–96°); ir (CCl_4) 3620 (OH) and 1067 cm^{-1} (CO); nmr ($CDCl_3$) δ 3.81 (doublet of doublets, 1, J = 9 and 6 Hz, H-2α). The 3,5-dinitrobenzoate of clovan-2β-ol had a melting point of 132–133° (lit.[29] mp 134–135°).

B. By the Caglioti Reaction.—The reaction of tosylhydrazone **18** (0.40 g, 0.99 mmol) with lithium aluminum hydride (0.40 g, 10.5 mmol) in dry tetrahydrofuran for 14 hr at reflux gave, after work-up, 0.14 g (64%) of a mixture consisting of 60% hydroxyolefin **19**, 15% clovan-2β-ol, 21% clovane-2β,9α-diol and clovane-2β,9β-diol, and 4% unidentified material. Preparative glpc and sublimation gave pure **19**, mp 55–57°, identical by ir spectrum with **19** obtained from the Bamford–Stevens reaction. The reaction of tosylhydrazone **18** with lithium aluminum tri-*t*-butoxy hydride gave a crude product which contained only 49% **19**.

Clov-9-en-2β-ol-9-*d* (20).—Treatment of tosylhydrazone **18** (1.00 g, 2.47 mmol) with lithium aluminum hydride (1.00 g, 26.3 mmol) in dry tetrahydrofuran (30 ml) for 24 hr under reflux, followed by successive treatment with D_2O (1.0 ml), 15% sodium deuterioxide (1.0 ml), and D_2O (3.0 ml), gave 0.075 g (14%) of deuterioolefin **20** after preparative glpc and sublimation: mp 55.5–58°; identical with **19** by glpc; ir (CS_2) 3615 (OH), 3025 and 3012 (olefinic CH), 2240 (olefinic CD), and 671 cm^{-1} (*cis*-disubstituted olefin); nmr (CCl_4) δ 3.62 (doublet of doublets, 1, J = 5 and 2 Hz, H-2α) and 5.68 (t, poorly resolved, 1, J = 3.5 Hz, H-10); 8% d_0 and 92% d_1.

Reaction of tosylhydrazone **18** with lithium aluminum deuteride, followed by D_2O work-up as above, also gave deuterioolefin **20** (11–12% d_0 and 88–89% d_1). Reaction of the tosylhydrazone with lithium aluminum deuteride followed by aqueous work-up gave olefin **19** (97% d_0 and 3% d_1). No detectable deuterium incorporation (<1%) was observed (absence of ir band at 671 cm^{-1}) when pure olefin **19** was treated with lithium aluminum hydride and D_2O under the conditions of the Caglioti reaction.

(38) Infrared CD stretching frequencies are useful for the qualitative assignment of axial or equatorial character in cyclohexane systems;[27] however, in our compounds as well as in the published literature[27] these bands are usually broad, unsymmetrical, and sometimes have multiple peaks, and are therefore unsuitable for quantitative determination of mixtures.

Clov-9-en-2β-ol Trimethylsilyl Ether (19a).—The reaction of hydroxyolefin **19** (1.50 g, 6.8 mmol) in dry pyridine (8 ml) with trimethylsilyl chloride (3.0 ml, 2.5 g, 23 mmol) at room temperature gave, after work-up as described above for **7a**, 1.99 g (100%) of **19a** as a pale yellow oil: >97% pure by glpc; ir (neat film) 3010 (olefinic CH), 1248 and 837 [$Si(CH_3)_3$], 1059 (SiO), 713 cm^{-1} (*cis*-disubstituted olefin); nmr (CCl_4) δ 0.06 (s, 9, $SiCH_3$), 3.63 (doublet of doublets, 1, J = 5 and 2 Hz, H-2α), 5.21 (doublet of triplets, 1, J = 10 and 2 Hz, H-9), and 5.76 (poorly resolved doublet of triplets, 1, J = 10 and 3.5 Hz, respectively, H-10). Hydrolysis of **19a** (2-hr reflux with 50% aqueous methanol) gave **19**.

Clov-9-en-2β-ol-9-*d* Trimethylsilyl Ether (20a).—In a similar manner **20** was converted into its trimethylsilyl ether **20a**: ir (CS_2) 3025 and 3012 (olefinic CH), 2240 (olefinic CD), 1247 and 838 [$Si(CH_3)_3$], 1058 and 1047 (SiO), 673 cm^{-1} (*cis*-disubstituted olefin). Pure **20** could be regenerated by hydrolysis of **20a**.

Clovane-2β,10α-diol (24). Hydroboration of 19a.—A slurry of lithium aluminum hydride (1.24 g, 32.6 mmol) in dry ether (15 ml) was added over a period of 15 min to a stirred, cooled (0°) solution of boron trifluoride etherate (5.5 ml, 6.17 g, 43.4 mmol) and olefin **19a** (1.27 g, 4.34 mmol) in dry ether (30 ml) under nitrogen. The resulting mixture was stirred at 0° for 1 hr and then for 36 hr at room temperature. The reaction mixture was then oxidized with 3 *N* sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) for 2 hr. The product after work-up (1.03 g, 100%) was treated with dry pyridine (8 ml) and trimethylsilyl chloride (3 ml) for 2 hr. Glpc analysis showed the trimethylsilyl ethers of the following diols: 2% **23**, 61% **24**, 25% **22**, and 1% **21** (listed in order of increasing retention time).

Preparative glpc and hydrolysis (2-hr reflux with 50% aqueous methanol) of the first major component afforded 0.27 g (26%) of the desired diol **24** after recrystallization from ether–hexane: mp 150.5–151.5° (first crop) and 145–147.5° (second crop); ir ($CHCl_3$) 3600 (OH), 1070 and 1021 (CO), and 997 cm^{-1}; nmr ($CDCl_3$) δ 3.81 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 4.02 (br m, 1, total width 32 Hz, H-10β).[39] Four additional recrystallizations from ether–hexane gave a sample, mp 155–155.5°.

Anal. Calcd for $C_{15}H_{26}O_2$ (mol wt, 238.36): C, 75.58; H, 11.00. Found: C, 75.38; H, 10.87.

Collection and hydrolysis of the second major component gave 0.11 g (10%) of clovane-2β,9α-diol (**22**) after recrystallization from ether–hexane: mp 151–152°; nmr ($CDCl_3$) δ 3.32 (br s, 1, H-9β) and 3.80 (doublet of doublets, 1, J = 10 and 6 Hz, H-2α); ir ($CHCl_3$) 3600 (OH), 1153, 1069, 1032, 990, 958, and 941 cm^{-1}, identical with the ir spectrum of authentic **22** (lit.[2a] mp 152–153°).

Clovane-2β,10α-diol-9α-*d* (26). Deuterioboration of 19a.—In an analogous fashion **19a** (1.99 g, 6.88 mmol) was treated with lithium aluminum deuteride (Metal Hydrides, 99% minimum isotopic purity) and boron trifluoride etherate to give a mixture of deuterated diols after peroxide oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, afforded 0.20 g (12%) of deuterated diol **26**: mp 151–152°; ir ($CHCl_3$) 3606 (OH), 2140 (axial CD), and 1070 and 1029 cm^{-1} (CO); nmr ($CDCl_3$) δ 3.77 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 3.95 (br m, 1, total width 21 Hz, H-10β);[39] 9–11% d_0, 89–90% d_1, 0–1% d_2.

Collection and hydrolysis of the second major component gave 0.24 g (15%) of clovane-2β,9α-diol-10α-*d* (**25**) after recrystallization from ether–hexane: mp 151.5–152.5°; ir ($CHCl_3$) 3600 (OH), 2160 (equatorial CD), 1069 and 1048 (CO), and 990 cm^{-1}; nmr ($CDCl_3$) δ 3.30 (poorly resolved doublet, 1, J = 2 Hz, H-9β) and 3.79 (doublet of doublets, 1, J = 10 and 6 Hz, H-2α).

Clovane-2β,10α-diol-9β-*d* (28). Hydroboration of 20a.—Similarly, **20a** (1.19 g, 4.07 mmol) was treated with lithium aluminum hydride and boron trifluoride etherate to give a mixture of deuterated diols after peroxide treatment. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, gave 0.12 g (12%) of deuterated diol **28**: mp 152.5–153.5°; ir ($CHCl_3$) 3605 (OH), 2152 (equatorial CD), 1070 (CO), 1042, and 996 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 3.98 (br m, 1, total width 26 Hz, H-10β);[39] 6% d_0 and 94% d_1.

Collection and hydrolysis of the second major component gave 0.09 g (9%) of clovane-2β,9α-diol-9β-*d* (**27**) after recrystallization from ether–hexane: mp 150.5–151.5°; ir ($CHCl_3$) 3600 (OH), 2100 (broad, CD), 1069 (CO), and 998 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (doublet of doublets, 1, J = 10 and 6 Hz, H-2). There was also a weak signal at δ 3.30 which indicated the presence of *ca.* 9% unlabeled diol **22**.

Clovane-2β,10α-diol Dibrosylate (24a).—Diol **24** (0.043 g, 0.18 mmol) was treated with brosyl chloride (0.11 g, 0.43 mmol) in dry pyridine (1.0 ml) for 24 hr at room temperature to give, after work-up and recrystallization from ether–hexane, 0.084 g (69%) of **24a**: mp 114.5–115° dec; ir ($CHCl_3$) 1575 (aromatic C=C) and 1365 and 1176 cm^{-1} (SO_2); nmr ($CDCl_3$ (δ 4.50 (t, 1, J = 6 Hz, H-2α), 4.92 (seven-line multiplet, 1, H-10β, see discussion for interpretation), and 7.72 (s, 8, aromatic H). Four recrystallizations from ether–hexane gave a sample, mp 114.5 115° dec.

Anal. Calcd for $C_{27}H_{32}Br_2O_6S_2$ (mol wt, 676.51): C, 47.94; H, 4.77. Found: C, 47.91; H, 4.86.

Clovenic Anhydride (4) from 24a.—Dibrosylate **24a** (0.078 g, 0.115 mmol) in dry tetrahydrofuran (10 ml) under nitrogen was treated with lithium aluminum hydride (0.087 g, 2.3 mmol) for 34 hr under reflux. The product after work-up was a mixture (0.031 g) shown by ir and glpc to consist of 23% clov-2-ene (**3**), 11% clov-9-en-2β-ol (**19**), 31% clovan-2β-ol, plus several minor unidentified compounds. This product, in glacial acetic acid (5 ml), was oxidized with CrO_3 (0.25 g, in 0.25 ml of water) for 132 hr at room temperature. The excess of CrO_3 was destroyed with methanol, and most of the acetic acid was removed *in vacuo*. Ether extraction gave a crude product which was digested with 10% NaOH for 30 min at 100°. The alkaline solution was extracted with ether to remove any neutral material, and then acidified with 3 *N* HCl to precipitate clovenic acid (0.012 g). This material was pyrolyzed for 10 min at 195–200° in a glass tube closed at one end and then sublimed at 100–110° (0.2 mm) to give the known anhydride **4**.

Clovane-2β,10α-diol-9α-*d* Dibrosylate (26a).—Diol **26** (0.13 g, 0.535 mmol) was converted in 71% yield into dibrosylate **26a**: mp 113.5–114.5° dec; ir ($CHCl_3$) 2150 (CD), 1575 (aromatic C=C), and 1365 and 1175 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 4.49 (t, 1, J = 6 Hz, H-2α), 4.90 (five-line multiplet, 1, H-10β, see discussion), and 7.71 (s, 8, aromatic H).

Clovenic Anhydride-6α-*d* (4a).—Treatment of dibrosylate **26a** (0.36 g, 0.53 mmol) with lithium aluminum hydride gave a crude mixture of products which was oxidized with CrO_3 (1.0 g, in 10 ml of water) as described above to give 0.043 g of crude deuterated clovenic acid. Pyrolysis and sublimation as described above for the preparation of **4** gave 0.033 g (25% yield from the dibrosylate) of **4a** as oily crystals, 98% pure by glpc. Three fractional sublimations at 40–60° (0.2 mm) gave 0.0085 g (6% yield) of **4a**: mp 47–48°; 99.3% pure by glpc; ir (CCl_4) 2161 (weak shoulder, CD), 2142 (axial CD),[3e] 1808 and 1760 (anhydride C=O), 1085, 1073, 1038, 1028, 1018, 992 cm^{-1}; 2–4% d_0 and 96–98 d_1.

Clovane-2β,10α-diol-9β-*d* Dibrosylate (28a).—Diol **28** (0.054 g, 0.23 mmol) was converted in 71% yield into dibrosylate **28a**: mp 114–115° dec; ir ($CHCl_3$) 2160 (equatorial CD), 1575 (aromatic C=C), and 1365 and 1175 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 4.50 (t, 1, J = 6, H-2α), 4.91 (six-line multiplet, 1, H-10β, see discussion), and 7.71 (s, 8, aromatic H).

Clovenic Anhydride-6β-d (4b).—Treatment of dibrosylate **28a** (0.200 g, 0.295 mmol) with lithium aluminum hydride gave a crude mixture which was oxidized with CrO_3 to give 0.016 g of crude deuterated clovenic acid. Pyrolysis and sublimation gave 0.011 g (15% yield from the dibrosylate) of crude **4b**. Fractional resublimation gave 0.0067 g (9%) of **4b**: mp 46–47°; 98.4% pure by glpc; ir (CCl_4) 2162 (equatorial CD), 1808 and 1759 (anhydride C=O), 1089, 1048, 1029, 1010, and 1005 cm^{-1}; 4–6% d_0 and 94–96% d_1.

Infrared Spectra of Mixtures of 4a and 4b.—A graded series of ten mixtures ranging from pure **4a** to pure **4b** were prepared and their infrared spectra were recorded. The 6α-*d* epimer **4a** has characteristic fingerprint bands at 1073 (w), 1038 (s), and 1018 cm^{-1} (m), where the 6β-*d* epimer **4b** has minima; **4b** has characteristic bands at 1048 (s), where **4a** has a weak shoulder, and at 1010 (m) and 1005 cm^{-1} (m) where **4a** has minima. The limits of detectability (see discussion) were determined from the mixtures on the basis of these bands.

(39) Part of this multiplet was obscured by the adjacent signal of H-2α.

Registry No.—**1**, 87-44-5; **2a**, 23736-82-5; **2b**, 23736-83-6; **4**, 3898-00-0; **4a**, 23736-85-8; **4b**, 23736-

86-9; **6**, 23736-87-0; **7**, 23736-88-1; **7** 3,5-dinitrobenzoate, 23809-49-6; **7a**, 23736-89-2; **8**, 23736-90-5; **8a**, 23736-91-6; **9**, 4870-61-5; **11**, 23809-50-9; **11a**, 23736-93-8; **13**, 23736-94-9; **14**, 23736-95-0; **14a**, 23736-96-1; **15**, 23736-97-2; **16**, 23809-51-0; **16a**, 23809-52-1; **18**, 23809-53-2; **19**, 23736-98-3; **19** 3,5-dinitrobenzoate, 23736-99-4; **19a**, 23737-00-0; **20**, 23809-54-3; **20a**, 23737-01-1; **22**, 23737-02-2; **24**, 23737-03-3; **24a**, 23809-55-4; **25**, 23809-56-5; **26**, 23737-04-4; **26a**, 23737-05-5; **27**, 23737-06-6; **28**, 23737-07-7; **28a**, 23737-08-8.

Acknowledgment.—We are grateful to Dr. J. B. DiGiorgio for helpful discussions and to Dr. F. J. McGuire, Mrs. S. Singmaster, Mr. L. Fields, Mr. R. Fisk, and Mr. P. Tomasulo for technical assistance. We also thank Dr. D. Hollis and Dr. J. Oliver for the determination of nmr spectra and Dr. S. Meyerson, Dr. M. Bursey, and Mr. R. Rhodes for the mass spectra.

Halogenated Ketenes. XII. The Reaction of Some Acid Halides with Triethylamine. α-Halovinyl Esters[1,2]

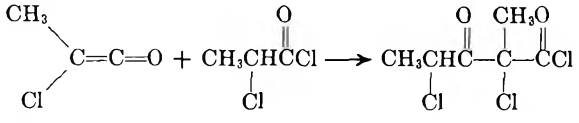
William T. Brady, Fred H. Parry, III,[3] Robert Roe, Jr., Edwin F. Hoff, and Larry Smith

Department of Chemistry, North Texas State University, Denton, Texas

Received July 24, 1969 76203

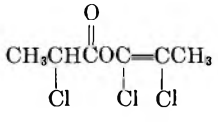
The reaction of triethylamine with an excess of some acid halides to produce α-halovinyl esters (enol esters of acid halides) has been investigated. The α-halovinyl esters produced are considered to be the result of acylation of an intermediate enolate ion. The reaction is most appropriate for disubstituted acetyl halides where at least one of the substituents is halogen. Some of the implications of the enolate ion intermediate are discussed and the synthesis of several representative examples of this new class of compounds is described.

It has recently been reported from this laboratory that in an attempted preparation of the dimer of methylchloroketene by the dehydrochlorination of α-chloropropionyl chloride, a novel compound was isolated.[4] This material was assigned the structure of a β-keto acid halide and was assumed to be the result of a reaction of methylchloroketene and the acid halide, since conducting the reaction in the presence of cyclopentadiene produced a good yield of cycloadduct. This type of reaction was described by



Staudinger, and by others since that time, and more recently by us.[5-9] Nevertheless, upon investigation of this situation further it has become apparent to us and others that the material produced is not a β-keto acid halide.

Dreiding and coworkers have recently confirmed and supplemented our initial report on the α-chloropropionyl chloride system, but have assigned the material the following structure.[10]

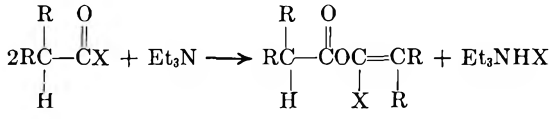


Lavanish has reported that similar results are obtained with dichloroacetyl chloride and triethylamine and assigns the structure as trichlorovinyl dichloroacetate.[11]

The purpose of this report is to correct our previous structure assignment and to reveal the results of a more extensive and comprehensive study of this reaction, which we believe involves the synthesis of a new class of compounds.

Results

In addition to the two systems that have already been reported, we have examined the reaction of triethylamine with a number of other acid halides in an effort to produce other α-halovinyl esters. This reaction may be represented as indicated.



It becomes immediately apparent that this is not a general reaction of acid halides. Table I lists the acid halides which we found will react with a deficiency of triethylamine to produce the α-halovinyl esters.

Attempts to prepare α-halovinyl esters from several other acid halides were unsuccessful; *e.g.*, acetyl chloride, chloroacetyl chloride, propionyl chloride, isobutyryl chloride, α-phenylbutyryl chloride, and diphenylacetyl chloride did not produce α-halovinyl esters.

A different type of α-halovinyl ester was also prepared from α-chloropropionyl chloride. After the treatment of α-chloropropionyl chloride with a stoichiometric amount of triethylamine, a stoichiometric

(1) Part XI: W. T. Brady, E. F. Hoff, R. Roe, Jr., and F. H. Parry, III, *J. Amer. Chem. Soc.*, **91**, 5679 (1969).

(2) Support of this investigation by the Robert A. Welch Foundation and a National Science Foundation Grant (GP-7386) is gratefully acknowledged.

(3) NDEA Title IV Fellow.

(4) W. T. Brady and R. Roe, Jr., *Tetrahedron Lett.*, No. 16, 1977 (1968).

(5) H. Staudinger, O. Gohring, and M. Scholler, *Chem. Ber.*, **47**, 40 (1914).

(6) F. Sorm, J. Smrt, and J. Beranek, *Chem. Listy*, **48**, 679 (1954).

(7) F. Sorm, J. Smrt, and J. Beranek, *ibid.*, **49**, 73 (1955).

(8) H. D. Stachel, *Arch. Pharm.* (Weinheim), **294**, 775 (1961).

(9) W. T. Brady and L. Smith, *J. Org. Chem.*, **33**, 4550 (1968).

(10) R. Giger, M. Rey, and A. S. Dreiding, *Helv. Chim. Acta*, **51**, 1466 (1968).

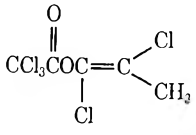
(11) J. M. Lavanish, *Tetrahedron Lett.*, No. 57, 6003 (1968).

TABLE I

α-HALOVINYL ESTERS

Acid halide	Compd	α-Halovinyl ester
α-Bromopropionyl chloride	I	$CH_3CHCOC{=}CCH_3$ (Br; Cl, Br)
α-Chlorobutyryl chloride	II	$C_2H_5CHCOC{=}CC_2H_5$ (Cl; Cl, Cl)
α-Chlorobutyryl bromide	III	$C_2H_5CHCOC{=}CC_2H_5$ (Cl; Br, Cl)
α-Chloro-α-phenylacetyl chloride	IV	$C_6H_5CHCOC{=}CC_6H_5$ (Cl; Cl, Cl)
α-Chloropropionyl bromide	V	$CH_3CHCOC{=}CCH_3$ (Cl; Br, Cl)
Dibromoacetyl chloride	VI	$CHBr_2COC{=}CBr_2$ (Cl)

amount of trichloroacetyl chloride was added. This resulted in the formation of both isomers of VII.



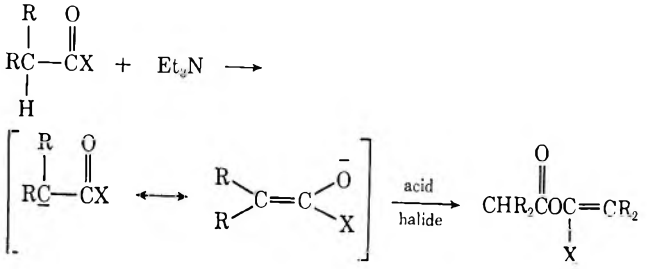
VII

However, efforts to synthesize a similar material from propionyl chloride and chloroacetyl chloride with trichloroacetyl chloride were unsuccessful.

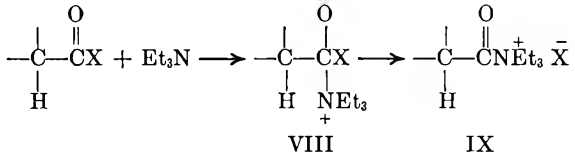
The α-halovinyl esters appear to more closely resemble acid halides in physical properties than esters. These compounds usually possess a disagreeable odor and are susceptible to hydrolysis (some fume in air), and the carbonyl absorptions in the infrared are shifted out of the ester region into the acid halide region.

Discussion

It has already been proposed that the formation of α-halovinyl esters (enol esters of acid halides) is the result of an initial proton abstraction by triethylamine



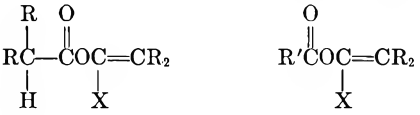
and subsequent acylation of the resulting enolate ion.[10,11] However, this seems inconsistent with several reports in the literature. There is strong evidence that the reaction of acid halides with triethylamine initially involves a quaternary ammonium intermediate.[12-14]



VIII IX

Perhaps VIII undergoes an elimination which produces the enolate ion rather than the obvious initial proton abstraction.

The α-halovinyl esters may be of two distinct types,



"simple" "mixed"

"simple" and "mixed." If the enolate ion is acylated by the acid halide from which it was derived, a "simple" α-halovinyl ester results. If the enolate ion is acylated by a foreign acid halide, such as trichloroacetyl chloride, a "mixed" α-halovinyl ester is produced.

The lack of formation of "simple" α-halovinyl esters from acetyl chloride, chloroacetyl chloride, propionyl chloride, isobutyryl chloride, α-phenylbutyryl chloride, and diphenylacetyl chloride suggests that an enolate ion is not produced and another mechanistic pathway to ketene is operative. The inability of chloroacetyl chloride to form a "simple" α-halovinyl ester indicates that the acidity of the α hydrogen of the acid halide is not the only factor involved in formation of the enolate ion, since the α hydrogen of α-chloropropionyl chloride is even less acidic.

A comparison of acid chlorides to acid bromides reveals that the former are more desirable for this reaction, as the yields are better and the work-up is easier. Apparently, the better leaving group promotes the second step (the ketene-forming step) and more polymer is obtained.

Truce and Bailey have recently reported on the mechanism of alcoholysis of some acid halides in the presence of triethylamine.[14] The reaction of acid halides and triethylamine was performed in the presence of methanol-*d*. It was stated that the formation of monodeuterated ester is ample evidence for the ketene intermediate. We would like to submit that monodeuterated ester may also be produced from the enolate ion, and perhaps this is the case in some of the systems investigated by Truce and Bailey.

Experimental Section

Proton nmr spectra were recorded on a Varian A-60 instrument employing tetramethylsilane as an internal standard. Vapor phase chromatography was accomplished on an F & M Model 700 chromatograph. Hexane was used after being dried over

(12) H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).

(13) G. B. Payne, *ibid.*, **31**, 718 (1966).

(14) W. E. Truce and P. S. Bailey, Jr., *ibid.*, **34**, 1341 (1969).

Linde type 4-A Molecular Sieve. α-Chloro-α-phenylacetyl chloride was prepared according to the method of Walden.[15] All of the other acid halides were prepared from the corresponding acids and an appropriate reagent according to standard procedures.

1-Chloro-2-bromopropenyl 2-Bromopropanoate (I).—To a stirred solution of 47.8 g (0.28 mol) of α-bromopropionyl chloride in 200 ml of hexane at room temperature was added dropwise 14.2 g (0.14 mol) of triethylamine in 50 ml of hexane. After stirring overnight, filtration afforded a theoretical amount of amine salt. Evaporation of the solvent and distillation of the residue yielded 19.4 g (45%) of I: bp 60° (0.15 mm); ir 1788 (C=O) and 1661 cm^{-1} (C=C); nmr (CCl_4) δ 1.90 (doublet, 3 H) 2.27 and 2.40 (singlets, 3 H total, two isomers), and 4.45 (quartet, 1 H).

Anal. Calcd for $C_6H_7Br_2ClO_2$: C, 23.5; H, 2.28. Found: C, 24.0; H, 2.23.

1,2-Dichloro-1-butenyl 2-Chlorobutanoate (II).—An 8.9-g (0.088 mol) portion of triethylamine in 50 ml of hexane was added dropwise to a stirred solution of 25 g (0.18 mol) of α-chlorobutyryl chloride in 200 ml of hexane at room temperature. After the solution had been stirred for 4 hr, a theoretical amount of amine salt was filtered. The filtrate was evaporated and vacuum distilled at 59° (0.45 mm) to yield 8.8 g (41%) of II: ir 1788 (C=O) and 1653 cm^{-1} (C=C); nmr (CCl_4) δ 1.16 (multiplet, 6 H), 2.30 (multiplet, 4 H), and 4.28 (triplet, 1 H).

Anal. Calcd for $C_8H_{11}Cl_3O_2$: C, 39.1; H, 4.47. Found: C, 39.2; H, 4.40.

1-Bromo-2-chloro-1-butenyl 2-Chlorobutanoate (III).—To a stirred solution of 14.25 g (0.077 mol) of α-chlorobutyryl bromide in 200 ml of hexane was added dropwise at room temperature 3.87 g (0.04 mol) of triethylamine in 50 ml of hexane. After the solution had been stirred for an additional 2 hr, the salt was removed by filtration and 3.5 g (31%) of III was obtained by distillation of the filtrate at 69° (0.1 mm): ir 1780 (C=O) and 1648 cm^{-1} (C=C); nmr (CCl_4) δ 1.20 (multiplet, 6 H), 2.22 (multiplet, 4 H), and 4.30 (triplet, 1 H). Treatment of III with methanol gave a compound which was chromatographically identical with and had an ir spectrum identical with that of an authentic sample of methyl α-chlorobutyrate.

1,2-Dichloro-2-phenylvinyl 2-Chloro-2-phenylacetate (IV).—To a well stirred solution of 36.2 g (0.19 mol) of α-chloro-α-phenylacetyl chloride in 200 ml of hexane was added dropwise a solution of 9.7 g (0.096 mol) of triethylamine in 25 ml of hexane at room temperature. Stirring was continued for 2 days and the salt was filtered and washed with two 100-ml portions of dry ether. The hexane filtrate was combined with the ether washings and evaporated. The resulting oil was recrystallized from ether to yield 18.7 g (54%) of IV: mp 59–60°; ir 1792 (C=O) and 1626 cm^{-1} (C=C); nmr (CCl_4) δ 5.19 (singlet, 1 H), 7.18 (singlet, 5 H), and 7.25 (singlet, 5 H).

Anal. Calcd for $C_{16}H_{11}Cl_3O_2$: C, 56.2; H, 3.22. Found: C, 56.2; H, 3.34.

1-Bromo-2-chloropropenyl 2-Chloropropanoate (V).—To a stirred solution of 46 g (0.27 mol) of α-chloropropionyl bromide in 200 ml of hexane was added dropwise 13.5 g (0.13 mol) of triethylamine in 50 ml of hexane. Stirring was continued at room temperature overnight. The salt was filtered and the solution was distilled to yield 15 g (43%) of V: bp 52° (0.17 mm); ir 1786 (C=O) and 1653 cm^{-1} (C=C); nmr (CCl_4) δ 1.75 (doublet, 3 H), 2.09 and 2.25 (singlets, 3 H total, two isomers) and 4.51 (quartet, 1 H). Treatment of V with methanol gave a compound which was chromatographically identical with and had an an ir spectrum identical with that of an authentic sample of methyl α-chloropropionate.

1-Chloro-2,2-dibromovinyl Dibromoacetate (VI).—A solution of 9.0 g (0.09 mol) of triethylamine in 25 ml of hexane was added dropwise to a solution of 42.3 g (0.18 mol) of dibromoacetyl chloride in 200 ml of hexane at −78°. After the solution had been warmed to room temperature overnight, the salt was filtered and the hexane solution was evaporated and distilled to yield 4.1 g (11%) of VI: bp 100° (0.15 mm); ir 1786 (C=O) and 1600 cm^{-1} (C=C); nmr (CCl_4) δ 5.92 (singlet).

Anal. Calcd for $C_4HBr_4ClO_2$: C, 10.99; H, 0.229. Found: C, 10.64; H, 0.376. A sample weighing 0.00766 g produced 0.01557 g of silver halide by the Carius method. The theoretical weight of silver halide for that weight of sample is 0.01569 g.

1,2-Dichloropropenyl Trichloroacetate (VII).—To a stirred solution of 31 g (0.24 mol) of α-chloropropionyl chloride in 200 ml of hexane at −78° was added dropwise a solution of 23.2 g (0.23 mol) of triethylamine in 50 ml of hexane. Stirring was continued for 1 hr at this temperature. A 45.5-g (0.25 mol) portion of trichloroacetyl chloride was added to the reaction mixture and stirring was continued as the mixture warmed to room temperature overnight. The salt was filtered and the filtrate was concentrated and vacuum distilled at 50° (0.1 mm) to yield 42 g (67%) of VII: ir 1799 (C=O) and 1661 cm^{-1} (C=C); nmr (CCl_4) δ 2.16 (singlet) and 2.29 (singlet), the relative areas indicate an isomer distribution of 1.85.

Anal. Calcd for $C_5H_3Cl_5O_2$: C, 22.0; H, 1.10; Cl, 65.14. Found: C, 21.7; H, 1.30; Cl, 64.93.

Registry No.—I, 23649-90-3; II, 23649-91-4; III, 23649-92-5; IV, 23649-93-6; V, 23649-94-7; VI, 23649-95-8; VII, 23649-96-9; triethylamine, 121-44-8.

(15) P. Walden, *Chem. Ber.*, **28**, 1287 (1895).

Acid-Catalyzed Disproportionation Reactions of Aliphatic Ketones. Scope and Mechanism[1a]

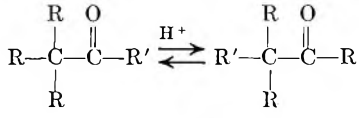
DENNIS D. FAULK,[1b] WALTER H. CORKERN,[1c] IKUO OOKUNI, AND ARTHUR FRY

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701

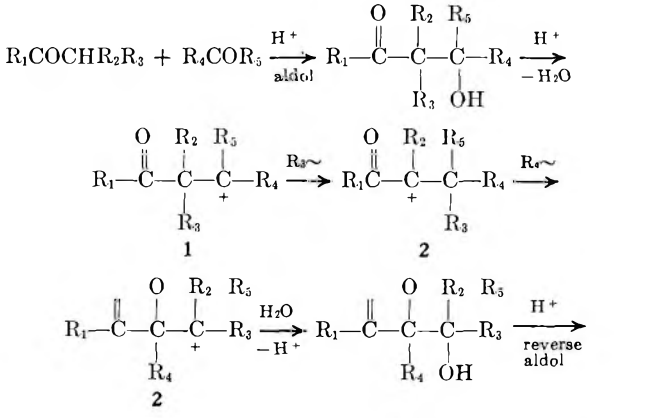
Received February 11, 1969

Upon treatment with perchloric acid, straight-chain aliphatic ketones disproportionate, in low yields, to straight-chain (but not to branched-chain) ketones of both higher and lower carbon number. This reaction appears to be general for straight-chain ketones, but does not occur for α-branched ketones. The proposed mechanism involves an aldol condensation, dehydration of the aldol conjugate acid to a carbonium ion, alkyl or hydrogen shifts in the carbonium ion, rehydration to an isomeric aldol, and reverse aldolization to rearranged ketones and/or aldehydes. Support for the mechanism was obtained by (1) carrying out product studies on simple ketones, (2) following the paths of olefinic ketones which were independently synthesized and which lead to proposed intermediate carbonium ions, and (3) identifying rearranged olefinic ketones and rearranged dihydrofurans. Dihydrofurans are readily formed from olefinic ketones under the reaction conditions in sufficient yields to show synthetic promise. Apparently, a relatively facile oxygen function rearrangement also occurs in ethyl and propyl straight-chain olefinic ketones.

Most of the many investigations of acid-catalyzed rearrangements of aldehydes and ketones to isomeric ketones can be rationalized on the basis of intramolecular mechanisms[2] involving alkyl and/or oxygen function shifts in the conjugate acids of the carbonyl compounds. Formally, the net result of all these intramolecular mechanisms is the exchange of a group attached directly to the carbonyl carbon with a group attached to the α carbon on the other side of the carbonyl carbon.[3]



In the course of a detailed study of the mechanisms of these rearrangements, it was discovered[4] that ketones of molecular weight both higher and lower than the starting material were formed. For instance, butanone forms acetone, 2-pentanone, 3-pentanone, 3-hexanone, and numerous other nonketonic compounds. A generalized form of the working hypothesis mechanism given by Ookuni and Fry[4] for this disproportionation reaction is given below.



$R_1COCHR_2R_3 + R_4COR_5$

R_1, R_4 and R_5 = alkyl; R_2 and R_3 = alkyl or hydrogen

(Other paths would lead to products with other combinations of R_2, R_3, R_4, and R_5.)

This mechanism involves an aldol condensation, dehydration of the aldol conjugate acid to a carbonium ion, alkyl or hydrogen shifts in the carbonium ion, rehydration to an isomeric aldol, and reverse aldolization to rearranged ketones and/or aldehydes. This bimolecular path for the ketone disproportionation reaction is similar to the bimolecular path established for rearrangements in the reactions of alkyl halides with acids.[5]

The report of the discovery of the disproportionation reaction[4] mentioned only straight-chain aliphatic ketones. However, from the mechanism suggested, there was no immediately obvious reason why branched-chain ketones should not undergo the disproportionation reaction, or why branched-chain compounds should not be obtained from straight-chain starting materials. For instance, two molecules of 2,4-dimethyl-3-pentanone ($R_1 = R_4 = R_5$ = isopropyl; $R_2 = R_3$ = methyl) might disproportionate to 2,4,5-trimethyl-3-hexanone and 3-methyl-2-butanone, and two molecules of butanone ($R_1 = R_2 = R_4$ = methyl; R_3 = H; R_5 = ethyl) might disproportionate to 3-methyl-2-butanone and propionaldehyde (or, with $R_1 = R_2 = R_5$ = methyl, R_3 = H, and R_4 = ethyl, to 3-methyl-2-pentanone and acetaldehyde). Accordingly, careful searches were made for disproportionation products in the reactions of branched-chain compounds, and for branched-chain products from straight-chain starting materials.

Another major effort in studying the mechanism of the disproportionation reaction was the investigation of the products formed by introduction into the reaction system of the proposed intermediate carbonium ions **1**, **2**, or **3** by independent paths. These carbonium ions would be expected to form by perchloric acid treatment of independently synthesized, appropriately substituted olefinic ketones. If the simple ketones at both ends of

(1) (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; taken in part from the Ph.D. Dissertations of D. D. F. and W. H. C.; presented in part at the Southwest Regional American Chemical Society Meeting, Albuquerque, N. M., Dec 2, 1966. (b) Texas Eastman Fellow, 1964–1965. (c) Monsanto Fellow, 1963–1964.

(2) For a summary of the proposed mechanisms and leading references to these investigations, see W. H. Corkern and A. Fry, *J. Amer. Chem. Soc.*, **89**, 5888 (1967).

(3) It should be noted that this result is accomplished by interchange of R and R′, or, alternatively, oxygen may interchange with two R groups (oxygen function rearrangement).

(4) I. Ookuni and A. Fry, *Tetrahedron Lett.*, 989 (1962).

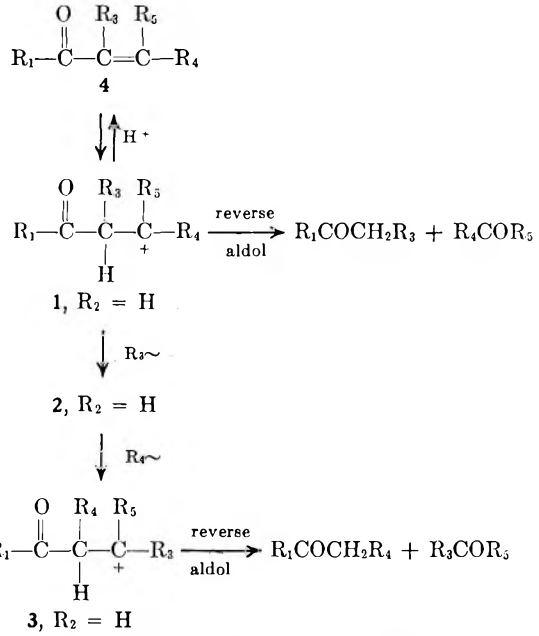
(5) G. J. Karabatsos, F. M. Vane, and S. Meyerson, *J. Amer. Chem. Soc.*, **83**, 4297 (1961); **85**, 733 (1963); G. J. Karabatsos and F. M. Vane, *ibid.*, **85**, 729 (1963).

TABLE I
SCOPE OF THE DISPROPORTIONATION REACTION

Reactant	Isolated products	Glpc-identified products	Products sought but not found
Acetone		Butanone[a]	
Butanone	2-Pentanone	Acetone[b]	Acetaldehyde
	3-Pentanone	3-Hexanone	Propionaldehyde
			$MeCOCHMe_2$
			MeCOCHMeEt
3-Pentanone	2-Pentanone[c]	Acetone (trace)[d,e]	EtCOCHMeEt
	3-Hexanone	Butanone	
		2-Hexanone (trace)[e]	
4-Heptanone		3-Hexanone	
		4-Octanone (?)	
Propiophenone	Butyrophenone	Acetophenone[f]	
	$PhCH_2COMe$[c]		
$MeCOCHMe_2$			Acetone
			Isobutyraldehyde
			$MeCOCHMeCHMe_2$
			$Me_2CHCOEt$
$Me_2CHCOEt$	MeCOCHMeEt[c]		Butanone
			$MeCOCHMe_2$
			$MeCOCH_2CHMe_2$[c]
$Me_2CHCOCHMe_2$	$MeCOCHMeCHMe_2$[c]		$MeCOCHMe_2$

[a] 4-Methyl-3-penten-2-one (mesityl oxide) (5), the aldol condensation product dehydration product, was also identified. [b] Aldol dehydration products *cis*- (6) and *trans*-3,4-dimethyl-3-hexen-2-one (7), *cis*- (8) and *trans*-3,4-dimethyl-4-hexen-2-one (9), and *cis*- (10) and *trans*-5-methyl-4-hepten-3-one (11) were also identified, and *cis*- (12) and *trans*-2,3,4,5-tetramethyl-4,5-dihydrofuran (13) were isolated. In an experiment with 2-butanone-1-^{14}C in 70% perchloric acid for 48 hr at 50°, added holdback carriers of acetone, 2-pentanone, 3-pentanone, and 3-hexanone, after reisolation and derivative preparation, all showed the presence of radioactivity. [c] Intramolecular rearrangement product. [d] Aldol dehydration products *cis*- (14) and *trans*-5-ethyl-4-methyl-5-hepten-3-one (15) were also identified, and *cis*- (16) and *trans*-2,4-diethyl-3,5-dimethyl-4,5-dihydrofuran (17) were isolated. [e] Disproportionation product derived from the 2-pentanone formed by intramolecular rearrangement of 3-pentanone; the 2-hexanone might also arise from oxygen function rearrangement of 3-hexanone. [f] F. E. Juge, Jr., private communication; methyl benzyl ketone was obtained in gross amounts, butyrophenone was isolated by preparative glpc and identified by spectral and derivative comparisons, and acetophenone was identified by glpc retention times on several columns.

the above mechanistic path were formed, the mechanism would be supported.



(Other paths would lead to products with other combinations of R_2, R_4, and R_5.)

Results and Discussion

The experiments on the scope of the disproportionation reactions of straight-chain and branched-chain aliphatic ketones are summarized in Table I. All straight-chain aliphatic ketones studied formed detectable amounts of disproportionation products. No branched-chain disproportionation products were obtained from straight-chain compounds. No aldehydes were detected as disproportionation products. (It is very likely that aldehydes were formed, but, being highly reactive, condensed immediately to polymeric materials; when aldehydes were subjected to the reaction conditions, no simple aldehydes were recovered.) The disproportionation reaction appears to be general for, but restricted to, the production of straight-chain aliphatic ketones from other straight-chain aliphatic ketones.[6]

The reactions of the straight-chain ketones to give straight-chain disproportionation products may be classified into three groups: (1) reactions in which R_2 = H and R_3 = alkyl, so that the sequence **1** → **2** → **3** involves tertiary → secondary → tertiary carbonium ions; (2) reactions in which $R_2 = R_3$ = H, so that **1** → **2** → **3** involves tertiary → secondary → secondary carbonium ions; and (3) reactions which must involve preliminary intramolecular rearrangements followed by group 1 and/or 2.

All of the reactions giving products which were in high enough yields to be isolated are in group 1, with the exception of the formation of 3-pentanone from butanone. The lower yields of the products in the other two groups is what would be expected on the basis of reversible reactions, taking into account the greater stability of tertiary compared with secondary carbonium ions, and the difficulty of formation of products by paths involving sequential intramolecular and intermolecular reactions. The relatively large yield of 3-pentanone

(6) If the chain branching is remote from the carbonyl group, disproportionation reactions would no doubt occur.

from butanone is almost certainly due to a large contribution from intramolecular rearrangement of the first-formed 2-pentanone, added to a smaller amount formed by a tertiary → secondary → secondary carbonium ion path. Furthermore, the formation of 2-pentanone starting from 3-pentanone must be intramolecular,[7] and the 2-hexanone and acetone observed in the long-time 3-pentanone reactions must be derived from the 2-pentanone by condensation with itself or with 3-pentanone, or, for 2-hexanone, from an oxygen function rearrangement of 3-hexanone.

The yields in all of these disproportionation reactions are very low, and it is clear that the reaction has no synthetic value. There is considerable mechanistic significance, however, since the results are quite striking. The low yields are readily understandable on the basis of carbonium ion stabilities and the existence of more favorable competing reaction paths. One would not expect tertiary ion **1** to rearrange readily to secondary ion **2** where the positive center is adjacent to a carbonyl carbon. Furthermore, the rearrangement must always compete with the formation of dihydrofurans (see below) and with the normal reverse aldol reaction. Considerable attention is given to the matter of relative yields in the Experimental Section.

In order for branched-chain disproportionation products to be formed from straight-chain ketones, the sequence **1** → **2** → **3** would need to involve a tertiary → tertiary → secondary carbonium ion path, the last step of which is unlikely in itself, but which is made doubly unattractive by the necessity for both R_2 and R_4 in **3** to be alkyl groups, resulting in serious steric crowding adjacent to the carbonyl group. This matter will be covered further in the olefinic ketone discussion below.

The inability of branched-chain ketones to give the disproportionation reaction is probably due to a variety of factors: (1) the competition of more favorable intramolecular processes leading to rearranged isomeric ketones (for instance, 2-methyl-3-pentanone rearranges readily to 3-methyl-2-pentanone); or (2) the favorable competition of paths leading to dihydrofurans from **2** (see below); or (3) the failure of initial aldol condensation for cases where R_2 and R_3 are both alkyl (again, there would be excessive steric crowding adjacent to the carbonyl group). It is known,[8] for example, that in acid solution 3-methyl-2-butanone condenses almost exclusively at the methyl carbon.

The strongest support for the proposed mechanism is given by the results of the experiments with externally synthesized olefinic ketones. In several cases (see Table I, footnotes *a*, *b*, and *c*), the olefinic ketones expected aldol dehydration products were shown to be present in the simple ketone–perchloric acid reaction system. Perchloric acid treatment of a series of olefinic ketones of this type resulted in the formation of both the unrearranged and rearranged simple ketones, as summarized in Table II.

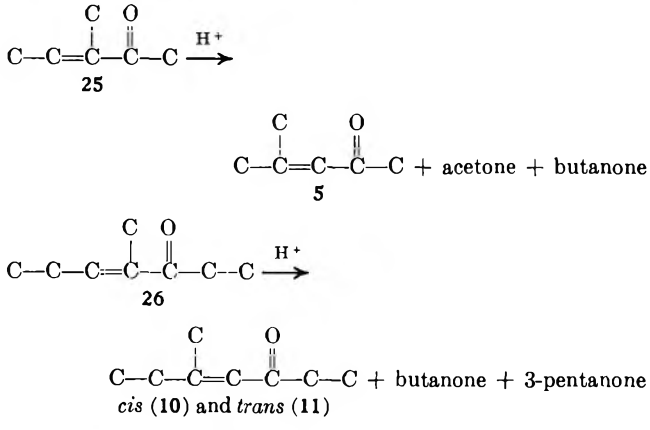
In all of these cases, in the general olefinic ketone formula **4**, R_4 and R_5 are alkyl groups, and the rearrangement sequence **1** → **2** always involves alkyl or hydrogen migration to a tertiary carbonium ion center, giving a secondary carbonium ion. Further rearrangement of **2** to **3** gives a secondary or tertiary carbonium ion, which reverts to the rearranged aldol decomposition products. The proposed pathway would be strongly supported if olefins derived from type **3** ions could be detected, and a careful search was made for them for the cases listed in Table II. None could be detected, so a more favorable case was sought.

TABLE II

SIMPLE KETONIC PRODUCTS FROM THE REACTIONS OF OLEFINIC KETONES WITH PERCHLORIC ACID

Compd	Reverse aldol products	Rearranged ketones
$Me_2C{=}CHCOMe$ (**5**)	Acetone	Butanone
EtMeC=CMeCOMe, *cis*- (**6**) and *trans*- (**7**)	Butanone	Acetone 2-Pentanone
EtMeC=CHCOEt, *cis*- (**10**) and *trans*- (**11**)	Butanone	3-Pentanone 3-Hexanone
$Et_2C{=}CMeCOEt$ (**18**)	3-Pentanone	Butanone 3-Hexanone
n-PrMeC=CHCO-*n*-Pr, *cis*- (**19**) and *trans*- (**20**)	2-Pentanone	3-Hexanone
$Me_2C{=}CEtCOMe$ (**21**)	Acetone 2-Pentanone	Butanone
$Me_2C{=}CHCOEt$ (**22**)	Acetone Butanone	3-Pentanone
$Me_2C{=}CHCO\text{-}n\text{-}Pr$ (**23**)	Acetone 2-Pentanone	3-Hexanone
MeCH=CMeCHEtCOEt (**24**)	Butanone 3-Hexanone	3-Pentanone

It was thought that the steady-state equilibrium of the intermediate rearranged olefinic ketone might be large enough to detect if the initial migration (**1** → **2**) were to the more favorable (more highly localized positive charge) secondary carbonium ion. Two such cases were tried. The rearranged olefinic ketones were detected in both cases, along with the rearranged and unrearranged simple ketones.



The rearrangement of **25** and **5** takes place to a considerable extent, as shown by the presence of 12% acetone in the acetone–butanone fraction recovered from the reaction of **25** with perchloric acid.

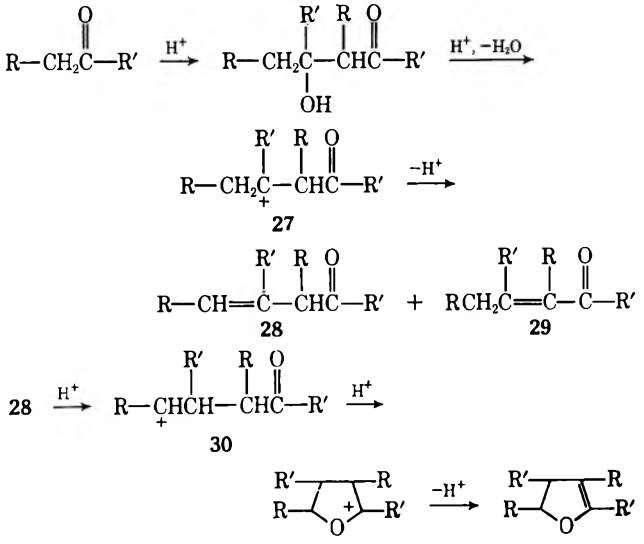
These two examples provide convincing evidence for intermediates throughout the reaction scheme, and hence strongly support the proposed mechanism.

In the original paper on the ketone disproportionation reaction[4] it was reported that unidentified volatile compounds were produced. These compounds have been characterized as dihydrofuran derivatives and, in fact, are the major volatile products of the reaction of aliphatic ketones with perchloric acid. For example, butanone reacts to give *cis*- (**12**) and *trans*-2,3,4,5-tetra-

(7) A. Fry and W. H. Corkern, *J. Amer. Chem. Soc.*, **89**, 5894 (1967).

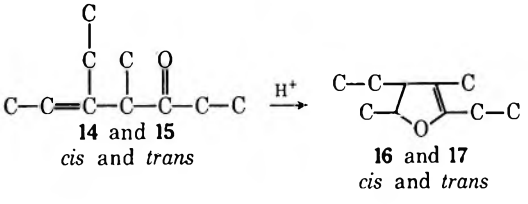
(8) W. H. Corkern, Ph.D. Dissertation, University of Arkansas, 1966, p 149.

methyl-4,5-dihydrofuran (**13**). It has been found that these compounds are readily produced from the reaction of the aldol condensation–dehydration product of butanone, 3,4-dimethyl-4-hexen-2-one (**8** and **9**), with perchloric acid, and somewhat more slowly from the conjugated isomer, 3,4-dimethyl-3-hexen-2-one (**6** and **7**). On the basis of these results the formation of dihydrofurans from simple ketones can be represented by the following reactions.



Intermediate **30** could also be formed *via* a hydride shift in **27** which, of course, is a precursor of **28** and **29**.

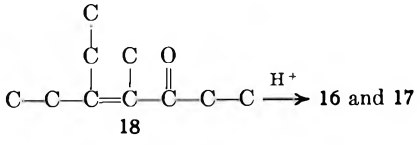
The fact that dihydrofuran derivatives are readily formed from some olefinic ketones was used to advantage in the mechanistic investigation. For example, olefinic ketones **14** and **15** readily react with perchloric acid to give dihydrofurans **16** and **17**. These olefinic ketones and dihydrofurans were also found in the 3-pentanone–perchloric acid reaction mixture.



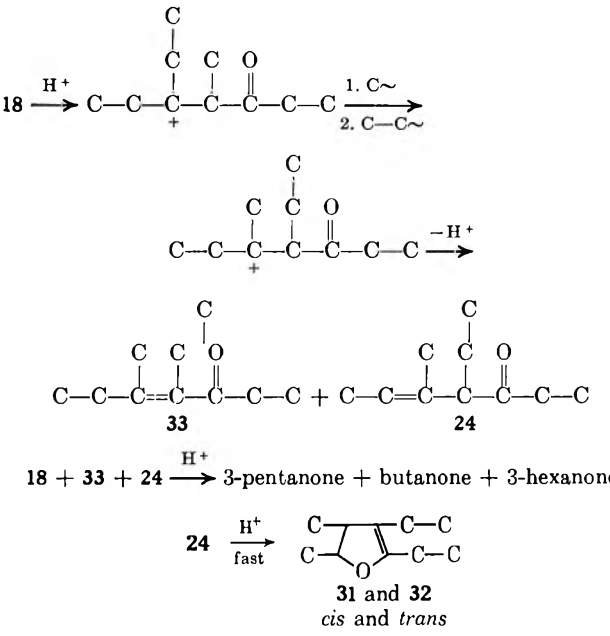
14 and **15**
cis and *trans*

16 and **17**
cis and *trans*

Compound **18**, the conjugated isomer of **14** and **15**, gives dihydrofurans **16** and **17** somewhat more slowly, in addition to giving the rearrangement reaction.

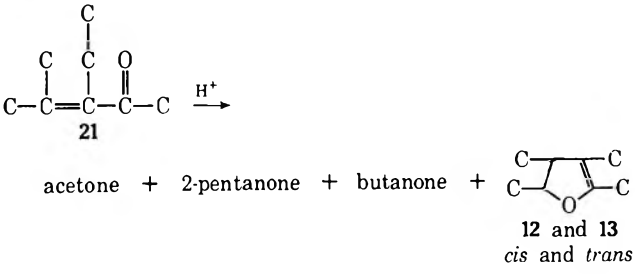


Also, of considerable mechanistic significance, in the disproportionation reaction of **18**, rearranged dihydrofurans **31** and **32** are formed, presumably as follows.



31 and **32**
cis and *trans*

In a similar reaction, olefinic ketone **21** gave **12** and **13**.



12 and **13**
cis and *trans*

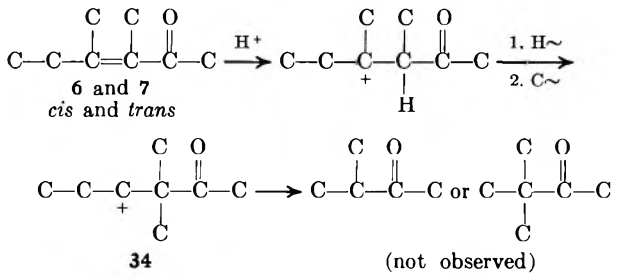
Here, dihydrofurans **12** and **13** are rearranged products formed in a reaction analogous to the one described in detail above. These two compounds are the primary products formed in the reaction of butanone with perchloric acid and in the reaction of 3,4-dimethyl-4-hexen-2-one (**8** and **9**) (an aldol condensation–dehydration product of butanone) with perchloric acid.

The above results demonstrate conclusively that rearranged olefinic ketones and dihydrofurans are formed from the aldol condensation–dehydration products; that these rearranged olefinic ketones decompose to the observed disproportionation products; and that the rearranged olefinic ketones also revert to the simple ketones from which the initial aldol condensation products were derived. These facts support the proposed mechanism for the disproportionation reaction very strongly.

Under conditions mild enough to prevent extensive polymerization, the main reaction of simple aliphatic ketones and olefinic ketones with perchloric acid is the formation of dihydrofuran derivatives. Dihydrofuran formation from olefinic ketones (particularly β,γ-unsaturated ketones) is faster than from the simple ketones, and this reaction may be of general synthetic utility.

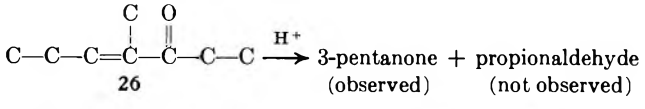
Reactions of olefinic ketones provide an additional and perhaps more critical test of the possibility that branched-chain ketones might be formed from straight-chain starting marerials. The formation of 3-pentanone from **10** and **11** (Table II) involves a hydride transfer followed by a methyl migration. If this occurs it might be expected that **6** and **7**, for example, would

show a hydrogen–methyl interchange to lead to 3-methylbutanone; however, this compound could not be detected. (The possibility that intermediate **34** could cleave at the β,γ bond was considered; however, no 3,3-dimethylbutanone could be found in this reaction.)



It is seen that the loss of a proton from intermediate **34** can lead only to the nonconjugated ketone. It is known that nonconjugated ketones readily react with perchloric acid to give dihydrofurans. Possibly, this occurs with intermediate **34** if the indicated migrations actually take place. However, as mentioned earlier, it is probable that the steric compression of attaching three alkyl groups on one of the carbons α to the carbonyl group is too great to permit appreciable reaction through such an intermediate.

The work with olefinic ketones also sheds some light on the question of aldehyde formation in the disproportionation reaction. For some of the reaction paths leading to rearranged ketones, aldehydes would be the other rearrangement product, but none have been found (Table I). This observation is thought to be due to the fact that aldehydes disappear (polymerize) very rapidly under the reaction conditions. Acid treatment of olefinic ketone **26** should surely give propionaldehyde from the initial reverse aldol reaction, but it could not be detected.



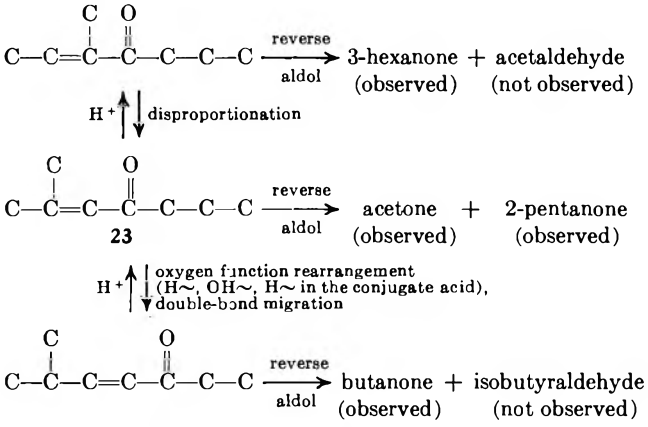
Reactions of olefinic ketones, having R_1 in general formula **4** an ethyl or a propyl group, yield simple rearranged ketones which cannot be explained by the above disproportionation mechanism. These reactions are summarized in Table III.

TABLE III

OLEFINIC KETONES GIVING SIMPLE KETONIC PRODUCTS NOT PREDICTED BY THE DISPROPORTIONATION MECHANISM

Olefinic ketone	Simple ketonic products
EtMeC=CHCOEt *cis*- (**10**) and *trans*- (**11**)	Acetone
Et_2C=CMeCOEt (**18**)	Acetone
n-PrMeC=CHCO-*n*-Pr *cis*- (**19**) and *trans*- (**20**)	Butanone
Me_2C=CHCOEt (**22**)	Acetone
Me_2C=CHCO-*n*-Pr (**23**)	Butanone
MeCH=CMeCHEtCOEt (**24**)	Acetone
EtCH=CMeCOEt (**26**)	Acetone 2-Pentanone

All of the products obtained in these reactions are readily explainable on the basis of an oxygen function rearrangement[2,7] in the olefinic ketone, followed by a reverse aldol reaction. For instance, the reactions of **23** may be summarized as follows.



4-Methyl-4-hepten-3-one (**26**) gives acetone and 2-pentanone according to this mechanism. In fact the yield of 2-pentanone is 11.0% compared with 83.6% for the normal reverse aldol product, 3-pentanone, which shows that rearrangement of this compound by an oxygen migration is considerably more extensive than the disproportionation reaction.

Experimental Section

General Procedures for the Disproportionation Reaction.—Samples of the various ketones were stirred (or shaken) with 70% perchloric acid at appropriate temperature for various times. Typically, at 50°, the material became light yellow immediately after mixing and turned to a light brown after 24 hr and to a dark brown after 72 hr. The reaction mixtures were poured over cracked ice, and the solutions were neutralized with sodium hydroxide, saturated with sodium chloride, and extracted with ether. After removal of the ether, the remaining volatile material was collected by distillation. The components of the various fractions were analyzed by gas–liquid partition chromatography (glpc) on a variety of columns, and preparative glpc was used to isolate and purify compounds for spectral comparisons and derivative preparation in several instances.

A great many experiments were performed, involving variations in time from a few minutes to many days, in temperature from room temperature to 100°, and in ketone to acid ratio of from one to five. Recovery of volatile material was essentially quantitative for short-time, low-temperature experiments, and ranged downward to a few per cent (the rest being polymeric material) for high-temperature, long-time experiments. In many cases, the course of the reaction was followed by injection of a very small aliquot of the reacting mixture directly onto a glpc column. In the short-time, low-temperature experiments, barely detectable amounts of rearrangement products were formed. As conditions became more drastic, increasing ratios of rearranged to unrearranged products were found, but the amount of volatile material recovered decreased to only a few per cent.

A wide variety of analytical and preparative glpc columns of different polarity was used; frequently this resulted in a different order of elution on two columns for a series of ketones, thus facilitating positive identification. Gas chromatographs with both thermal conductivity and hydrogen flame detectors were used. A typical analysis consisted of injecting a glpc sample followed by (or preceded by) an authentic mixture of ketones under the same elution conditions. Retention times were then compared. Since the reaction product contained starting ketone, an internal standard was present which permitted the calculation of retention ratios and corrected for any minute change in conditions from one injection to another. In some cases, a small amount of known compound was added to the product and analyzed to provide further information. For the reactions of olefinic ketones, the reverse aldol reaction readily produces simple ketones as internal standards to permit the calculation of retention ratios. Details concerning many of the individual experi-

ments are contained in the Ph.D. dissertations of W. H. C.[8] and D. D. F.[9] Many of the nmr spectra and all of the mass spectra were taken by Dr. P. Flannigan and Mr. H. T. Ford of Continental Oil Co. We are deeply indebted to them for their assistance.

Experiments with Simple Ketones.—The results of the exploratory experiments with simple ketones are given in Table I. Positive identification of the disproportionation products and condensed olefinic ketones is vital to the research, and a typical glpc analysis of the material recovered from the reaction of butanone with 70% perchloric acid follows. For a 20% triethylene glycol on 60/80 firebrick column (100 ml/min He, 74°), retention times relative to butanone for the known compound and the reaction product mixture, respectively, follow: acetone, 0.71, 0.70; butanone, 1.00, 1.00; 2-pentanone, 1.44, 1.44; 3-pentanone, 1.36, 1.36; 3-hexanone, 1.81, 1.81. For a 200-ft capillary column of didecyl phthalate (5 ml/min He, 93°), the corresponding values follow: acetone, 0.88, 0.88; butanone, 1.00, 1.00; 2-pentanone, 1.22, 1.22; 3-pentanone, 1.24, 1.24; 3-hexanone, 1.68, 1.67. For a 20% Carbowax 4000 on 60/80 firebrick column (100 ml/min He, 94°), the values follow: acetone, 0.68, 0.67; butanone, 1.00, 1.00; 2- and 3-pentanone unresolved mixture, 1.47, 1.47 (the 3-hexanone peak was obscured by another product). For a 20% silicone gum rubber SE-30 on Celite column (100 ml/min He, 65°), the values follow: butanone, 1.00, 1.00; 2- and 3-pentanone unresolved mixture, 1.89 and 1.90 (the acetone and 3-hexanone peaks were obscured by other peaks). For the mixture of olefinic ketones formed, the relative steady-state concentrations, calculated from retention data on 1,2,3-tris(2-cyanoethoxy)propane, silicone gum rubber SE-30, and silicone fluid nitrile XF-1150 columns, was 4.1% unresolved **8** and **9**, 22.6% **10**, 67.1% unresolved **6** and **11**, and 6.2% **7**.

The 2- and 3-pentanone fraction from one experiment with butanone was recovered by preparative glpc and shown to be 10% 3-pentanone and 90% 2-pentanone by comparing its infrared spectra with that of an authentic sample. A 3-hexanone fraction was separated from a 3-pentanone reaction mixture by preparative glpc on a 20% triethylene glycol on 60/80 firebrick column, and identified by its infrared spectrum (neat) and the formation of a semicarbazone [mp 110–112° (lit.[10] mp 113°)] comparison with an authentic sample, mp 111–112°. Details of identification and derivative preparation for 2-pentanone formed from 3-pentanone are given elsewhere.[11]

In investigating the question of the formation of aldehydes from the disproportionation reaction, an experiment was carried out in a sweep system in an effort to remove the low-boiling aldehydes as quickly as they were formed. Butanone (10 g) was treated with 50 ml of 70% perchloric acid at 50° for 48 hr while being swept with 100 ml/min of dry nitrogen. After bubbling through the reaction mixture, the nitrogen was passed through a Dry Ice trap and then through sodium hydroxide bubblers. The liquid collected in the cold trap (mostly butanone) was analyzed by glpc and no acetaldehyde or propionaldehyde could be detected. No carbon dioxide (oxidation product) of hydrogen chloride (perchloric acid reduction product?) could be detected in the sodium hydroxide bubblers upon attempts to precipitate barium carbonate and silver chloride.

Exhaustive searches were carried out for branched-chain disproportionation products from straight-chain ketones, and for disproportionation products from α branched-chain ketones utilizing glpc analytical procedures similar to those described above.[8] As outlined in Table I, no such products were found. Detection limits of 0.05–1.0% relative to the recovered starting ketone were set. Control experiments demonstrated that the "expected" disproportionation products were sufficiently stable under the reaction conditions to be detected readily if they had been formed. In the course of these studies the reversibility of the intramolecular interconversion of 3-methyl-2-pentanone and 2-methyl-3-pentanone was established. The main products (*ca.* 50% actual yield) from the reaction of 3-methylbutanone with perchloric acid are two readily intercovertible compounds of molecular formula $C_{10}H_8O$. These compounds have not been identified as yet, but they are probably dihydrofurans. They are not C_{10} olefinic ketones.

(9) D. D. Faulk, Ph.D. Dissertation, University of Arkansas, 1966.

(10) R. L. Shiner, 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 316.

(11) A. Fry, I. Ookuni, G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Org. Chem.*, **27**, 1914 (1962).

Preparation, Isolation, and Identification of Olefinic Ketones and Dihydrofurans.—The preparation and characterization of compounds **6**, **7**, **10**, **11**, **18–23**, **25**, and **26** are described elsewhere.[12]

4-Ethyl-5-methyl-5-hepten-3-one (24).[13]—Ethyl 2-ethyl-3-hydroxy-3-methylpentanoate (**35**), bp 85–87° (10 mm), was prepared in 81% yield by dropwise addition at reflux of an ether solution of 46 g (0.65 mol) of butanone and 100 g (0.51 mol) of ethyl α-bromobutyrate to 13 g of magnesium and 1.0 g of mercuric chloride.

Data for **35** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.88 (t, 6 H, CH_2CH_3), 1.09 (s, 3 H, CCH_3), 1.28 (t, 3 H, OCH_2CH_3), *ca.* 1.47 (m, 4 H, CCH_2CH_3 and $CHCH_2CH_3$), 2.15 (t, 1 H, $CHCH_2$), 2.62 (s, broad, 1 H, OH), and 4.16 (q, 2 H, OCH_2CH_3); ir (neat) ν_{max}^{NaCl} 3480 (m, broad, OH), 1715 (s, C=O), and 1188 cm^{-1} (s, ester COC stretching frequency).

Hydroxy ester **35** was dehydrated by refluxing for 20 min with iodine in a water separator to give an 87% yield of ethyl 2-ethyl-3-methyl-3-pentenoate, bp 66.5–71° (10 mm). The olefinic ester was hydrolyzed in aqueous alcoholic sodium hydroxide to give a 92% yield of 2-ethyl-3-methyl-3-pentenoic acid (**36**), bp 104–110° (10 mm). The nmr spectrum indicated the presence of a *cis–trans* mixture.

Data for **36** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.87 (t, 3 H, CH_2CH_3), 1.64 (s, fine splitting, 3 H, $CH{=}CCH_3$), 1.65 (d, 3 H, $CH_3CH{=}C$), 1.70 (m, partially obscured, 2 H, $CHCH_2CH_3$), 2.82 (t, <1 H, α H of the geometric isomer having the γ H and the carboxyl group *cis*), 3.38 (t, <1 H, α H of the geometric isomer having the γ H and the carboxyl group *trans*), 4.97 (q, broad, <1 H, γ H *trans* to the carboxyl group), 5.41 (q, broad, <1 H, γ H *cis* to the carboxyl group), and 11.22 (s, 1, H, OH); ir (neat) ν_{max}^{NaCl} 2950 (s, broad, OH), 1700 (s, carboxylic acid dimer C=O), 1411 (m, dimeric OH in-plane bending frequency coupled with CO stretching frequency), 1220 (s, CO stretching frequency coupled with OH in-plane bending frequency), 932 (m, broad, OH out-of-plane bending frequency of an acid dimer), and 812 cm^{-1} (m, CH bending frequency of a trisubstituted double bond).

Thionyl chloride was dried dropwise to the acid **36** at 70°, giving a 90% yield of 2-ethyl-3-methyl-3-pentenoyl chloride (**37**), bp 56–64° (10 mm).

Data for **37** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.88 (t, 3 H, CH_2CH_3), 1.63 (d, 3 H, $C{=}CHCH_3$), 1.65 (s, fine splitting, 3 H, $CH{=}CCH_3$), *ca.* 1.70 (m, partially obscured, 2 H, $CHCH_2CH_3$), 2.81 (t, 1 H, CH_2CH), and 5.40 (q, broad, 1 H, $CH_3CH{=}CCH_3$); ir (neat) ν_{max}^{NaCl} 1795 cm^{-1} (s, acid chloride C=O).

Acid chloride **37** in benzene solution was added to a benzene solution of diethylcadmium to give an 81% yield of 4-ethyl-5-methyl-5-hepten-3-one (**24**), bp 58.5–59.5° (10 mm).

Data for **24** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.78 (t, 3 H, $CHCH_2CH_3$), 0.98 (t, 3 H, $COCH_2CH_3$), 1.48 (s, fine splitting, 3 H, $CH{=}CCH_3$), 1.63 (d, fine splitting, 3 H, $CH_3C{=}CHCH_3$), 1.64 (quintet, partially obscured, 2 H, $CHCH_2CH_3$), 2.32 and 2.40 (pair of quartets, 2 H, $COCH_2CH_3$), 2.87 (t, <1 H, α H of the geometric isomer having the γ H *cis* to the carbonyl group), 3.41 (t, <1 H, α H of the geometric isomer having the γ H *trans* to the carbonyl group), and 5.40 (q, 1 H, $CH_3CH{=}C$); ir (neat) ν_{max}^{NaCl} 3016 (w, vinyl H), 1712 (s, C=O), and 808 cm^{-1} (m, CH bending frequency of a trisubstituted double bond); uv λ_{max}^{EtOH} 291 mμ (log ε 2.65); mass spectrum *m/e* (rel intensity) 154 (parent peak) (1.7), 125 (29), 97 (44), 69 (28), 57 (80), 55 (100), 43 (11), 41 (31), 39 (19), 29 (62), and 27 (34).

***cis*- (12) and *trans*-2,3,4,5-Tetramethyl-4,5-dihydrofuran (13).**—The main nonpolymeric products from the reaction of butanone with 70% perchloric acid are **12** and **13**. This may be the method of choice for the preparation of compounds of this type. In an experiment with 1 g of butanone per 5 ml of 70% perchloric acid at 95° for 4 hr, the yield of a mixture of **12** and **13** was 21% (56% of the butanone weight was recovered as high-boiling polymeric material). In butanone–perchloric acid experiments under mild conditions (low temperature, short time), the **12** to **13** ratio was *ca.* four, and this decreased to less than one for high-temperature, long-time experiments. It appears that **12** is formed faster than **13** but **13** is more stable than **12**, although precise rate and equilibration studies were not carried out. Further details concerning yields, relative yields, etc., are found in the Ph.D. thesis of D. D. F.[9] We are indebted to Dr. P. Flannigan and Mr. H. T. Ford of Continental Oil Co. for assistance in

(12) D. D. Faulk and A. Fry, *ibid.*, **35**, 364 (1970).

(13) J. Colonge and D. Joly, *Ann. Chim.* (Paris), **18**, 308 (1943).

TABLE IV

RELATIVE YIELDS OF SIMPLE KETONES IN REACTIONS OF OLEFINIC KETONES WITH PERCHLORIC ACID

Compd	Ml of $HClO_4$/g of ketone	Time, hr	Temp, °C	Relative yields, % MeCOMe	EtCOMe	EtCOEt	*n*-PrCOMe	*n*-PrCOEt
Me_2C=CHCOMe (**5**)	3.0	100.00	25	98.6[a]	1.4	...	...	...
EtMeC=CMeCOMe (**6** and **7**)	5.0	1.0	50	...	99.6[a]	...	0.4	...
EtMeC=CMeCOMe (**6** and **7**)	0.02	0.017	25	1.9	91.4[a]	...	6.7	...
EtMeC=CHCOEt (**10** and **11**)	3.0	634.0	0	0.3	96.6[a]	3.1	...	...
EtMeC=CHCOEt (**10** and **11**)	3.0	3.0	50	0.1	91.6[a]	8.3	...	...
Et_2C=CMeCOEt (**18**)	3.3	8.0	50	...	0.9	99.1[a]	...	...
Et_2C=CMeCOEt (**18**)	2.0	0.017	25	2.1	1.1	94.0[a]	...	2.8
n-PrMeC=CHCO-*n*-Pr (**19** and **20**)	5.0	2.5	50	...	0.6	...	99.4[a]	Trace
Me_2C=CEtCOMe (**21**)	5.0	0.5	50	24.5[a]	1.9	...	73.6[a]	...
Me_2C=CHCOEt (**22**)	5.0	24.0	25	...	99.7[a]	0.3	Trace	...
MeC=CMeCHEtCOEt (**24**)	3.0	1.5	20	...	...	0.4	...	99.6[a]
MeCH=CMeCOMe (**25**)	6.0	1.0	50	12.0	88.0[a]	...	...	...
EtCH=CMeCOEt (**26**)	5.0	10.0	25	1.9	1.8	83.6[a]	11.0	1.7

[a] Unrearranged reverse aldol product; other values are for rearranged products.

the interpretation of the nmr and mass spectra of these and other dihydrofurans.

Data for **12** follow: bp 137–138°; d^{24} 0.870 g/ml; $n^{25}D$ 1.439; nmr $\delta_{CCl_4}^{TMS}$ 0.86 (d, 3 H, OCCHC**H**$_3$), 1.17 (d, 3 H, OCHC**H**$_3$), 1.52 [s, fine splitting, 3 H, OC(CH$_3$)=CC**H**$_3$], 1.60 [s, fine splitting, 3 H, OC(C**H**$_3$)=CCH$_3$], 2.53 (broad quintet, 1 H, OCHCHCH$_3$), and 4.32 and 4.48 [pair of quartets, 1 H, OC**H**(CH$_3$)CH, $J_{OCHCHCH_3}$ = 8.6 Hz]; ir (neat) ν_{max}^{NaCl} 1708 (s, C=C), 1214 (s, asymmetric stretching frequency of =COC), 1063 (m, symmetric stretching frequency of =COC), and 908 cm^{-1} (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum *m/e* (rel intensity) 126 (parent peak) (19), 111 (66), 83 (16), 67 (23), 56 (6), 55 (41), 53 (11), 43 (100), 41 (36), 39 (26), 29 (16), 28 (10), 27 (30), and 15 (23); positive potassium permanganate double bond test.

Data for **13** follow: bp 128–129°; $n^{25}D$ 1.438; nmr $\delta_{CCl_4}^{TMS}$ 0.98 (d, 3 H, OCCHC**H**$_3$), 1.22 (d, 3 H, OCHC**H**$_3$), 1.48 [s, fine splitting, 3 H, OC(CH$_3$)=CC**H**$_3$], 1.61 [s, fine splitting, 3 H, OC(C**H**$_3$)=CCH$_3$], 2.28 (broad quintet, 1 H, OCHC**H**CH$_3$), and 3.79 and 3.90 [pair of quartets, 1 H, OC**H**(CH$_3$)CH, $J_{OCHCHCH_3}$ = 7.6 Hz]; ir (neat) ν_{max}^{NaCl} 1711 (s, C=C), 1202 (s, asymmetric stretching frequency of =COC), 1060 (m, symmetric stretching frequency of =COC), and 910 (m, ring-bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum *m/e* (rel intensity) 126 (parent peak) (19), 111 (75), 83 (12), 67 (19), 56 (12), 55 (39), 53 (11), 43 (100), 41 (36), 39 (27), 29 (16), 28 (18), 27 (31), and 15 (23); positive potassium permanganate double bond test.

cis- (**16**) and *trans*-2,4-**Diethyl-3,5-dimethyl-4,5-dihydrofuran** (**17**).—The main nonpolymeric products from the reaction of 3-pentanone with 70% perchloric acid are **16** and **17**. These compounds are also major products in the reaction of 5-ethyl-4-methyl-5-hepten-3-one (**14** and **15**) with perchloric acid. Pure samples were prepared by preparative glpc using a 0.375 in. × 10 ft 30% Carbowax 4000 on 60/80 firebrick column. Further details concerning these compounds are found in the Ph.D. thesis of W. H. C.[8]

Data for **16** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.80–2.02 (overlapping complex, 13 H, CHC**H**$_2$CH$_3$, C=CC**H**$_2$CH$_3$, and OCHC**H**$_3$), 1.53 (s, 3 H, C=CCH$_3$), 2.39 [m, 1 H, C=CCH(CH$_2$–)CH], and 3.90 and 4.41 [pair of quartets, 1 H, OCH(CH$_3$)CH]; ir (neat) ν_{max}^{NaCl} 1701 cm^{-1} (s, C=C); mass spectrum *m/e* (rel intensity) 154 (parent peak) (20), 125 (100), 69 (20), 67 (11), 57 (21), 55 (37), 53 (11), 43 (86), 41 (36), 39 (21), 29 (44), and 27 (32).

Data for **17** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.83–1.49 (overlapping complex, 11 H, CHC**H**$_2$CH$_3$, C=CC**H**$_2$CH$_3$, and OCHC**H**$_3$), 1.49 (s, 3 H, C=CC**H**$_3$), *ca.* 2.02 [overlapping quartets, 3 H, CH$_3$C**H**$_2$=C and C=CC**H**(CH$_2$–)CH], and 4.01 [quintet, 1 H, OC**H**(CH$_3$)CH]; ir (neat) ν_{max}^{NaCl} 1705 cm^{-1} (s, C=C); mass spectrum *m/e* (rel intensity) 154 (parent peak) (19), 125 (100), 69 (13), 57 (17), 55 (31), 43 (83), 41 (31), 39 (18), 29 (40), and 27 (28).

cis- (**31**) and *trans*-**2,3-Diethyl-4,5-dimethyl-4,5-dihydrofuran** (**32**).—A mixture of compounds **31** and **32**, bp 55–84° (mainly 76.5–79°) (10 mm), was formed in 63% yield upon treatment of 4-ethyl-5-methyl-5-hepten-3-one (**24**) with 70% perchloric acid at 30° for 1.5 hr. Pure samples of **31** and **32** were separated by preparative glpc on a 0.375 in. × 12 ft 30% Carbowax 4000 on 60/80 firebrick column.

Data for **31** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.85 (d, 3 H, CCHC**H**$_3$), 0.94 (t, 3 H, OC=CCH$_2$C**H**$_3$), 0.98 (t, 3 H, OCCH$_2$C**H**$_3$), 1.17 (d, 3 H, OCHC**H**$_3$) 1.98 (q, 2 H, OC=CC**H**$_2$CH$_3$), 2.00 (q, 2 H, OCC**H**$_2$CH$_3$), 2.68 (broad quintet, 1 H, OCHC**H**CH$_3$), and 4.27 and 4.41 [pair of quartets, 1 H, OC**H**(CH$_3$)CH, $J_{OCHCHCH_3}$ = 8.80 Hz]; ir (neat) ν_{max}^{NaCl} 1891 (m, C=C), 1208 (m, asymmetric stretching frequency of =COC), 1040 (m, symmetric stretching frequency of =COC), and 880 (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum *m/e* (rel intensity) 154 (parent peak) (26), 140 (11), 139 (100), 137 (10), 111 (14), 97 (12), 95 (10), 83 (11), 81 (15), 69 (36), 67 (11), 57 (77), 56 (10), 55 (47), 53 (16), 43 (60), 41 (46), 39 (29), 29 (61), 28 (19), 27 (42), 18 (35), and 15 (15).

Data for **32** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.93 (t, 3 H, OC=CCH$_2$C**H**$_3$), 0.96 (d, 3 H, CCHC**H**$_3$), 0.97 (t, 3, H, OCCH$_2$C**H**$_3$), 1.20 (d, 3 H, OCHC**H**$_3$), 1.95 (q, 2 H, OC=CC**H**$_2$CH$_3$), 2.01 (q 2 H, OCC**H**$_2$CH$_3$), 2.41 (broad quintet, 1 H, OCHC**H**CH$_3$), and 3.76 and 3.87 [pair of quartets, 1 H, OC**H**(CH$_3$)CH, $J_{OCHCHCH_3}$ = 6.7 Hz]; ir (neat) ν_{max}^{NaCl} 1887 (m, C=C), 1197 (m, asymmetric stretching frequency of =COC), 1027 (s, symmetric stretching frequency of =COC), and 890 (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum *m/e* (rel intensity) 154 (parent peak) (23), 140 (14), 139 (100), 137 (31), 111 (18), 97 (24), 95 (11), 83 (16), 81 (13), 69 (42), 67 (15), 57 (90), 56 (16), 55 (55), 53 (19), 43 (93), 41 (63), 39 (37), 29 (76), 28 (26), 27 (55), 18 (23), and 15 (20).

Reactions of Olefinic Ketones with Perchloric Acid.—Olefinic ketones were treated with perchloric acid and the products were analyzed utilizing the procedures described above. In some cases, several reactions were performed with a particular olefinic ketone so that the optimum conditions for the rearrangement reaction could be determined. In other cases, the supply of olefinic ketone permitted only one reaction. Since the optimum conditions are not the same for all olefinic ketones, it was necessary to use past experience to choose the reaction conditions. It was desirable to choose conditions which permitted significant recovery of starting olefinic ketone so that a comparison could be made between the simple reverse aldol reaction and the reverse aldol reaction of the rearranged olefinic ketone. The main products from the reactions of most olefinic ketones with perchloric acid appear to be dihydrofuran derivatives which are formed at rates depending on structure, *i.e.*, highly branched olefinic ketones form dihydrofurans at a faster rate. Therefore, to prevent gross conversion into dihydrofuran derivatives, highly branched olefinic ketones were reacted in relatively low acid concentration and/or at relatively low temperatures. Representative results of these experiments are given in Table IV. The relative yield values given for the simple aliphatic ketones are for the products from that part of the reaction going through the reverse aldol reaction.

From Table IV, it is seen that mesityl oxide (**5**) gives *ca.* 2.8% rearrangement [(100 × % butanone × 2)/% acetone] for the 100-hr reaction at 25°, since the rearrangement reaction gives one molecule of butanone and one molecule of acetaldehyde, while the reverse aldol reaction gives two molecules of acetone. [This assumes that acetone and butanone are consumed in other (polymerization) reactions at the same rate after they are formed.]

Similarly, the reaction of a mixture of the geometric isomers of 5-methyl-4-hepten-3-one (**10** and **11**) at 50° for 3.0 hr indicates 17.8% [100 (8.3 × 2)/91.6] rearrangement for that part of the reactants going through the reverse aldol reaction. However, in this case, the actual yield of butanone and 3-pentanone is low and the starting material is almost completely reacted. In this reaction, acetone cannot conceivably be produced *via* the proposed disproportionation mechanism; it is probably formed *via* an oxygen function migration in the olefinic ketone prior to dealdolization (see Discussion).

In the reaction of **18** with perchloric acid, the dihydrofuran fraction was also isolated and analyzed. It consisted of 95.8% unrearranged *cis* and *trans* dihydrofurans **16** and **17**, and 3.5% of **31** plus 0.7% of **32**, the *cis* and *trans* rearranged dihydrofurans. Dihydrofurans are relatively stable in perchloric acid, so this 4.2% rearrangement is probably a good measure of relative rates of rearrangement and dihydrofuran formation.

Rearranged dihydrofurans **12** and **13** were also detected in the reaction of **21** with perchloric acid.

It is interesting to note that **21** produces a significantly higher ratio of 2-pentanone to acetone than the 1:1 mixture expected from the reverse aldol reaction. Based on this fact and general observations about the reactivity of various ketones, it appears that lower molecular weight ketones disappear (polymerize) faster in perchloric acid than their higher molecular weight homologs. For this reason the relative yields in Table IV are highly dependent on reaction conditions.

Registry No.—Acetone, 67-64-1; butanone, 78-93-3; 3-pentanone, 96-22-0; 4-heptanone, 123-19-3; propiophenone, 93-55-0; $MeCOCHMe_2$, 563-80-4; $Me_2CHCOEt$, 565-69-5; $Me_2CHCOCHMe_2$, 565-80-0; perchloric acid, 7601-90-3; **12**, 23537-60-2; **13**, 23537-61-3; **16**, 23537-62-4; **17**, 23537-63-5; *cis*-**24**, 23537-64-6; *trans*-**24**, 23537-65-7; **31**, 23537-66-8; **32**, 23537-67-9; **35**, 23537-68-0; *cis*-**36**, 23537-69-1; *trans*-**36**, 23537-70-4; **37**, 23537-71-5.

Mass Spectrometry in Structural and Stereochemical Problems. CLXXXI.[1] Further Studies of Remote Group Interactions after Electron Impact in 4-Substituted Cyclohexanones[2]

ROBIN T. GRAY,[3a] RICHARD J. SPANGLER,[3b] AND CARL DJERASSI

Department of Chemistry, Stanford University, Stanford, California 94305

Received July 3, 1969

The mass spectral properties of a series of 4-substituted cyclohexanones have been investigated in an attempt to determine the scope and limitation of an electron impact induced oxygen rearrangement previously reported in the 4-hydroxy and 4-methoxy analogs. With the use of deuterium labeling, a similar rearrangement has been elucidated for 4-ethoxycyclohexanone, albeit to a smaller extent than in the methoxy analog. The mass spectral decomposition of 4-benzyloxycyclohexanone results in another important rearrangement process, giving styrene and a γ,δ-unsaturated acid as the final products, both of which retain part of the ionizing current. For several other analogs, including some containing a different oxygenated substituent, and others bearing a heteroatom (chlorine, sulfur) other than oxygen at the 4 position, no rearrangement processes are observed. Instead, the major fragmentation pathways are governed by the position of initial ionization, as determined by the relative ionization potentials of the different substituent groups.

The use of mass spectrometry in the structure elucidation of organic molecules is now widely accepted, and the characteristic fragmentation patterns associated with individual functional groups have been well documented.[4] Although the techniques of high-resolution analysis, isotopic labeling, and metastable analysis have assisted the chemist greatly in the structure determination of fragment ions, erroneous conclusions are still possible if a fragmentation pathway involves a molecular rearrangement process.

Until recently most reported electron impact induced rearrangements have involved transfer of a hydrogen atom or a simple alkyl radical,[4,5] usually producing a more stable fragment ion. Recent work, however, has uncovered rearrangements of larger groups.[5] For example, during the course of a systematic study of bifunctionalized monocyclic systems in this laboratory, it was reported[6] that abundant fragment ions of masses 60 and 74, respectively, occurred in the mass spectra of 4-hydroxycyclohexanone (I) and 4-methoxycyclohexanone (II). From the elemental composition of these ions ($C_2H_4O_2$ and $C_3H_6O_2$, respectively) it followed that they were produced through a rearrangement process, bringing the two oxygen functions closer together in the daughter than they were in the parent ion. With the use of extensive deuterium labeling the rearrangement mechanism was deduced to be as in Scheme I.

In addition to the oxygen rearrangement summarized in Scheme I, other fragmentation pathways containing rearrangements of heteroatoms have been reported in the mass spectra of such compounds as methylglycosides,[7] β-(alkylthio)propionic acids and esters,[8a] dimethyl esters,[8b] and 1,4-naphthoquinone dimers.[8c] Also, we have recently found that a rearrangement, similar to that reported by Green and Djerassi, occurs in the corresponding α-decalone series,[1] except that in this system charge retention occurred on the more highly substituted hydrocarbon, rather than the oxygen-containing portion of the molecule.

(1) Part CLXXX: R. T. Gray, M. Ikeda, and C. Djerassi, *J. Org. Chem.*, **34**, 4091 (1969).

(2) Financial support from the National Institutes of Health (Grants GM-06840 and AM-04257) is gratefully acknowledged.

(3) (a) Postdoctoral Fellow, 1968–1969; (b) National Institutes of Health Postdoctoral Fellow, 1967–1968.

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967.

(5) P. Brown and C. Djerassi, *Angew. Chem.*, **79**, 481 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(6) M. M. Green, D. S. Weinberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 3883 (1966); M. M. Green and C. Djerassi, *ibid.*, **89**, 5190 (1967).

(7) K. Heyns and D. Müller, *Tetrahedron*, **21**, 55 (1965); *Tetrahedron Lett.*, No. 4, 449 (1966); N. K. Kochetkov and O. S. Chizhov, *Tetrahedron*, **21**, 2029 (1965).

(8) (a) S.-O. Lawesson, L. Dalgaard, J. O. Madsen, J. H. Bowie, and D. B. Cobb, *Chem. Commun.*, 218 (1969); (b) I. Howe and D. H. Williams, *J. Chem. Soc.*, 202 (1968); (c) J. Dekker and D. P. Venter, *J. Amer. Chem. Soc.*, **90**, 1225 (1968).

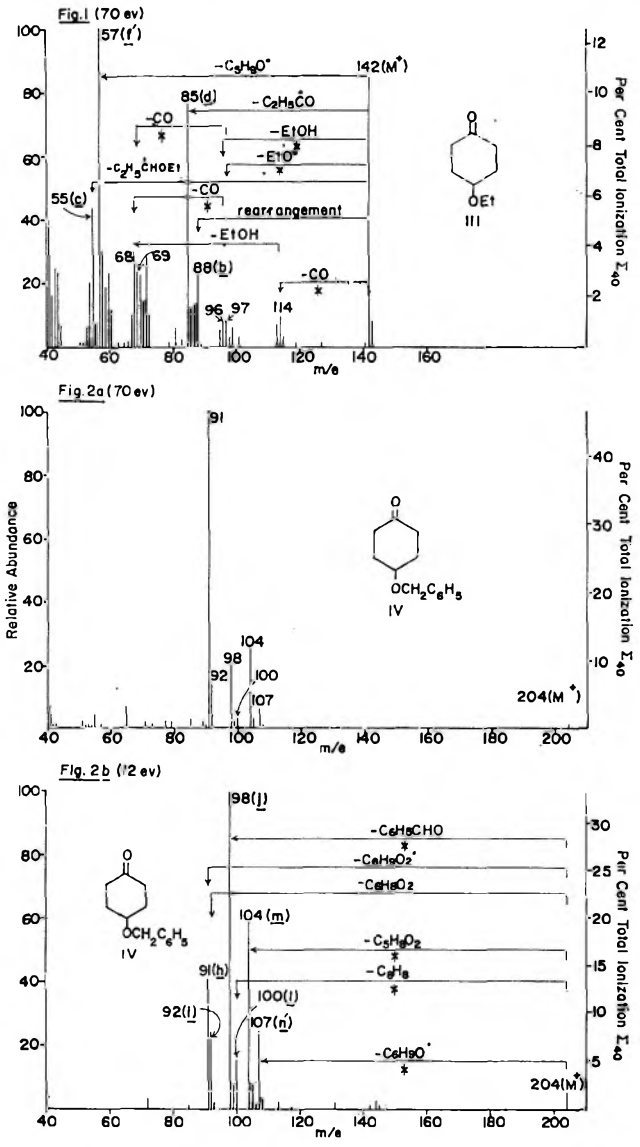
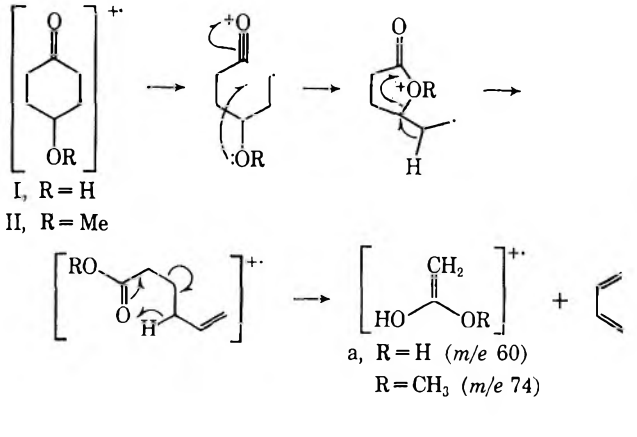


Figure 1.—Mass spectrum of 4-ethoxycyclohexanone (III).
Figure 2.—Mass spectrum of 4-benzyloxycyclohexanone (IV): (a) at 70 eV; (b) at 12 eV.

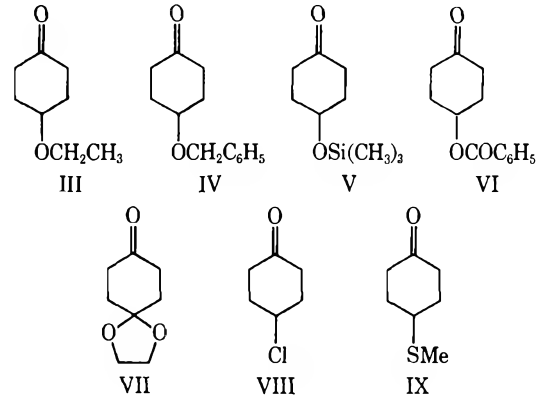
It is evident from Scheme I that the lone pair of electrons on the oxygen atom is attributed a leading role in the formation of fragment ion a. Hence, in an attempt to determine the scope and limitations of such a rearrangement process, we have undertaken a mass spectral investigation of a series of other 4-substituted cyclohexanones. Each of these compounds contains a heteroatom directly attached to the 4 position of the ring, giving the possibility for a transannular interaction such as found in the spectra of I and II. Principal emphasis has been placed on those fragmentations which appear to be triggered by the functional groups in each molecule and to examine what effect, if any, one group exerted on another. In those cases where such an interaction is evident, it has been useful to measure also the mass spectra of isotopically labeled analogs of the parent compounds in order to determine the specificity of bond cleavage and migration in such fragmentation pathways.

SCHEME I



Results and Discussion

To determine the generality of electron impact induced transannular interaction between two remote[9] functional groups, such as that found in the mass spectra of 4-hydroxy- and 4-methoxycyclohexanone (I and II), we have synthesized the following series of analogous compounds (III–IX).



As a simple extension of our earlier work,[6] 4-ethoxycyclohexanone (III) was prepared. It seemed reasonable to expect a functional-group interaction between the ethoxyl and carbonyl groups, especially since an important electron impact induced rearrangement process had been found in the mass spectrum of 4-ethoxy-1-decalone.[1] The spectrum (Figure 1)[10] of III shows a peak of 23% relative abundance at *m/e* 88, which corresponds to the oxygen rearrangement peak at *m/e* 74 (a in Scheme I) from the methylated analog II. High-resolution measurements indeed show this fragment ion to have the elemental composition $C_4H_8O_2$,[11] indicating that a transannular interaction of the two functionalities must be occurring, albeit to a smaller extent than in compounds I and II. Conclusive evidence for such a rearrangement was obtained from the mass spectra of 4-d_1-4-ethoxycyclohexanone (X) and 1′,1′-d_2-4-ethoxycyclohexanone (XI). As shown in Table I, this fragment ion is divided

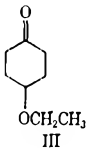
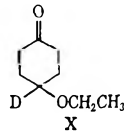
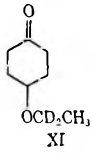
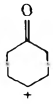
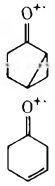
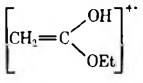
(9) "Remote" is meant to designate numbers of bonds rather than spatial relationships.

(10) All mass spectra were measured at both 12 and 70 eV. Unless otherwise stated, however, the spectra discussed in the text are those obtained at 70 eV.

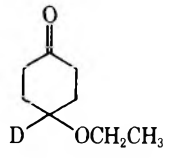
(11) The composition of all relevant peaks were determined by high-resolution measurements.

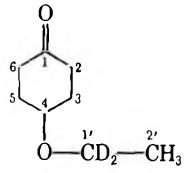
TABLE I

m/e VALUES FOR VARIOUS FRAGMENT IONS OF 4-ETHOXYCYCLOHEXANONE (III) AND DEUTERATED DERIVATIVES (PER CENT RELATIVE ABUNDANCE)

	M+	M − EtO·	M − EtOH	$C_4H_8O_2$	C_5H_9O	C_3H_9	C_3H_8	C_3H_5O	C_3H_3[a]
 III	142 (85)	97 (8)	96 (8)	88 (23)	85 (76)	69 (22)	68 (30)	57 (100)	55 (22)
 X [b]	143 (100)	98 (11)	97 (9)	88 (26)[c] 89 (9)	86 (92)	70 (54)	69 (33)	58 (98)	55 (26)
 XI [d]	144 (100)	97 (9)	96 (10)	90 (20)	87 (76)	69 (21)	68 (31)	57 (92)	55 (21)
Proposed structure in parent	Molecular ion	 							

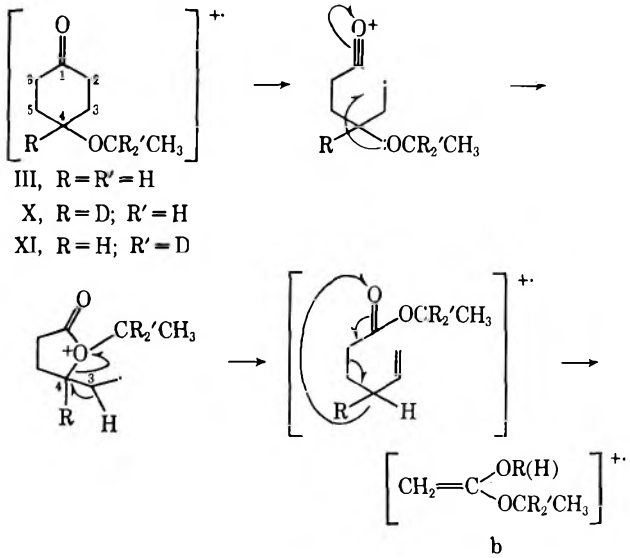
[a] By high-resolution the fragment ion at *m/e* 55 consists of C_3H_3O and C_4H_7. Only the relative abundance of the oxygenated portion is given here. [b] 98% d_1, 2% d_0. [c] By high resolution, the *m/e* 88 peak contains some $C_5H_{10}DO$; see text. [d] 97% d_2, 3% d_1 by mass spectrometry.


X


XI

between *m/e* 88 and 89 for X, as expected from a mechanism as shown in Scheme II. That this splitting does not give an equal abundance of ions at *m/e* 88 and 89 in X is due entirely to the fact that the peak at *m/e* 87 (100% $C_5H_{11}O$) in III has also shifted, at least in part, to *m/e* 88 ($C_4H_8O_2$, 58%; C_5H_{10} DO, 42%) in the spectrum of X. As expected from the proposed mechanism, retention of both deuterium atoms is quantitative (*m/e* 88 → 90) in the spectrum of XI.

SCHEME II

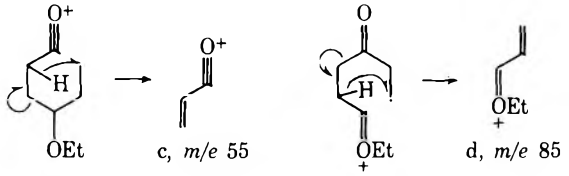


III, R = R′ = H
X, R = D; R′ = H
XI, R = H; R′ = D

b

III, *m/e* 88
X, *m/e* 88, 89
XI, *m/e* 90

As shown in Table II most of the other major peaks in the mass spectrum of III are derived from fragmentation pathways associated with the independent functionalities. For example, cleavage α to both the carbonyl and the ethoxyl functions are important processes, leading to the expected fragment ions c and d, respectively.

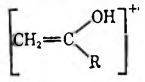

c, *m/e* 55 d, *m/e* 85

Of notable interest is the base peak of the spectrum at *m/e* 57 (100% C_3H_5O[11]). To understand the mechanism of its formation it is important to know which oxygen atom is bearing the charge in the fragment ion. Although no metastable ions are observed for its formation, the relative shifts of this peak in the spectra of the isotopically labeled compounds give unambiguous information concerning its genesis. Deuteration at C-4 (X) results (Table I) in a shift to *m/e* 58, an observation which may be explained by two different mechanisms.

The first possibility, as shown in Scheme III, would involve loss of a methyl radical from the alkoxy group to give the stable oxonium ion e. Similar fragmentations

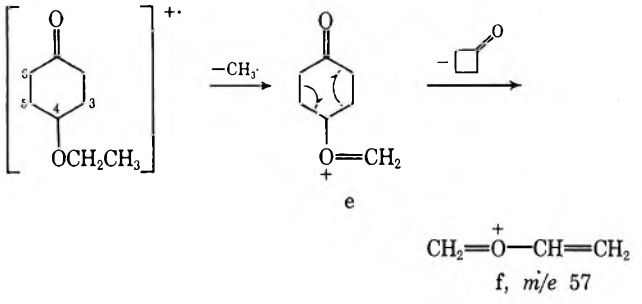
TABLE II

CHARACTERISTIC MASS SPECTRAL PEAKS IN THE SPECTRA OF 4-SUBSTITUTED CYCLOHEXANONES (PER CENT RELATIVE ABUNDANCE)

Peak	R = OH[a]	R = OMe[a]	R = OEt	R = OBz	R = $OSi(CH_3)_3$	R = $OCOC_6H_5$	R =	R = Cl	R = SMe
M^+	114 (100)	128 (82)	142 (85)	204 (1)	186 (18)	218 (<1)	156 (4)	132 (21), 134	144 (100)
M − R·	97 (2)	97 (8)	97 (8)	...	97 (1)	97 (6)	...	97 (12)	97 (19)
M − RH	96 (17)	96 (14)	96 (8)	...	96 (3)	96 (64)	...	96 (6)	96 (17)
M − (R· + CO)	69 (20)	69 (24)	69 (23)	...	...	69 (1)	...	69 (10)	69 (34)
M − (RH + CO)	68 (34)	68 (60)	68 (30)	...	...	68 (18)	...	68 (18)	68 (18)
M − CO	86 (4)	100 (6)	114 (9)	...	158 (2)	...	...	104, 106 (2)	116 (8)
	60 (83)	74 (100)	88 (23)	...	...	...	...	...	...
 *b*	55 (84)	55 (38)	55 (22)	55 (4)	55 (9)	55 (5)	55 (14)	55 (100)	55 (32)
	57 (69)	71 (93)	85 (76)	...	129 (46)	...	99 (100)	75, 77 (2)	87 (23)

[a] From the mass spectra of these compounds described in ref 6. [b] See Table I, footnote *a*.

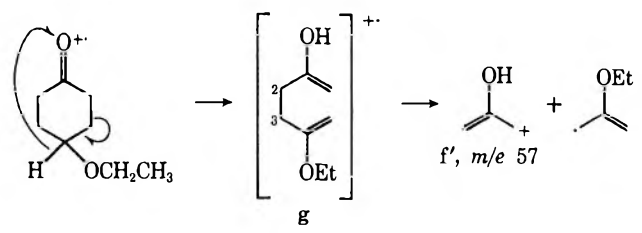
SCHEME III



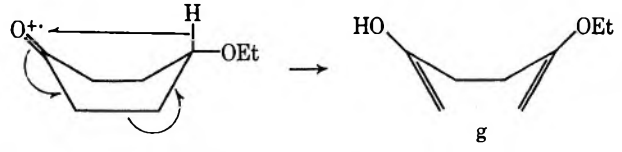
have been observed in straight-chain ethyl ethers,[12] and a minute M − 15 peak is observed in Figure 1. Scission of the 3–4 and 5–6 bonds, followed by loss of the elements of cyclobutanone, would then result in the stable ion f at *m/e* 57.

A second mechanism (Scheme IV) might involve ionization of the ketone function, followed by a six-centered McLafferty-type rearrangement of the hydrogen atom at C-4, to give species g. Cleavage of the 2–3 bond would then result in the stabilized allylic carbonium ion f′.

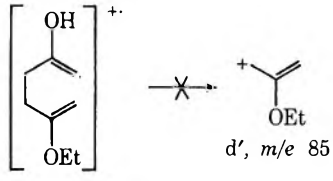
SCHEME IV



The validity of each mechanism may be tested by inspection of the mass spectrum (Table I) of 1′,1′-d_2-4-ethoxycyclohexanone (XI). According to Scheme III, the peak at *m/e* 57 in Figure 1 should shift by two mass units to *m/e* 59. In fact it remains exclusively at *m/e* 57, thus confirming Scheme IV as a plausible representation of this fragmentation pathway. For such an initial hydrogen transfer (Scheme IV) to take place, it appears from an inspection of molecular models for III that the molecule must be in a boat or twist conformation.



Also, it is apparent that the charge must remain with the carbonyl function throughout the fragmentation route. This conclusion is reached on the basis that if any charge distribution between the two oxygen atoms occurred during this sequence, a fragment ion at *m/e* 85 would result, with the charge localized on the ether oxygen. This fragment has the same mass value as that formed by simple cleavage α to the ether function,



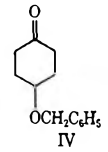
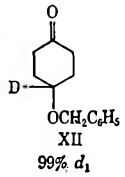
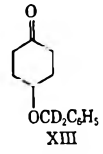
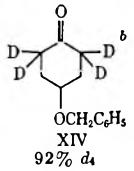
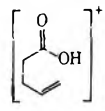
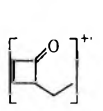
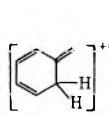
as described above. However, if any part of the abundant fragment ion at *m/e* 85 were formed by this mechanism, deuteration at C-4 in III would not effect its position. In fact it shifts completely to *m/e* 86 in the spectrum of X (Table I), indicating its formation to be exclusively by way of the simple α-cleavage pathway.

The data contained in Figure 1 and Table I thus demonstrate that 4-ethoxycyclohexanone (III) does exhibit some remote group interaction between the two functionalities, but its occurrence is considerably

(12) Reference 4, p 228.

TABLE III

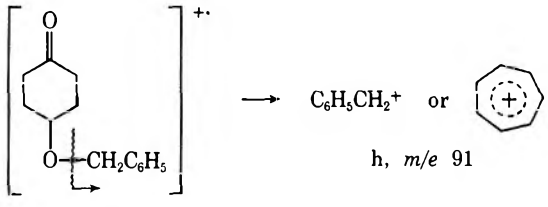
PRINCIPAL FRAGMENT IONS IN THE MASS SPECTRA OF 4-BENZYLOXYCYCLOHEXANONE AND ITS DEUTERATED DERIVATIVES AT 12 eV (PER CENT RELATIVE ABUNDANCE)[a]

Compd	M+	C_7H_7O	C_8H_8	$C_5H_8O_2$	$C_6H_{10}O$	C_7H_8	C_7H_7
 IV	204 (5)	107 (24)	104 (59)	100 (15)	98 (100)	92 (21)	91 (41)
 XII 99% d_1	205 (7)	107 (29)	104 (60)	101 (15)	99 (100)	93 (13)	91 (38)
 XIII 96% d_2	206 (14)	108 (16) 109 (26)	105 (76) 106 (54)	100 (44) 101 (24)	98 (11) 99 (100)	94 (56)	93 (48)
 XIV 92% d_4	208 (36)	107 (33) 108 (47)	106 (40) 104 (15)[e]	102 (100)[c] 104 (15)[e]	101 (94) 102 (100)[d]	92 (49)[d]	91 (8) 92 (49)[d]
Proposed structure in parent	Molecular ion $C_6H_5CH{=}\overset{+}{O}H$	$[C_6H_5CH{=}CH_2]^{+\cdot}$					

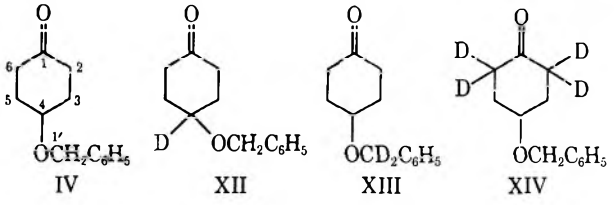
[a] Although 12 eV is a "nominal" low voltage, attempts have been made to keep the ionizing voltage constant. [b] This spectrum was measured on the Atlas CH-4 spectrometer. [c] Includes contributions from $C_5H_6D_2O_2$ and $C_6H_6D_4O$. [d] Includes contributions from C_7H_6D and C_7H_8. [e] Includes contributions from $C_6H_4D_4O_2$ and C_8H_8.

smaller than in the corresponding hydroxy (I) and methoxy (II) analogs. In order to explore further the scope and extent of this transannular migration, we have investigated the mass spectral properties of 4-benzyloxycyclohexanone (IV).

At high voltage the mass spectra of compounds containing benzyl groups are usually dominated by the highly stabilized benzyl or tropylium ion,[13] and indeed 4-benzyloxycyclohexanone is no exception to this rule. At 70 eV (Figure 2a) the fragment ion at *m/e* 91 (h) carries nearly 50% of the total ionizing current.



The fragmentation pattern changes dramatically at low voltages (Figure 2b). The ion at *m/e* 91 decreases in intensity, and peaks at *m/e* 92 (C_7H_8), 98 ($C_6H_{10}O$), 100 ($C_5H_8O_2$), 104 (C_8H_8), and 107 (C_7H_7O) become significant in the spectrum. Of special significance are the fragment ions at *m/e* 100 and 104, since they must be formed through one or more skeletal rearrangement processes. In order to determine the specificity of bond cleavage in the major fragmentation pathways, we have synthesized the labeled compounds XII, XIII, and XIV.



As shown in Table III, several of the peaks observed in the mass spectrum of IV are derived from fragmentations associated with the phenyl ring.[14] In fact (Table II) very few of the navigable pathways usually taken by 4-substituted cyclohexanones after electron impact are followed by this compound. Even the ubiquitous fragment ion at *m/e* 55, originating from the usually facile cleavage α to the ketone function, is very small in this instance (4% relative abundance).

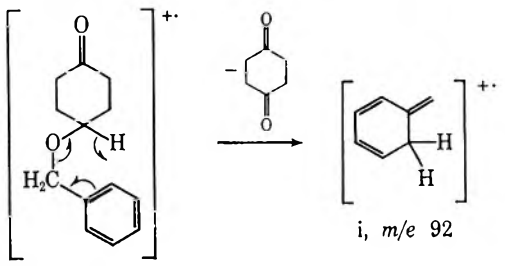
The fragment ion at *m/e* 92 (Figure 2a) is commonly observed in benzyl derivatives containing a γ proton[15] and is derived from a six-centered hydrogen transfer of this proton to the benzene ring (Scheme V). That

(13) Reference 4, p 248.

(14) This is not too surprising, since the ionization potential associated with the benzyl moiety (8.85 eV for benzyl methyl ether, is less than that for cyclohexanone (9.14 eV). For a compilation of ionization potentials see R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965.

(15) Reference 4, p 247.

SCHEME V

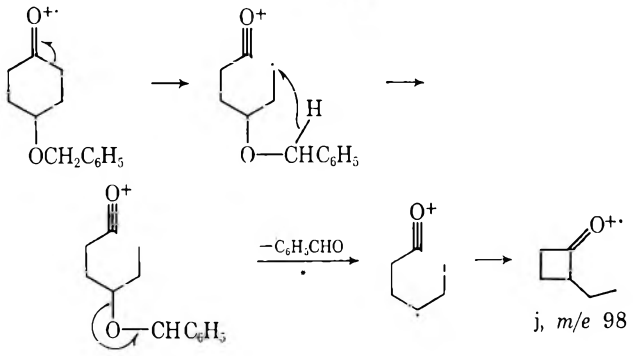


i, *m/e* 92

this rearrangement is completely site-specific for IV is shown unambiguously by the fact that the peak is shifted quantitatively to *m/e* 93 in the mass spectrum of 4-d_1-4-benzyloxycyclohexanone (XII, see Table III), and occurs exclusively at *m/e* 94 in the spectrum of the 1′,1′-d_2 analog (XIII).

The base peak of the low-voltage spectrum (Figure 2b) occurs at *m/e* 98 and corresponds formally to the molecular ion of cyclohexanone. According to the labeling data (Table III), a hydrogen atom is transferred from the benzyl position to the ring, with concomitant loss of benzaldehyde. A possible mechanism for this fragmentation is shown in Scheme VI. Initial

SCHEME VI

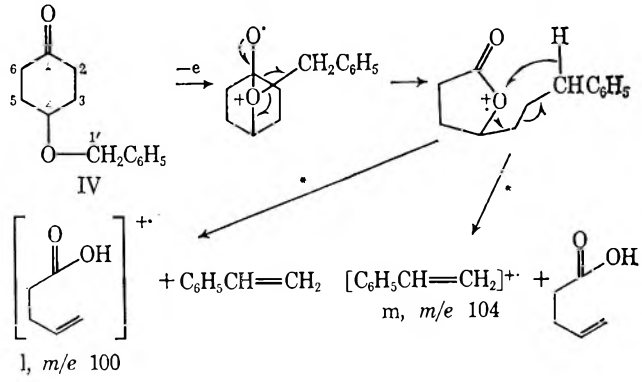


j, *m/e* 98

ionization of the ketone function, followed by a six-centered hydrogen transfer, would give a stabilized benzyl radical, which could decompose further, with generation of benzaldehyde, to yield ionized 2-ethylcyclobutanone (j) as the final product. The corresponding ion from 2,2,6,6-d_4-4-benzyloxycyclohexanone (XIV) is split between *m/e* 101 and 102 (Table III), and that from XIII between *m/e* 98 and 99. One possible explanation for these facts is deuterium scrambling between the benzyl and the α positions in the molecular ion prior to the decomposition, analogous to that observed in 2,2,6,6-d_4-4-methoxycyclohexanone[6,16] and 3,3,5,5-d_4-cyclohexanol.[17] The consequences of this phenomenon will be discussed below in relation to the other major ions observed in the mass spectrum of this compound.

As indicated earlier, peaks at *m/e* 100 ($C_5H_8O_2$) and 104 (C_8H_8), whose masses and elemental compositions together equal those of the molecular ion, must necessarily be formed through a rearrangement process. From a consideration of the corresponding peaks (Table III) in the spectra of the labeled compounds, it is apparent that these two fragments arise in the same process, with charge retention on each fragment. Indeed, the most satisfactory mechanism (Scheme VII) accounting for the available data leads to struc-

SCHEME VII



IV

l, *m/e* 100

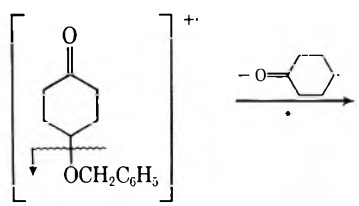
m, *m/e* 104

tures for these two fragments which are both capable of supporting the ionizing charge.

Since the peak (*m/e* 104 in Figure 2) corresponding to ionized styrene remains unlabeled in the spectrum of the 4-d_1 analog (XII), the possibility of a 1,2-benzyl or a 1,3-phenyl migration may be eliminated from any mechanistic considerations. The corresponding peak in the 1′,1′-d_2-4-benzyloxycyclohexanone (XIII) spectrum is split unevenly (3:2) between *m/e* 105 and 106, confirming a benzyl migration and suggesting that, to a large extent, one deuterium is lost from the benzyl position along the fragmentation route. The residue at *m/e* 106 may be accounted for by invoking deuterium scrambling prior to fragmentation. Similarly, the corresponding peak in XIV occurs predominantly at *m/e* 106 (Table III), suggesting the participation of C-2 (C-6) in the rearrangement pathway. A possible mechanism for these observations is shown in Scheme VII.

A transannular interaction between the two functional groups, similar to that observed in the 4-hydroxy- (I) and 4-alkoxy- (II, III) cyclohexanones, is postulated as the initial step, followed by cleavage of the 1–2 bond and rearrangement of the benzyl group to C-2. Hydrogen transfer in a six-centered transition state then gives two species, an unsaturated acid (l) and styrene (m), both capable of supporting the ionizing charge. Except for the small fragment ion at *m/e* 104 in the spectrum of the 2,2,6,6-d_4 analog (XIV), which may be formed by another, more subtle pathway, this mechanism accommodates all the available data from the labeled compounds.

The last significant peak in the low-voltage spectrum (Figure 2b) of IV occurs at *m/e* 107 (C_7H_7O), and is



n n′

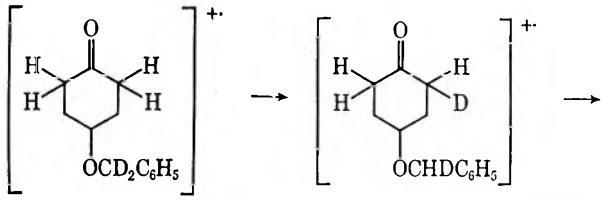
m/e 107

(16) Green[6] has postulated that a similar process was in effect before decomposition of the molecular ion of 2,2,6,6-d_4-4-methoxycyclohexanone.

(17) H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 158 (1964).

probably derived by simple cleavage of the benzyloxy group from the ring, with charge retention on the aromatic moiety. Although the formal structure of this fragment would be n, a more plausible representation may be n′. The labeling data supports such a mechanism (Table III), but even for this simple cleavage, it is apparent that some scrambling occurs prior to fragmentation, since peaks at *m/e* 109 and 108, in about a 2:1 ratio, are observed in the spectrum of the 1′,1′-d_2 analog (XIII). Scheme VIII outlines how such a process could give rise to *m/e* 108 from XIII.[16]

SCHEME VIII



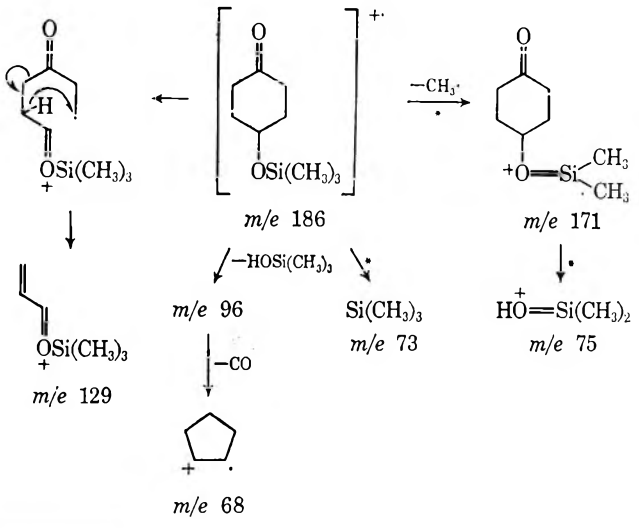
$[C_6H_5CHDO]^+$
n″, *m/e* 108

In order to define further the scope of these remote group interactions, it was decided to examine next the effect on the mass spectra of changing the type of group attached to the oxygen at the 4 position of a cyclohexanone ring, as well as of replacing the oxygen by other heteroatoms bearing a lone pair of electrons.

To investigate the first point we have measured the mass spectra of cyclohexanone-4-trimethylsilyl ether (V),[18] 4-benzoyloxycyclohexanone (VI),[19] and 1,4-cyclohexanedione monoethylene ketal (VII). In none of the spectra was there evidence of an electron impact induced rearrangement process. In fact, the major fragmentation patterns are those expected from the individual groups in the corresponding monofunctionalized molecules (Table II).

The spectrum of V (Figure 3) is relatively uncomplicated, and possible routes to the major fragment ions are shown in Scheme IX. The absence of any obvious rearrangement processes is very striking, in view of the

SCHEME IX



(18) This compound was made in these laboratories by Dr. J. Diekman.
(19) Synthesized by Dr. M. M. Green.

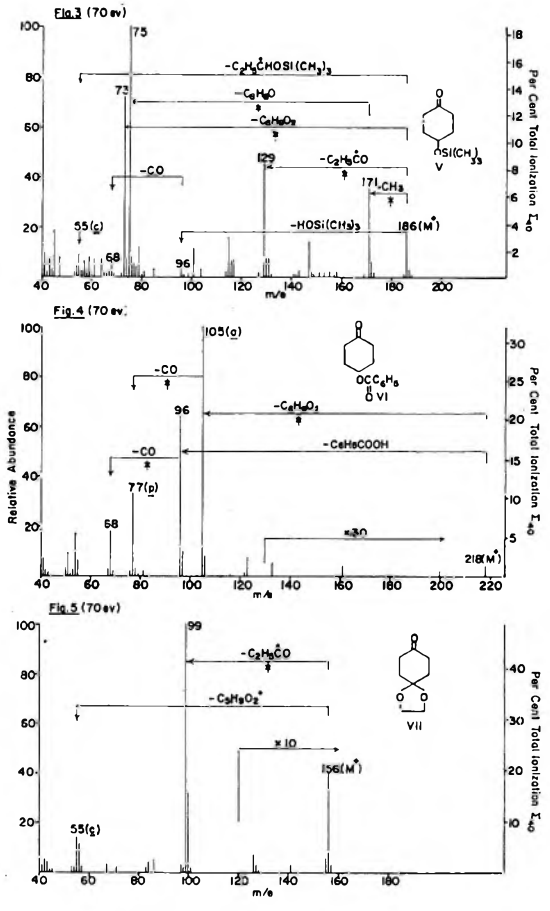
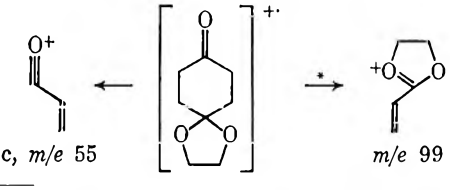


Figure 3.—Mass spectrum of cyclohexanone-4-trimethylsilyl ether (V).
Figure 4.—Mass spectrum of 4-benzoyloxycyclohexanone (VI).
Figure 5.—Mass spectrum of 1,4-cyclohexanedione monoethylene ketal (VII).

copious number of such fragmentations found in the mass spectra of other trimethylsilyl derivatives.[20]

Although the ionization potentials of the two functional groups are similar,[21] the major navigable pathways in the fragmentation (Figure 4) of 4-benzoyloxycyclohexanone (VI) are directed by the ester grouping and are in fact quite characteristic of simple benzoic acid esters[22] (see *m/e* 105 and 77). The other major peaks at *m/e* 96 and 68 are derived from loss of benzoic acid, followed by elimination of carbon monoxide, as shown in Scheme X.

In a similar way the mass spectrum (Figure 5) of cyclohexanedione monethylene ketal (VII) is dominated by fragmentations triggered by initial ionization of the ketal moiety (Σ_{40} = 49% for *m/e* 99). In fact,



c, *m/e* 55 *m/e* 99

(20) For examples, see (a) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967); **33**, 2271 (1968); (b) P. Capella and C. M. Zorzut, *Anal. Chem.*, **40**, 1458 (1968); (c) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968).
(21) The ionization potential of methyl benzoate (10.0 eV) is higher than that of cyclohexanone (9.14 eV) (see ref 14). However, the relative stability of the product ions and radicals probably determine the navigability of each fragmentation pathway for this compound.
(22) Reference 4, p 197.

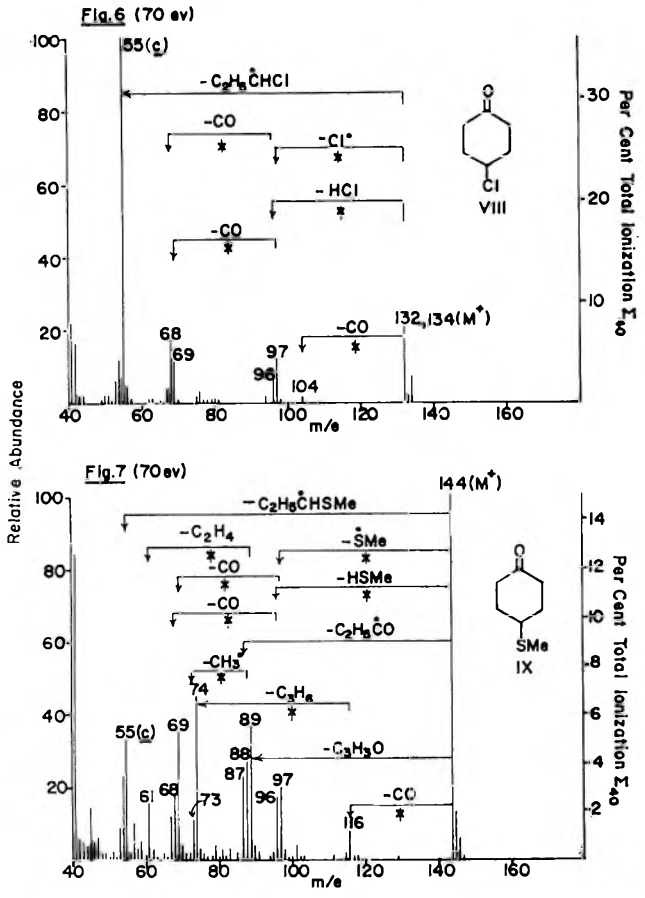
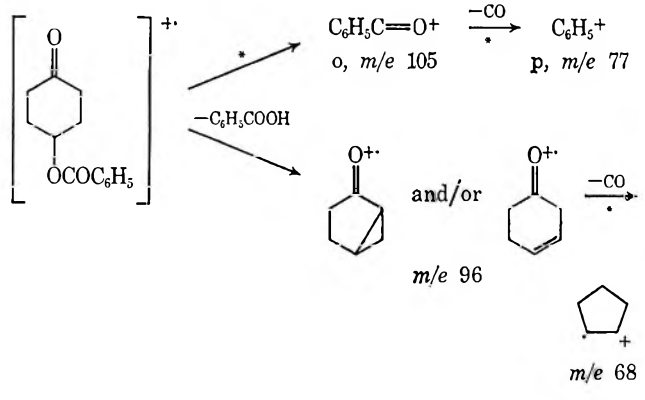


Figure 6.—Mass spectrum of 4-chlorocyclohexanone (VIII).
Figure 7.—Mass spectrum of 4-thiomethylcyclohexanone (IX).

SCHEME X

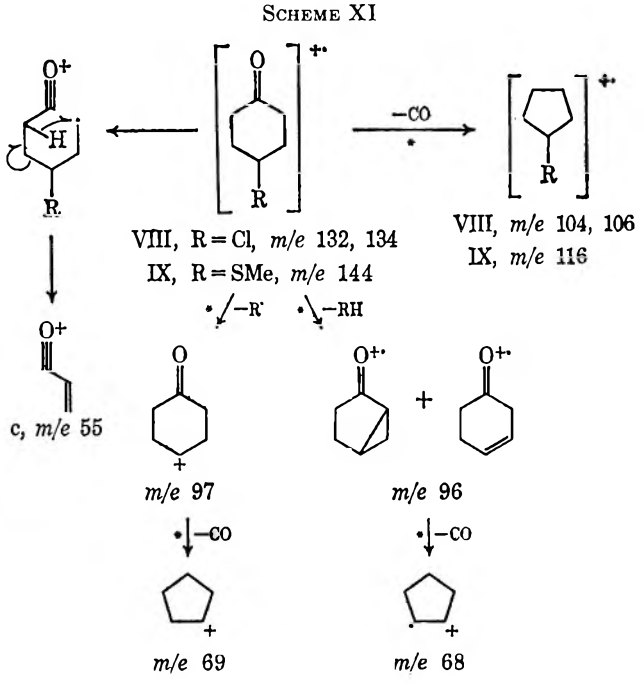


the corresponding ion from initial ionization of the ketone function (c, *m/e* 55) is responsible for only 6.9% of the same current at 70 eV. These results are in full agreement with earlier observations that ionization of the ketal function dominates the mass spectra of most compounds in which it is present.[23]

We have also examined the mass spectra of 4-chlorocyclohexanone (VIII) and 4-thiomethylcyclohexanone (IX), to see if any transannular interaction occurs between a ketone group and a heteroatom other than oxygen. Apparently there are no such rearrangements among the electron impact induced fragmentations observed for these compounds. Instead, the modes of bond cleavage and charge retention are very similar for both compounds (Scheme XI), indicating that ionization around the ketone function can be visualized as the trigger for most of the decompositions.

As can be seen in Table II and Figure 6, important bond cleavages for VIII involve expulsion of a chlorine radical and hydrogen chloride, followed by elimination of carbon monoxide in each case to yield ions at *m/e* 69 and 68, respectively. As may be expected from a comparison of the ionization potentials of cyclohexanone (9.14 eV) and of ethyl chloride (*ca.* 11.0 eV),[24] the base peak of this compound, as for cyclohexanone itself,[25] occurs at *m/e* 55 and carries 36.1% of the total ionizing current.

SCHEME XI



In addition to those fragmentations shown in Scheme XI, the mass spectrum (Figure 7) of 4-thiomethylcyclohexanone (IX) contains evidence for fragment ions in which charge retention is on the sulfur atom. This is not too surprising, since, on the basis of a comparison of the ionization potentials of the two functionalities,[26] initial ionization of IX may actually occur on the thiomethyl group. High-resolution measurements and metastable ion data form the basis for the suggested decomposition paths summarized in Scheme XII.

Worthy of special note are the fragment ions at *m/e* 74 and 87 in Figure 7, because their genesis is apparently quite similar to that of the corresponding ions in the alkoxy series. However, since no fragment ions resulting from rearrangement processes are observed, it can be seen that the ability of a heteroatom to use its lone pair of electrons to initiate a fragmentation pathway is not a prerequisite for transannular interaction with another functional group. In fact, a more plausible basis for prediction of the major fragmentation pathways of 4-substituted cyclohexanones is a comparison of the relative ionization

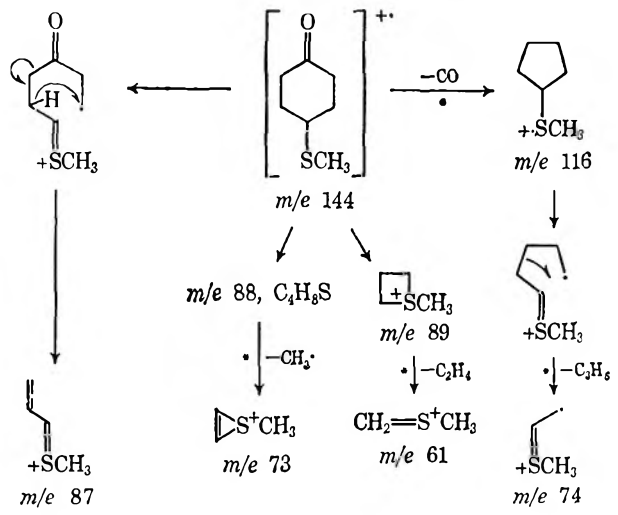
(23) Reference 4, p 265.

(24) R. I. Reed, "Ion Production by Electron Impact," Academic Press, New York, N. Y., 1962, p 9.

(25) D. H. Williams, H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 166 (1964).

(26) The ionization potential of methyl isopropyl sulfide (8.7 eV, see ref 14) is in fact lower than that of cyclohexanone (9.14 eV).

SCHEME XII

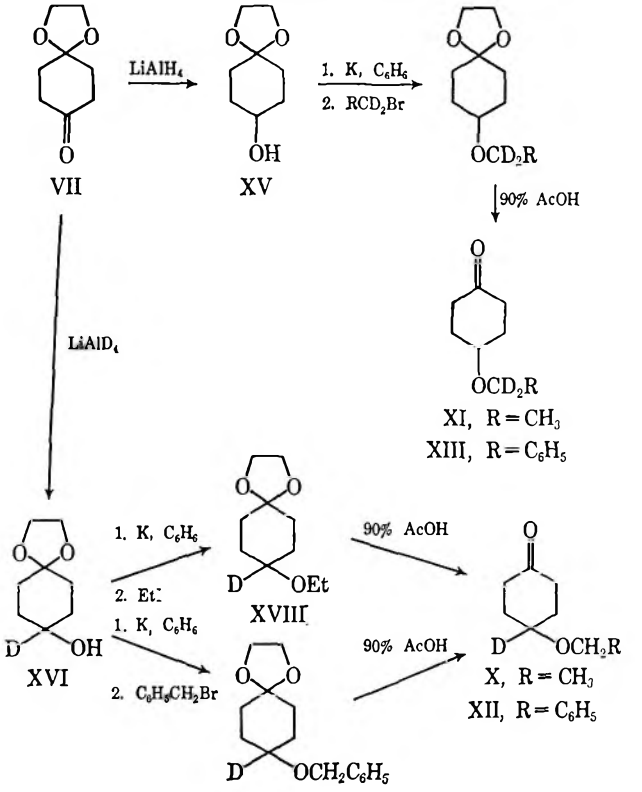


potentials of the two functionalities, which in turn govern the position of initial ionization after electron impact.

Synthesis of Labeled Compounds.—For this investigation it was necessary to synthesize one compound with deuterium at the activated 2 and 6 positions, and others labeled at the "nonactivated" 1′ and 4 positions of the cyclohexanone ring.

Using a previously described procedure,[1,6] the former compound (XIV) was prepared by repeated equilibration of the parent ketone with sodium in a mixture of deuteriomethanol and deuterium oxide. A suitable precursor to 4-substituted cyclohexanones with a deuterium at C-1′ (XI and XIII) and C-4 (X and XII) proved to be 1,4-cyclohexanedione monoethylene ketal (VII), which in turn was prepared from 1,4-cyclohexanediol (see Experimental Section). The overall reaction pathway is shown in Scheme XIII.

SCHEME XIII



Experimental Section

Low-resolution mass spectra were measured by Mr. R. G. Ross using an A.E.I. MS-9 double-focussing spectrometer, and by Mr. R. Conover using an Atlas CH-4 spectrometer. High-resolution measurements with the MS-9 spectrometer were obtained by Mr. R. G. Ross. All compounds for mass spectral analysis were purified and checked for purity by vpc. The column used in each purification was 5% SE-30 on Chromosorb W (5 ft × 0.25 in.). The oven temperature varied between 110 and 140°.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 spectrophotometer, and elemental analyses were done by Mr. S. Meier and Mr. J. Consul of the Stanford microanalytical laboratory.

4-Benzoyloxycyclohexanone (VI)[19] and 4-hydroxycyclohexanone (I) were prepared according to the method of Jones and Sondheimer.[27] Compound VI was thus obtained as a white, crystalline solid, mp 59–61° (lit.[27] mp 63°).

Anal. Calcd for $C_{13}H_{14}O_3$: mol wt, 218. Found: mol wt, 218 (mass spectrum).

4-Hydroxycyclohexanone Ethylene Ketal (XV) and 1,4-Cyclohexanedione Monoethylene Ketal (VII).—Using a previously described procedure,[28] from 16 g (0.14 mol) of I and 9.3 g of ethylene glycol was obtained 8 g (36%) of XV as a colorless oil.

Following the procedure of Prins,[29] oxidation of 3.5 g (0.022 mol) of XV with chromium trioxide in pyridine gave a good yield of VII as colorless prisms, mp 65–67° (lit.[29] mp 72–73°).

Anal. Calcd for $C_8H_{12}O_3$: mol wt, 156. Found: mol wt, 156 (mass spectrum).

4-Ethoxycyclohexanone (III).—A mixture of 190 mg (0.0012 mol) of XV and 150 mg (0.0038 g-atom) of potassium metal in 10 ml of dry benzene was heated at reflux under nitrogen for 18 hr. To this solution was added 5 ml of ethyl iodide all at once, and the mixture was heated for a further 6 hr. After cooling, methanol was added, followed by water and ether. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated, giving **4-ethoxycyclohexanone ethylene ketal** (200 mg, 100%) as a pale yellow oil.

A solution of this total product in 5 ml of 90% acetic acid was heated at 60° for 17 hr when water (5 ml) and ether (20 ml) were added. The organic layer was then separated, washed successively with saturated Na_2CO_3 solution (three times) and water, dried ($MgSO_4$), and evaporated, giving 140 mg (60%) of III as a pale yellow oil: ir (film) 1720 (C=O) and 1120 cm^{-1} (COC); mass spectrum *m/e* 142 M^+).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.44; H, 9.91.

4-d_1-Ethoxycyclohexanone (X).—To a stirred suspension of 100 mg (0.0024 mol) of lithium aluminum deuteride (Roth Chemicals) in 5 ml of dry ether was added a solution of 100 mg (0.64 mmol) of VII in 5 ml of ether. The mixture was heated at reflux for 2 hr, when excess deuteride was destroyed with saturated Na_2SO_4 solution. After filtration and evaporation there was obtained 100 mg (98%) of **4-d_1-4-hydroxycyclohexanone ethylene ketal** (XVI) as a colorless oil.

Following a procedure similar to that described above for the preparation of III, deketalization of this total product gave 85 mg (92% from VII) of X as a pale yellow oil. Mass spectral analysis showed that the compound consisted of the d_1 (98%) and d_0 (2%) species.

Anal. Calcd for $C_8H_{13}DO_2$: mol wt, 143. Found: mol wt, 143 (mass spectrum).

1′,1′-d_2-4-Ethoxycyclohexanone (XI).—Using the same procedure as that described above for III, from 115 mg (0.74 mmol) of XV, 110 mg (0.0028 g-atom) of potassium metal, and 2 ml of 1,1-d_2-ethyl bromide,[30] there was obtained 75 mg (81% from XV)

(27) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).
(28) H. Plieninger and H. J. Grasshoff, *Chem. Ber.*, **90**, 1973 (1957).
(29) D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957).
(30) This compound was prepared in 54% overall yield by reduction of acetic acid with lithium aluminum deuteride in diglyme [L. Friedman and A. T. Jurewicz, *J. Org. Chem.*, **33**, 1254 (1968)], followed by treatment of the resulting alcohol with bromine and triphenylphosphine in DMF [G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964)].

of XI as a pale yellow oil. A pure sample was obtained by vpc and consisted of 97% d_2 and 3% d_1 species by mass spectrometry.

Anal. Calcd for $C_8H_{12}D_2O_2$: mol wt, 144. Found: mol wt, 144 (mass spectrum).

4-Benzyloxycyclohexanone (IV)[29] and Its 2,2,6,6-d_4 Analog (XIV).—Using a similar preparative procedure to that described above for the synthesis of III, from 200 mg (0.0013 mol) of XV, 150 mg (0.0038 g-atom) of potassium metal, and 350 mg (0.0021 mol) of benzyl bromide there was obtained an oily residue. After the total product had been heated in 10 ml of 90% acetic acid at 60° for 18 hr, a conventional work-up gave 250 mg of a mixture of three major components. Separation was accomplished by vpc, giving IV as a colorless oil: ir (film) 1720 (C=O) and 1110 cm^{-1} (COC); mass spectrum m/e 204 (M^+).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 8.00.

Using a procedure described earlier,[1,6] four repeated equilibrations of a portion of IV with 2 ml of a standard solution of sodium metal (75 mg) in deuteriomethanol (4.5 ml) and deuterium oxide (1.5 ml) gave a good return of XIV. Mass spectral analysis indicated a mixture of the d_4 (92%) and d_3 (8%) species.

Anal. Calcd for $C_{13}H_{12}D_4O_2$: mol wt, 208. Found: mol wt, 208 (mass spectrum).

4-d_1-4-Benzyloxycyclohexanone (XII).—Using a procedure similar to that described for X, from 100 mg (0.64 mmol) of 4-d_1-4-hydroxycyclohexanone ethylene ketal (XVI), 80 mg (0.0020 g-atom) of potassium metal, and 190 mg (0.0012 mol) of benzyl bromide there was obtained a yellow oil (150 mg). Deketalization in 90% acetic acid, followed by final purification with vpc, gave XII as a colorless oil, consisting of >99% of the d_1 species by mass spectrometry.

Anal. Calcd for $C_{13}H_{15}DO_2$: mol wt, 205. Found: mol wt, 205 (mass spectrum).

1,1'-d_2-4-Benzyloxycyclohexanone (XIII).—A similar preparative procedure to that described for IV was utilized, except that 1,1-d_2-benzyl bromide[31] was used as the alkylating agent. Final purification by vpc gave XIII (96% d_2, 4% d_1) as a colorless oil.

Anal. Calcd for $C_{13}H_{14}D_2O_2$: mol wt, 206. Found: mol wt, 206 (mass spectrum).

Cyclohexanone-4-trimethylsilyl Ether (V).[18]—Using a previously described procedure,[20a] from 230 mg (0.0020 mol) of I and 0.25 ml of hexamethyldisilazane there was obtained a good yield of V. Final purification with vpc gaveV as a colorless oil.

Anal. Calcd for $C_9H_{18}O_2Si$: mol wt, 186. Found: mol wt, 186 (mass spectrum).

4-Chlorocyclohexanone (VIII).—Utilizing a modification of a previously described procedure,[32] hydrogen chloride gas was passed for 2 hr through 50.76 g (0.52 mol) of 7-oxabicyclo[2.2.1]-heptane maintained at 120°. Vacuum distillation of the product gave a colorless oil which crystallized on cooling. Recrystallization from cyclohexane gave 53.1 g (73%) of 4-chlorocyclohexanol as colorless prisms, mp 84–86° (lit.[32] mp 82–83°).

Oxidation of 2.69 g (0.023 mol) of this product with chromium trioxide in acetone,[33] followed by a conventional work-up procedure, gave 1.89 g (70%) of VIII as a colorless oil, bp 106–107° (16 mm), ir (film) 1715 cm^{-1} (C=O).

Anal. Calcd for C_6H_9ClO: mol wt, 132, 134. Found: mol wt, 132, 134 (mass spectrum).

4-Thiomethylcyclohexanone (IX).—Using a previously described procedure,[34] from 11.81 g (0.102 mol) of quinitol and 16.26 g (0.085 mol) of *p*-toluenesulfonyl chloride there was obtained 20.25 g (74%) of **4-tosyloxycyclohexanol** as a white solid.

Oxidation of 9.7 g (0.036 mol) of this product with chromium trioxide in an acetone–acetic acid mixture[34] gave a good yield of **4-tosyloxycyclohexanone** as a white, crystalline solid, mp 97–98°. Ketalization of 1.88 g (0.007 mol) of this compound with ethylene glycol in benzene, as described earlier for the preparation of XV,[28] gave 2.02 g (94%) of **4-tosyloxycyclohexanone ethylene ketal** as a colorless oil which crystallized on standing. Recrystallization from an ether–pentane mixture gave colorless prisms, mp 69–71°.

Into a mixture of 0.5 g (0.022 g-atom) of sodium metal in 25 ml of DMF was bubbled methyl mercaptan gas until reaction was complete. After passing nitrogen through the system for 10 min, a solution of 1.59 g (0.0051 mol) of 4-tosyloxycyclohexanone ethylene ketal in 5 ml of DMF was slowly added. The mixture was stored in the dark for 116 hr, when a conventional work-up was performed. There was thus obtained 0.60 g (67%) of **4-thiomethylcyclohexanone ethylene ketal** as a pale yellow oil.

Deketalization with 90% acetic acid as described above gave 0.35 g (77%) of IX as a pale yellow oil, ir (film) 1720 cm^{-1} (C=O) mass spectrum m/e 144 M(+).

Anal. Calcd for $C_7H_{12}OS$: C, 58.32; H, 8.33. Found: C, 58.64; H, 8.48.

Registry No.—III, 23510-92-1; IV, 2987-06-6; V, 23510-94-3; VI, 23510-95-4; VII, 4746-97-8; VIII, 21299-26-3; IX, 23510-98-7; X, 23510-99-8; XI, 23511-00-4; XII, 23511-01-5; XIII, 23511-02-6; XIV, 23511-03-7; 4-tosyloxycyclohexanone, 23511-04-8; 4-tosyloxycyclohexanone ethylene ketal, 23511-05-9.

(31) Prepared in 84% overall yield by reduction of ethyl benzoate with lithium aluminum deuteride, followed by treatment of the resulting labeled alcohol with 48% hydrobromic acid, as described by A. F. Gerrard and C. Djerassi *J. Amer. Chem. Soc.*, **91**, 6808 (1969).

(32) E. A. Fehnel, S. Goodyear, and J. Berkowitz, *ibid.*, **73**, 4978 (1951).

(33) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(34) N. A. Nelson and G. A. Mortimer, *ibid.*, **22**, 1146 (1957).

On the Mechanism of the Photoisomerization of 1(2H)-Naphthalenones[1]

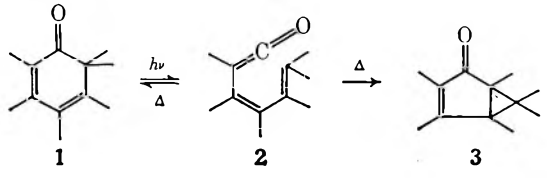
HAROLD HART AND ROGER K. MURRAY, JR.[2]

Department of Chemistry, Michigan State University, East Lansing, Michigan 48823

Received September 2, 1969

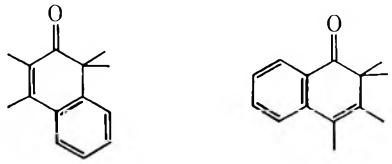
The mechanisms operative in the photoisomerization of 2,2,3,4-tetramethyl-1(2H)-naphthalenone (**5**) to 3,4-benzo-1,5,6,6-tetramethylbicyclo[3.1.0]hexen-2-one (**6**) and in the subsequent photorearrangement of **6** to 2,3,4,4-tetramethyl-1(4H)-naphthalenone (**7**) have been investigated. Irradiation of an ether solution of 2,2,4-trimethyl-1(2H)-naphthalenone (**9**), prepared by the oxidation of 1,2,4-trimethylnaphthalene with peroxytrifluoroacetic acid–boron fluoride etherate, provided 3,4,4-trimethyl-1(4H)-naphthalenone (**14**). This result strongly suggests that the photorearrangement of naphthalenone **5** to benzobicyclic ketone **6** proceeds by a "bond-crossing" mechanism, and does not involve alkyl migration. Photolysis of a hexane solution of napthalenone **5** containing dimethylamine gave **6**. Irradiation of a solution of **5** in methanol afforded naphthalenone **7** *via* **6**. These results suggest that ketene **8** is not involved in the photoisomerization of **5** to **6**. Irradiation of an ether solution of 4-ethyl-2,2-dimethyl-1(2H)-naphthalenone (**20**), prepared by the oxidation of 4-ethyl-1,2-dimethylnaphthalene with peroxytrifluoroacetic acid–boron fluoride etherate, gave 4-ethyl-3,4-dimethyl-1(4H)-naphthalenone (**22**). This result strongly supports a 1,2-methyl migration mechanism for the photoisomerization of **6** to **7**.

It has now been established[3,4] that hexamethyl-2,4-cyclohexadienone (**1**) photoisomerizes to a ketene (**2**) which, in the absence of a strong nucleophile, thermally rearranges either to the starting dienone or to a bicyclo[3.1.0]hexenone (**3**). In order to study the influence on



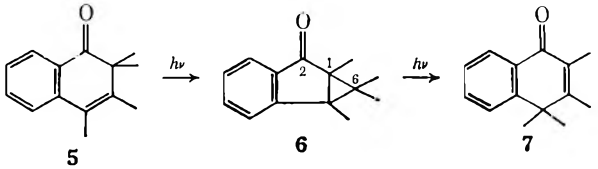
1 **2** **3**

the photochemistry of highly substituted 2,4-cyclohexadienones when one of the two carbon–carbon double bonds of the cyclohexadienone system belongs to a fused aromatic ring, naphthalenones **4** and **5** were synthesized.[5] As previously reported by us,[5] no



4 **5**

volatile products could be detected from the photolysis of naphthalenone **4** in ether or methanol. However, irradiation of naphthalenone **5** in ether provided benzobicyclo[3.1.0]hexenone **6** as the primary photoproduct. Further irradiation gave naphthalenone **7**. In the present paper we describe an investigation of the

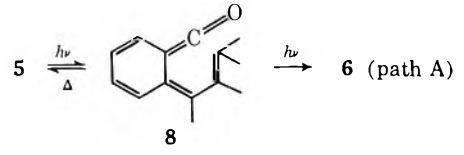


5 **6** **7**

mechanisms for the photoisomerizations **5** → **6** and **6** → **7**.

Results and Discussion

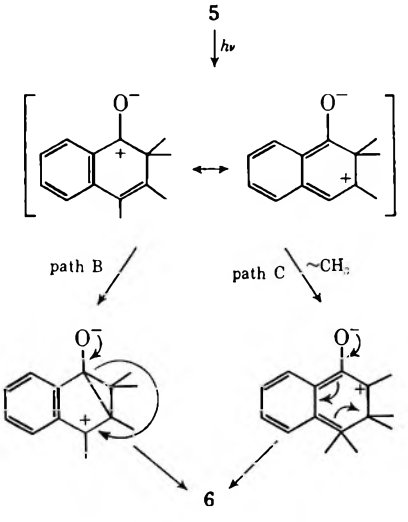
Mechanistic Considerations.—In view of previous mechanistic photochemical studies of 2,4-cyclohexadienones, three gross mechanisms can be suggested to account for the photoisomerization of 2,2,3,4-tetramethyl-1(2H)-naphthalenone (**5**) to 3,4-benzo-1,5,6,6-tetramethylbicyclo[3.1.0]hexen-2-one (**6**). One likely mechanism (path A) is photochemical cleavage of the 1,2 bond in naphthalenone **5** and electron reorganization to provide ketene intermediate **8**. Such a ketene intermediate could thermally cyclize to the starting naphthalenone **5** or to the observed product, benzobicyclic ketone **6**.[3] Photochemical cleavage of the 1,6



8

bond in 2,4-cyclohexadienones to form *cis*-diene ketenes occurs efficiently (but not necessarily exclusively) from the n, π^* singlet state of the dienone.[6]

The photochemical conversion of **5** into **6** can also be formulated as proceeding *via* a "bond-crossing" mechanism (path B) that does not involve the intermediacy of a ketene. Ionic intermediates are used for convenience. Such a mechanism is tenable, as Griffiths and Hart[6]



(1) We are grateful to the National Science Foundation for financial support of this research.

(2) National Institutes of Health Predoctoral Fellow, 1967–1968.

(3) J. Griffiths and H. Hart, *J. Amer. Chem. Soc.*, **90**, 3297 (1968).

(4) Similar observations have been made in a report concerning the photochemistry of 2,4,6-triphenyl-*o*-quinolesters: H. Perst and K. Dimroth, *Tetrahedron*, **24**, 5385 (1968). See also J. E. Baldwin and M. C. McDaniel, *J. Amer. Chem. Soc.*, **90**, 6118 (1968); M. R. Morris and A. J. Waring, *Chem. Commun.*, 526 (1969).

(5) H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **32**, 2448 (1967).

(6) J. Griffiths and H. Hart, *J. Amer. Chem. Soc.*, **90**, 5296 (1968).

TABLE I

PROPERTIES OF THE OXIDATION AND PHOTOPRODUCTS

Compd	Nmr spectra[a] Chemical shift (J)[b]	Assignment[c]	Ir spectra[d] $\nu_{C=O}$, cm^{-1}	$\nu_{C=C}$, conjd, cm^{-1}	$\nu_{C=C}$, arom, cm^{-1}	Uv spectra[e] λ, mμ	Log ϵ	Elemental analysis[f] Empirical formula		C, %	H, %
			A. 1(2H)-Naphthalenones								
9	8.78 (s)	C-2 *gem*-dimethyls	1673	1635	1600	333	3.23	$C_{13}H_{14}O$	Calcd	83.83	7.58
	7.89 (d, 1.5)	C-4 methyl				283	3.35		Found	83.71	7.47
	4.15 (q, 1.5)	C-3 vinyl				274	3.56				
	2.30–2.70 (m)	Aromatic				266	3.54				
	1.85–2.10 (m)	Aromatic				236	4.53				
20	8.80 (s)	C-2 *gem*-dimethyls	1675	1640	1600	333	3.32	$C_{14}H_{16}O$	Calcd	83.95	8.05
	8.80 (t, 7.8)	Methyl (ethyl)				283	3.42		Found	83.85	8.02
	7.50 (q, 7.8)	C-4 methylene				274	3.61				
	4.25 (s, $W_{1/2}$ = 3.3)	C-3 vinyl				266	3.61				
	2.55–3.13 (m)	Aromatic				236	4.74				
	2.0–2.2 (m)	Aromatic									
			B. 2(1H)-Naphthalenones								
13	8.62 (s)	C-1 *gem*-dimethyls	1660	1628	1604	304	4.10	$C_{13}H_{14}O$	Calcd	83.83	7.58
	7.68 (d, 0.9)	C-4 methyl				238	4.09		Found	83.69	7.54
	4.03 (s, $W_{1/2}$ = 4.0)	C-3 vinyl				234	4.09				
	2.51–2.86 (m)	Aromatic									
24	8.69 (t, 7.8)	Methyl (ethyl)	1660	1622	1602	303	4.11	$C_{14}H_{16}O$	Calcd	83.95	8.05
	8.62 (s)	C-1 *gem*-dimethyls				237	4.10		Found	83.87	8.01
	7.29 (q, 7.8)	C-4 methylene				232	4.10				
	4.07 (s)	C-3 vinyl									
	2.48–2.95 (m)	Aromatic									
			C. 1(4H)-Naphthalenones								
7	8.52 (s)	C-4 *gem*-dimethyls	1648	1626	1605	272	4.03	$C_{14}H_{16}O$	Calcd	83.95	8.05
	8.02 (s, br)	C-2 methyl				256	4.06		Found	84.04	8.18
	7.93 (s, br)	C-3 methyl									
	2.57 (m)	Aromatic									
	1.9–2.1 (m)	Aromatic									
14	8.52 (s)	C-4 *gem*-dimethyls	1660	1632	1605						
	7.91 (d, 1.5)	C-3 methyl									
	3.85 (q, 1.5)	C-2 vinyl									
	2.45–2.85 (m)	Aromatic									
	1.85–2.10 (m)	Aromatic									
22	9.62 (t, 7.8)	Methyl (ethyl)	1660	1631	1604	269	4.07	$C_{14}H_{16}O$	Calcd	83.95	8.05
	8.55 (s)	C-4 methyl				252	4.17		Found	84.02	8.09
	8.05 (q, 7.8)	C-4 methylene									
	7.94 (d, 1.5)	C-3 methyl									
	3.79 (s, $W_{1/2}$ = 3.6)	C-2 vinyl									
	2.67 (m)	Aromatic									
	1.93–2.12 (m)	Aromatic									

[a] All spectra were determined in CCl_4. [b] Shifts are reported as τ values, with TMS as an internal reference. All spectra were run at 60 MHz. [c] All areas are consistent with the assignments. [d] All spectra are in CCl_4 and are calibrated (polystyrene). [e] All spectra are in 95% ethanol. [f] Analyses are by Spang Microanalytical Laboratories, Ann Arbor, Mich.

have found that 2,4-cyclohexadienones can be *directly* photoisomerized to bicyclo[3.1.0]hexenones *via* the first π,π^* singlet state of the dienone, if the dienone can be sufficiently perturbed by medium effects to cause inversion of the n,π^* and first π,π^* singlet states. Finally, the photoisomerization of **5** to **6** can be rationalized by a mechanism involving a 1,2-methyl migration (path C).

Whereas the primary photoproduct from the irradiation of naphthalenone **5** in ether is benzobicyclic ketone **6**, continued irradiation gave 2,3,4,4-tetramethyl-1-(4H)-naphthalenone (**7**).[7] Naphthalenone **7**, a white solid, mp 76–78°, was shown to be isomeric with naphthalenone **5** by its elemental analysis and a parent peak at m/e 200 in the mass spectrum. The infrared, ultraviolet, and nmr spectra (see Table I) of **7** are all consistent with the assigned structure and compare well with similar data reported for the closely related compound 3,4,4-trimethyl-1(4H)-naphthalenone (**14**).[8] Independent irradiation of an approximately 0.5% solution of benzobicyclic ketone **6** in diethyl ether gave an 80% yield of naphthalenone **7**. Thus ketone **6** can be considered as the intermediate in the photoisomerization of **5** to **7**.

Although a few photoisomerizations of bicyclo[3.1.0]-hexenones to 2,5-cyclohexadienones are known,[9] the reverse path is a much more common photochemical reaction.[10] The reported photorearrangements of bi-

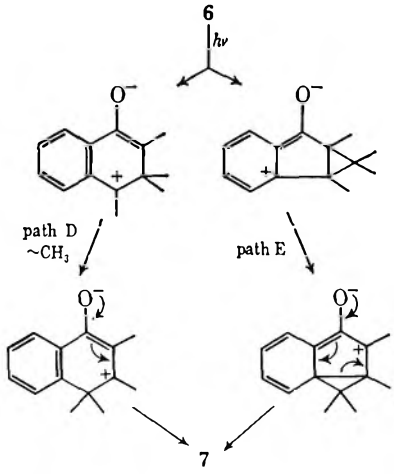
(7) This observation was casually mentioned previously (ref 5, footnote 19), but is documented for the first time here.

(8) J. F. Huffman and T. W. Bethea, *J. Org. Chem.*, **30**, 2956 (1965).

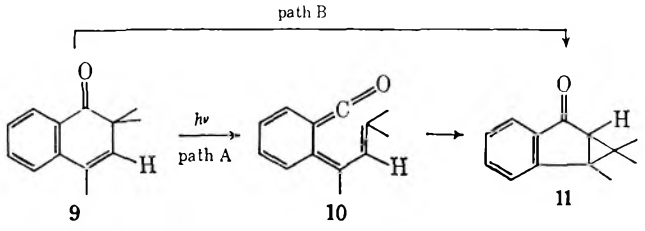
(9) D. H. R. Barton and W. C. Taylor, *J. Chem. Soc.*, 2500 (1958); J. Frei, C. Ganter, D. Kägi, K. Kocsis, M. Miljkovic, A. Siewinski, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1049 (1966); D. I. Schuster and A. C. Fabian, *Tetrahedron Lett.*, 4093 (1966).

(10) For reviews see P. J. Kropp, *Org. Photochem.*, **1**, 1 (1967); K. Schaffner, *Advan. Photochem.*, **4**, 81 (1966); O. L. Chapman, *ibid.*, **1**, 323 (1963).

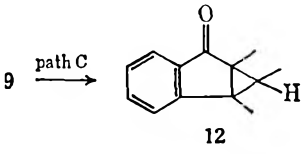
cyclo[3.1.0]hexenones to 2,5-cyclohexadienones usually proceed by 1,2-alkyl migration mechanisms. An analogous mechanism (path D) would account for the photoisomerization of **6** to naphthalenone **7**. The conversion of **6** into **7** can also be explained by a "bond-crossing" mechanism (path E). In such a mechanism the alkyl substituents retain their original positions.



Synthesis and Photochemistry of Naphthalenone 9.— It appeared that paths A and B could be differentiated from path C for the photoisomerization of naphthalenone **5** to benzobicyclic ketone **6** by an examination of the photorearrangement of 2,2,4-trimethyl-1(2H)-naphthalenone (**9**). Photoisomerization of naphthalenone **9** *via* ketene intermediate **10** (path A) or by the "bond-crossing" mechanism (path B) would be expected to yield benzobicyclic ketone **11**. However,



photoisomerization of **9** by a mechanism that required a 1,2-methyl migration (path C) would give a different photoproduct, benzobicyclic ketone **12**.



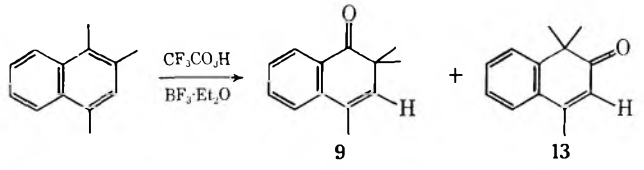
A reasonable synthesis for the desired naphthalenone **9** appeared to be the electrophilic oxidation of 1,2,4-trimethylnaphthalene. Peroxytrifluoroacetic acid–boron fluoride has been shown to be an excellent electrophilic oxidizing agent which can convert aromatic compounds directly into phenols,[11] alkenes into ketones,[12] and certain aromatics into 2,4-cyclohexadienones.[5,13]

(11) C. A. Buehler and H. Hart, *J. Amer. Chem. Soc.*, **85**, 2177 (1963); H. Hart and C. A. Buehler, *J. Org. Chem.*, **29**, 2397 (1964); H. Hart, C. A. Buehler, A. J. Waring, and S. Meyerson, *ibid.*, **30**, 331 (1965).

(12) H. Hart and L. Lerner, *J. Org. Chem.*, **32**, 2669 (1967).

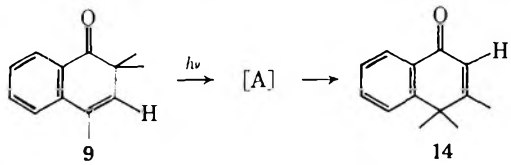
1,2,4-Trimethylnaphthalene was prepared *via* a modification of the method of Hewett.[14] 1,2-Dimethylnaphthalene was chloromethylated with paraformaldehyde and hydrogen chloride in acetic acid. Hydrogenolysis of the resulting 1-chloromethyl-3,4-dimethylnaphthalene with lithium aluminum hydride in tetrahydrofuran provided 1,2,4-trimethylnaphthalene (Hewett used catalytic hydrogenolysis).

1,2,4-Trimethylnaphthalene was oxidized at −20 to −10° with a 10% excess of peroxytrifluoroacetic acid in methylene chloride. Boron fluoride etherate was added at a molar rate equal to that of the oxidant. These conditions effected an 83% conversion of 1,2,4-trimethylnaphthalene. The volatile products were separated by distillation and column chromatography and finally purified by vpc. The composition of the distillate consisted of unreacted 1,2,4-trimethylnaphthalene (42%), 2,2,4-trimethyl-1(2H)-naphthalenone (**9**, 47%), 1,1,4-trimethyl-2(1H)-naphthalenone (**13**, 9%), and an unidentified product (2%). The structures of the products follow from their analyses, spectral properties, and mode of formation. The spectroscopic and analytical data for these compounds are presented in Table I.



Naphthalenone **9** was an oil that showed conjugated carbonyl and double-bond absorptions in the infrared region and an nmr spectrum that was consistent with the assigned structure. The infrared, ultraviolet, and nmr spectra of **9** all compare well with similar data reported for the analogous naphthalenone **5**.[5,15] Naphthalenone **13** was also an oil which had infrared, ultraviolet, and nmr spectra that compare favorably with corresponding data reported for naphthalenone **4**[5] and 1,1-dimethyl-2(1H)-naphthalenone.[16]

Irradiation of a solution of naphthalenone **9** in diethyl ether through a Pyrex filter was monitored by vpc. Photolysis led to a decrease in the concentration of **9** and the appearance of a photoproduct, A, whose concentration reached a maximum of 11% of the volatiles after 3-hr irradiation and then decreased as the photolysis was continued. Another photoproduct, **14**, was also detected and the concentration of **14** continued



(13) A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, **86**, 1454 (1964); H. Hart, P. M. Collins, and A. J. Waring, *ibid.*, **88**, 1005 (1966); H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966); P. M. Collins and H. Hart, *J. Chem. Soc.*, 895 (1967); H. Hart and D. C. Lankin, *J. Org. Chem.*, **33**, 4398 (1968).

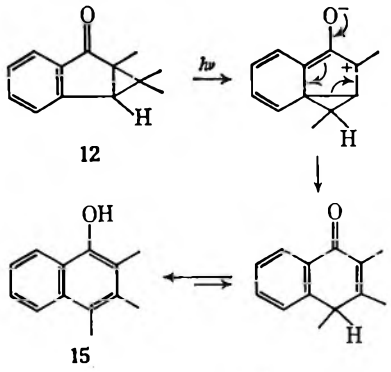
(14) C. L. Hewett, *J. Chem. Soc.*, 293 (1940).

(15) The signals at τ 8.05 and 7.90 in the reported[5] nmr spectrum of naphthalenone **5** can now be assigned definitely to the allylic C-3 and C-4 methyls of **5**, respectively.

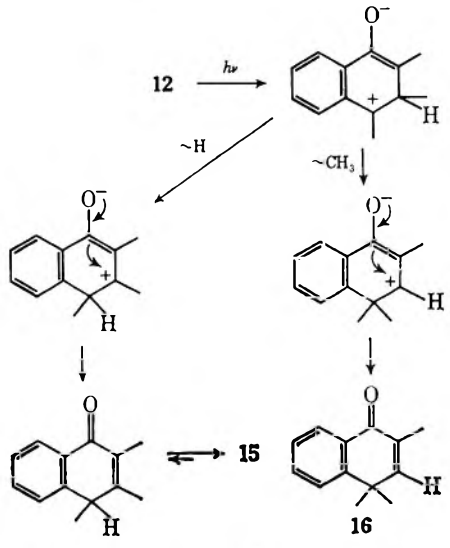
(16) N. H. Cromwell and R. C. Campbell, *J. Org. Chem.*, **22**, 520 (1957); R. C. Campbell and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 3456 (1957).

to increase until the photolysis was terminated. After 12-hr irradiation, vpc analysis of the photolysate indicated that the volatiles were composed of naphthalenone **9** (18%), A (3%), and **14** (78%). Photoproduct **14** has been identified as 3,4,4-trimethyl-1(4H)-naphthalenone. The infrared and nmr spectra of **14** are recorded in Table I. The identity of **14** was firmly established by comparison of the 2,4-dinitrophenylhydrazone derivative of the photoproduct with an authentic sample of the 2,4-dinitrophenylhydrazone of 3,3,4-trimethyl-1(4H)-naphthalenone prepared independently by Huffman and Bethea.[8,17]

In view of the known photochemistry[5] of 2,2,3,4-tetramethyl-1(2H)-naphthalenone (**5**), photoproduct A is presumed to be a benzobicyclo[3.1.0]hexenone, though it was not trapped, nor was its structure investigated. If A had structure **11**, then further rearrangement by mechanisms analogous to either path D or path E would lead to the observed photoprocuct **14**. If A had structure **12**, however, then further photoisomerization to a 1(4H)-naphthalenone would be expected to provide ultimately 2,3,4-trimethyl-1-naphthol (**15**) by a "bond-crossing" mechanism analogous to path E, and a mixture of **15** and naphthalenone **16** *via* a mecha-

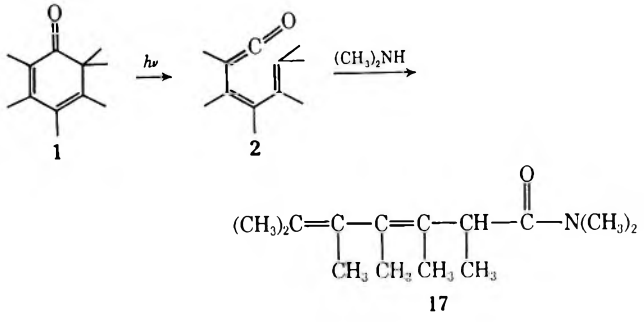


nism involving a 1,2-alkyl migration analogous to path D.



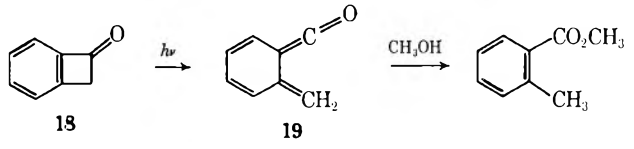
As the final photoproduct isolated in the photoisomerization of naphthalenone **9** was naphthalenone **14**, the intermediate benzobicyclohexenone (A) in the conversion of **9** into **14** must be 3,4-benzo-5,6,6-trimethylbicyclo[3.1.0]hexen-2-one (**11**). Therefore the photorearrangement of a 1(2H)-naphthalenone to a benzobicyclo[3.1.0]hexenone cannot involve methyl migration, and must occur either *via* a ketene intermediate (path A) or by a "bond-crossing" mechanism (path B). Path C can safely be excluded as a mechanism for the photorearrangement.

In an effort to decide between paths A and B, several attempts were made to trap the ketene **8**. The ketene intermediate **2**, formed in the photoisomerization of dienone **1** to ketone **3**, was successfully trapped by the inclusion of a strong nucleophile in the photolysis solution.[3] Thus irradiation of **1** in alcohol or hexane with dimethylamine present provided amide **17** in high yield. However, similar irradiation of a hexane solution of tetramethylnaphthalenone **5** with an excess of



dimethylamine present was found to give only benzobicyclic ketone **6**. No other products could be detected by vpc or nmr analysis of the photolysate.

One explanation for this result is that a ketene intermediate is not involved in the photoisomerization of **5** to **6**. Contrarily, it can be contended that the reaction does proceed by a ketene intermediate, but owing to the strong driving force for rearomatization of the ketene, it thermally cyclizes to **5** or **6** faster than it reacts with an available nucleophile. However, Cava and Spangler have reported trapping a closely related ketene with a weaker nucleophile than dimethylamine.[18] Thus benzocyclobutenone (**18**) is smoothly converted into methyl *o*-toluate by irradiation in methanol. The reaction is rationalized as occurring *via* ketene **19**. In a



similar experiment, irradiation of a methanol solution of naphthalenone **5** provided a high yield of naphthalenone **7** *via* the intermediate **6**. No methyl esters or other products were detected by vpc or nmr analysis of the photolysate.

Therefore it can be concluded that the photoisomerization of a 1(2H)-naphthalenone to a benzobicyclo-[3.1.0]hexenone most likely occurs by a "bond-crossing" mechanism that probably does not involve the intermediacy of a ketene. The reaction may be analogous to the direct photoisomerization of a 2,4-cyclohexadienone to a bicyclo[3.1.0]hexenone from the first π,π^* singlet state of the dienone.[4] Alternately, if the π

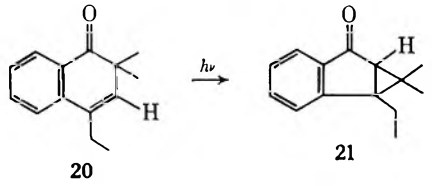
(17) We thank Professor John W. Huffman of Clemson University for kindly providing a comparison sample of the 2,4-dinitrophenylhydrazone of 3,4,4-trimethyl-1(4H)-naphthalenone.

(18) M. P. Cava and R. J. Spangler, *J. Amer. Chem. Soc.*, **89**, 4551 (1967).

electrons of the aromatic ring in 1(2H)-naphthalenones do not strongly influence the photochemistry of these compounds, then the photochemistry of 1(2H)-naphthalenones can be compared with that of 3-cyclohexenones. Williams and Ziffer have shown that the characteristic photoreaction of 3-cyclohexenones in solution is isomerization to bicyclo[3.1.0]hexanones.[19]

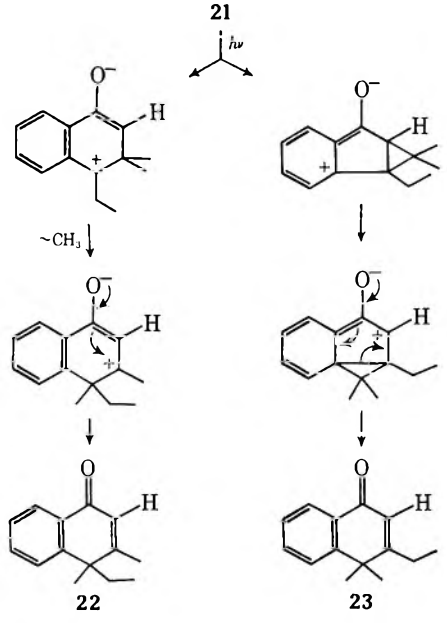
Synthesis and Photochemistry of Naphthalenone 20. —As discussed above, the observed photochemical conversion of benzobicyclic ketone **6** into naphthalenone **7** can be formulated as proceeding by a 1,2-methyl migration (path D) or *via* a rearrangement of the "bond-crossing" type (path E). To differentiate between these alternatives, the photochemistry of 4-ethyl-2,2-dimethyl-1(2H)-naphthalenone (**20**) was examined.

Since the first step in the photoisomerization of a 1(2H)-naphthalenone to a benzobicyclo[3.1.0]hexenone occurs by a "bond-crossing" mechanism, as just demonstrated, irradiation of naphthalenone **20** should provide ketone **21**. Photoisomerization of **21** by a



20 21

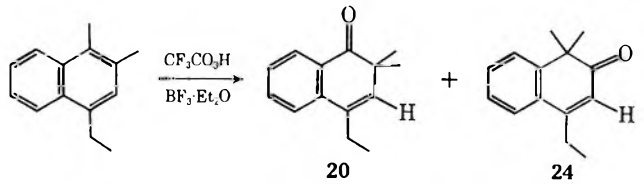
mechanism that required a 1,2-methyl migration would be expected to give naphthalenone **22**. However, photorearrangement of **21** by a "bond-crossing" mechanism would be expected to yield another product, naphthalenone **23**. The two ketones should be readily distinguishable by their nmr spectra. Identification of the 1(4H)-naphthalenone would permit a choice between the two mechanisms.



22 23

A suitable synthesis for the desired naphthalenone **20** appeared to be the electrophilic oxidation of 4-ethyl-1,2-dimethylnaphthalene. 1,2-Dimethylnaphthalene was acetylated with acetyl chloride–aluminum chloride.[20] Clemmensen reduction of the resulting 1-acetyl-3,4-dimethylnaphthalene provided 4-ethyl-1,2-dimethylnaphthalene.

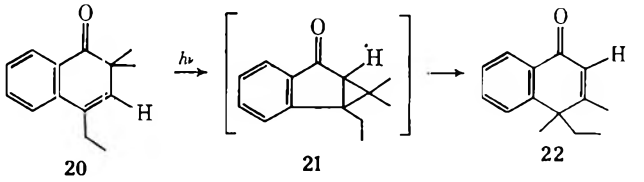
Oxidation of 4-ethyl-1,2-dimethylnaphthalene with peroxytrifluoroacetic acid–boron fluoride etherate at −20 to −10° effected a 78% conversion of 4-ethyl-1,2-dimethylnaphthalene. The volatile products were separated by distillation and column chromatography and finally purified by vpc. The distillate consisted of unreacted 4-ethyl-1,2-dimethylnaphthalene (41%), 4-ethyl-2,2-dimethyl-1(2H)-naphthalenone (**20**, 49%), and 4-ethyl-1,1-dimethyl-2(1H)-naphthalenone (**24**, 10%). The spectroscopic and analytical data (Table I)



20 24

for naphthalenones **20** and **24** are consistent with the assigned structures and compare very favorably with corresponding data reported for other 1(2H)[5]- and 2(1H)[5,15]-naphthalenones, respectively.

Irradiation of a solution of naphthalenone **20** in diethyl ether through a Pyrex filter was monitored by vpc. Photolysis produced a decrease in the concentration of naphthalenone **20** and the appearance of a photoproduct whose concentration reached a maximum of 15% of the volatiles after 5-hr irradiation, then decreased as the photolysis was continued. This photoproduct is tentatively assigned the structure of 3,4-benzo-5-ethyl-6,6-dimethylbicyclo[3.1.0]hexen-2-one (**21**). As the irradiation was continued, another photoproduct was also detected and the concentration of this product continued to increase until the photolysis was terminated. The latter compound was isolated and has been identified as 4-ethyl-3,4-dimethyl-1(4H)-naphthalenone (**22**). After 12-hr irradiation, vpc analysis



20 21 22

of the photolysate indicated that the volatile products were composed of **20** (30%), **21** (7%), and **22** (63%). In an attempt to increase the yield of **21**, a solution of naphthalenone **20** in trifluoroethanol[6] was irradiated through a uranium glass filter (short wavelength cut-off at *ca.* 360 mμ). Vpc analysis of the photolysis solution after brief irradiation showed that the volatile products were composed of **20** (51%), **21** (11%), and **22** (38%). Further irradiation provided an excellent yield of naphthalenone **22**.

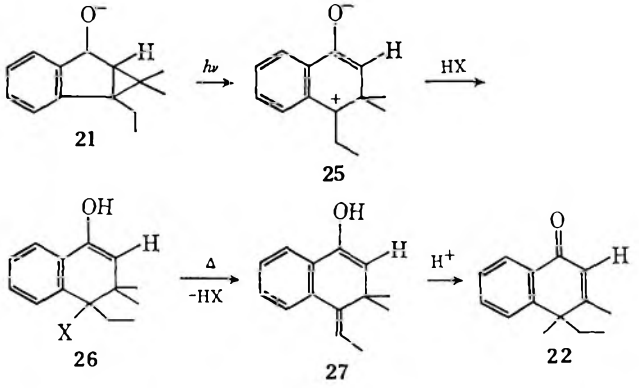
Naphthalenone **22** was an oil which showed analytical and spectroscopic data (Table I) consistent with the assigned structure. In particular, the allylic methyl (τ 7.94) of **22** is established as being at C-3, as the allylic methyl in naphthalenone **14** appears at τ 7.91, while the allylic methyls at C-2 and C-3 in naphthal-

(19) J. R. Williams and H. Ziffer, *Chem. Commun.*, 194, 469 (1967). See also K. Kojima, K. Sakai, and K. Tanabe, *Tetrahedron Lett.*, 1925 (1969).

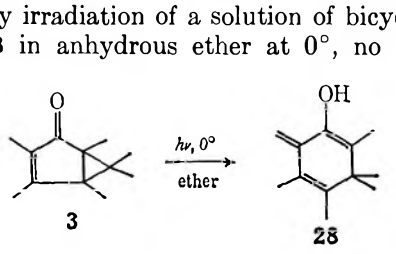
(20) P. A. Plattner and A. Ronco, *Helv. Chim. Acta*, **27**, 400 (1944).

enone **7** are assigned to the signals at τ 8.02 and 7.93, respectively.[21]

Since the photoproduct isolated in the photoisomerization of naphthalenone **20** is naphthalenone **22**, the photorearrangement of a benzobicyclo[3.1.0]hexenone to a 1(4H)-naphthalenone must occur *via* a 1,2-alkyl migration. Other reported photorearrangements of bicyclo[3.1.0]hexenones to 2,5-cyclohexadienones also proceed by apparent 1,2-alkyl migration mechanisms.[9] However, the rearrangement of **20** to **22** can also be rationalized by a mechanism analogous to that elucidated by Hart and Swatton for the conversion of bicyclo[3.1.0]hexenone **3** into hexamethyl-2,5-cyclohexadienone.[22] Thus the dipolar intermediate **25**, photochemically generated from **21**, could be trapped by a suitable nucleophile to give **26**. Thermal or acid-catalyzed elimination of the nucleophile from **26** would provide the enolic triene **27**, which could yield **22** on further treatment with acid.



Although Swatton[23] was able to obtain the enolic triene **28** by irradiation of a solution of bicyclo[3.1.0]-hexenone **3** in anhydrous ether at 0°, no analogous



intermediates have been detected thus far in the photoisomerization of benzobicyclo[3.1.0]hexenones to 1(4H)-naphthalenones.

Experimental Section

General Photolysis Procedure.—All irradiations were conducted with a 450-W Hanovia Type L mercury arc lamp with the light filtered through a Pyrex or Corning 3320 uranium borosilicate glass sleeve. The solution to be irradiated was placed in a Pyrex test tube, sealed with a serum cap, and attached to the outside of a Hanovia water-cooled Pyrex immersion well, 2–3 cm from the center of the mercury lamp. This apparatus was then placed in a water bath, which maintained the temperature of the solution between 15 and 20° during irradiation.

For each successful irradiation experiment reported, a control experiment showed that no reaction occurred under similar conditions in the dark.

Extended Irradiation of Naphthalenone 5 in Diethyl Ether.—A solution of 115 mg of naphthalenone **5**[5] in 7 ml of diethyl ether was irradiated through a Pyrex filter. The photolysis was monitored by vpc (10 ft × 0.25 in. Carbowax column, 225°, 50 ml/min of helium). Aliquots examined during the first 120 min of photolysis indicated a progressive decrease in the concentration of **5** (t_R 16.6 min) and an increase in the concentration of the primary photoproduct,[5] 3,4-benzo-1,5,6,6-tetramethylbicyclo[3.1.0]hexen-2-one (**6**, t_R 9.5 min). However, after 40 min of irradiation the appearance of another compound (t_R 23.6 min) was observed. After 120 min of irradiation the concentration of benzobicyclic ketone **6** decreased and the concentration of the new photoproduct sharply increased. The concentrations of **6** and the overphotoproduct were equal after 140 ± 4 min, and after 200 min of irradiation the concentration of **6** was negligible. The final photoproduct was purified by vpc (above conditions) and shown to be 2,3,4,4-tetramethyl-1(4H)-naphthalenone (**7**), a white solid, mp 76–78°, with spectral and analytical properties as presented in Table I.

Irradiation of Benzobicyclic Ketone 6 in Diethyl Ether.—A solution of 44 mg of benzobicyclic ketone **6**[6] in 8 ml of diethyl ether was irradiated through a Pyrex filter. Monitoring the photolysis by vpc (5 ft × 0.25 in. DEGS 60/80 Chromosorb W column, 180°, 100 ml/min of helium) indicated the formation of a single photoproduct. This compound was purified by vpc (above conditions) and was shown to be naphthalenone **7** (see Table I for spectral properties). The photoisomerization of **6** to **7** proceeded in 80% yield.

1,2,4-Trimethylnaphthalene.—A solution of 28.0 g (0.14 mol) of 1-chloromethyl-3,4-dimethylnaphthalene[14] in 200 ml of dry tetrahydrofuran was added over 1 hr to a suspension of 4.5 g (0.14 mol) of lithium aluminum hydride in 300 ml of dry, stirred, refluxing tetrahydrofuran. The mixture was stirred at reflux for an additional 24 hr and then cooled in an ice bath, and small pieces of ice were added to hydrolyze the excess lithium aluminum hydride. To this mixture was added 150 ml of 10% HCl and 150 ml of water. The resulting mixture was extracted with four 200-ml portions of ether and the separated ether layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent provided 32.0 g of an oil which solidified with cooling. Recrystallization of this residue from 95% ethanol gave 12.9 g (0.076 mol) of 1,2,4-trimethylnaphthalene, yield 55%, mp 48–50° (lit.[14] mp 49–50°). The ultraviolet[24] and nmr[25] spectra of 1,2,4-trimethylnaphthalene corresponded to those in the literature.

Oxidation of 1,2,4-Trimethylnaphthalene.—A solution of peroxytrifluoroacetic acid,[26] prepared from 0.65 ml (0.024 mol) of 90% hydrogen peroxide and 5.55 g (0.026 mol) of trifluoroacetic anhydride in 10 ml of freshly distilled methylene chloride, was cooled to −20° and added with stirring over 45 min to a solution of 3.7 g (0.022 mol) of 1,2,4-trimethylnaphthalene in 50 ml of methylene chloride which had previously been cooled to −20°. Boron trifluoride etherate (7.25 ml of 47% $BF_3 \cdot Et_2O$) was added concurrently with the addition of the peracid. The temperature of the solution was maintained between −20 and −10° throughout the addition. After further stirring for 45 min at −20°, the solution was poured into 200 ml of water and the organic layer was separated. The organic layer was washed with three 100-ml portions of water and three 150-ml portions of saturated sodium bicarbonate, extracted with three 100-ml portions of 10% aqueous sodium hydroxide, and washed with three 100-ml portions of water. The sodium hydroxide and methylene chloride fractions were investigated separately. The basic fraction was acidified with dilute hydrochloric acid and extracted with three 100-ml portions of methylene chloride, which yielded on evaporation 0.07 g of a dark, viscous oil. Vapor phase chromatography (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) indicated the presence of several components. This material was not investigated further.

The methylene chloride fraction was dried over anhydrous magnesium sulfate and evaporated to afford a deep red, viscous oil. Vacuum distillation of this material at 0.06 mm provided 1.52 g of a yellow liquid, bp 79–82°. The pot residue was 1.18 g of a deep red, very viscous material. Vapor phase chromatography (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) of the distillate showed that the crude oil had components with the following retention times: 4.6 (47%), 5.7 (42%), 6.1

(21) A methyl attached to the β carbon of a cyclic dienone exhibits a signal at lower field: P. J. Kropp, *J. Amer. Chem. Soc.*, **86**, 4053 (1964); see also ref 13.

(22) H. Hart and D. W. Swatton, *J. Amer. Chem. Soc.*, **89**, 1874 (1967).

(23) D. W. Swatton, Ph.D. Thesis, Michigan State University, 1967.

(24) E. Heilbronner, U. Fröhlicher, and P. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949).

(25) F. F. Yew, R. J. Kurland, and B. J. Mair, *Anal. Chem.*, **36**, 843 (1964).

(26) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3468 (1954).

(2%), and 9.8 min (9%). The distillate was chromatographed on silica gel in a 4 × 47 cm column. Elution with 1500 ml of pentane provided 0.64 g of 1,2,4-trimethylnaphthalene, which was identified by its melting point (49–51°), ir spectrum, and retention time (5.7 min). The conversion of 1,2,4-trimethylnaphthalene in the oxidation was 83%. Elution with 600 ml of methylene chloride provided a yellow oil which was shown to be homogeneous (t_R 4.6 min) by vpc (above conditions). Finally, elution with 350 ml of 95% ethanol provided an oil which vpc analysis indicated was composed of two compounds (t_R 6.1 and 9.8 min). Final purification of all compounds was achieved by vpc. Each compound was thermally stable under the vpc conditions. The products were identified as 2,2,4-trimethyl-1(2H)-naphthalenone (**9**, t_R 4.6 min) and 1,1,4-trimethyl-2(1H)-naphthalenone (**13**, t_R 9.8 min). Spectroscopic and analytical properties of each compound are presented in Table I and discussed in the text. An insufficient amount of the product with a retention time of 6.1 min (which composed 2% of the distillate) was obtained to permit identification.

Irradiation of Naphthalenone 9 in Diethyl Ether.—A solution of 198 mg of naphthalenone **9** in 20 ml of diethyl ether was irradiated through a Pyrex filter. Monitoring the photolysis by vpc (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) showed a progressive decrease in the concentration of **9** (t_R 4.6 min) and the appearance of two new compounds with retention times of 6.0 and 18.6 min. The concentration of the compound with a retention time of 6.0 min reached a maximum of 11% of the volatiles after 3-hr irradiation and then decreased, whereas the concentration of the compound with a retention time of 18.6 min continued to increase as the photolysis was continued. After irradiation for 12 hr, vpc analysis of the photolysate indicated that the volatile products were composed of **9** (18%), a compound with a retention time of 6.0 min (3%), and a compound with a retention time of 18.6 min (78%). The photoproduct with a retention time of 18.6 min was purified by vpc (above conditions) and shown to be 3,4,4-trimethyl-1(4H)-naphthalenone[8] (**14**), with spectral properties as presented in Table I. Reaction of naphthalenone **14** with 2,4-dinitrophenylhydrazine provided the 2,4-dinitrophenylhydrazone of **14**, which was recrystallized from ethanol–ethyl acetate to give deep violet crystals, mp 245–247° (lit.[8] mp 243–245°). A mixture of the 2,4-dinitrophenylhydrazone adduct of the photoproduct and an authentic sample[17] of the 2,4-dinitrophenylhydrazone of **14** also melted at 245–247°.

Irradiation of Naphthalenone 5 in Hexane–Dimethylamine.—A solution of 114 mg (5.7×10^{-4} mol) of naphthalenone **5** and 64 mg (1.4×10^{-3} mol) of dimethylamine in 10 ml of hexane was irradiated through a Pyrex filter. The photolysis was monitored by vpc (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium). Examination by vpc of the photolysis solution after 30-min irradiation indicated a decrease in the concentration of naphthalenone **5** (t_R 7.0 min) and the appearance of a photoproduct with a retention time of 3.6 min. Continued irradiation caused a progressive decrease in the concentration of **5** and a corresponding increase in the concentration of the photoproduct. Vpc examination of the photolysis solution after 3-hr irradiation only showed the presence of compounds with retention times of 3.6 (45%) and 7.0 min (55%). The nmr spectrum (CCl_4) of the crude photolysate after 3-hr irradiation only had singlets at τ 9.27, 8.84, 8.73, and 8.50, in addition to the signals for unreacted naphthalenone **5**. The photoproduct was purified by vpc (above conditions) and was identified by its ir spectrum (CCl_4) [1699 cm^{-1} (C=O)], nmr spectrum (CCl_4) [three-proton singlets at τ 9.27, 8.84, 8.73, and 8.50 and an aromatic multiplet centered at τ 2.60 (4 H)], and retention time as benzobicyclic ketone **6**.[5]

Irradiation of Naphthalenone 5 in Methanol.—A solution of 80 mg of naphthalenone **5** in 8 ml of methanol was irradiated through a Pyrex filter. The photolysis was monitored by vpc (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium). Examination of the photolysis solution by vpc after 10-min irradiation showed a significant decrease in the concentration of naphthalenone **5** (t_R 7.0 min) and the appearance of a photoproduct with a retention time of 3.6 min (compound **6**). After irradiation for 1 hr, analysis by vpc indicated the presence of only a single photoproduct with a retention time of 11.5 min. The nmr spectrum (CCl_4) of the crude photolysate (after irradiation for 1 hr) had a sharp singlet at τ 8.52, broad singlets at τ 8.02 and 7.92, and a complex aromatic multiplet centered at τ 2.60. The photoproduct with a retention time of 11.5 min was purified by vpc (above conditions) and was identified by its melting point, retention time, and infrared spectrum as naphthalenone **7**.

4-Ethyl-1,2-dimethylnaphthalene.—A 20.0-g sample of 1-acetyl-3,4-dimethylnaphthalene[20] was refluxed for 27 hr with a mixture of 70.0 g of amalgamated zinc, 70 ml of concentrated hydrochloric acid, 100 ml of methanol, and 50 ml of benzene. While the mixture was refluxing, three additional 10-ml portions of hydrochloric acid were added. The mixture was cooled and extracted with three 150-ml portions of benzene. The benzene solution was dried over anhydrous magnesium sulfate and evaporated to provide an oil. Vacuum distillation of this oil at 0.9 mm provided 11.2 g of 4-ethyl-1,2-dimethylnaphthalene, bp 130–131° [lit.[27] bp 136° (1 mm)]. Th nmr spectrum (CCl_4) of 4-ethyl-1,2-dimethylnaphthalene consisted of a three-proton triplet (J = 7.5 Hz) centered at τ 8.73, three-proton singlets at τ 7.68 and 7.58, a two-proton quartet (J = 7.5 Hz) centered at τ 7.09, a one-proton singlet at τ 3.12, and aromatic multiplets at τ 2.75–2.92 (2 H) and 2.15–2.31 (2 H).

Oxidation of 4-Ethyl-1,2-dimethylnaphthalene.—A solution of peroxytrifluoroacetic acid,[26] prepared from 1.53 ml (0.055 mol) of 90% hydrogen peroxide and 12.7 g (0.06 mol) of trifluoroacetic anhydride in 20 ml of freshly distilled methylene chloride, was cooled to 0° and added with stirring over 50 min to a solution of 9.2 g (0.05 mol) of 4-ethyl-1,2-dimethylnaphthalene in 125 ml of methylene chloride which had previously been cooled to −20°. Boron trifluoride etherate (16.6 ml of 47% $BF_3 \cdot Et_2O$) was added concurrently with the addition of the peracid. The temperature of the solution was maintained between −20 and −10° throughout the addition. After further stirring for 1 hr at −20°, the solution was poured into 300 ml of water and the organic layer was separated. The organic layer was washed with two 200-ml portions of water and three 100-ml portions of saturated sodium bicarbonate, extracted with three 300-ml portions of 10% aqueous sodium hydroxide, and washed with three 300-ml portions of water.

The methylene chloride fraction was dried over anhydrous magnesium sulfate and evaporated to afford a deep red, viscous oil. Vacuum distillation of this material at 0.3 mm provided 5.1 g of yellow oil, bp 113–115°. The pot residue was 4.0 g of a black, viscous material. Vapor phase chromatography (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) of the distillate showed that the crude oil had components with the following retention times: 4.1 (49%), 5.4 (41%), and 8.9 min (10%). The distillate was chromatographed on silica gel in a 4 × 45 cm column. Elution with 1000 ml of pentane provided 2.05 g of 4-ethyl-1,2-dimethylnaphthalene, which was identified by its ir spectrum and retention time (5.4 min). The conversion of 4-ethyl-1,2-dimethylnaphthalene in the oxidation was 78%. Elution with 600 ml of methylene chloride provided an oil which vpc analysis (above conditions) showed had two components with retention times of 4.1 (90%) and 8.9 min (10%). Finally, elution with 500 ml of a 1:1 mixture of methylene chloride–95% ethanol afforded an oil which was shown to be homogeneous (t_R 8.9 min) by vpc (above conditions). Final purification of all compounds was achieved by vpc. Each compound was thermally stable under the vpc conditions. In order of increasing retention times, the products were identified as 4-ethyl-2,2-dimethyl-1-(2H)-naphthalenone (**20**) and 4-ethyl-1,1-dimethyl-2(1H)-naphthalenone (**24**). Spectroscopic and analytical properties of each compound are presented in Table I and discussed in the text.

Irradiation of Naphthalenone 20 in Diethyl Ether.—A solution of 167 mg of naphthalenone **20** in 17 ml of diethyl ether was irradiated through a Pyrex filter. Monitoring the photolysis by vpc (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) showed a progressive decrease in the concentration of naphthalenone **20** (t_R 4.2 min) and the appearance of two new compounds with retention times of 5.4 and 15.5 min. The concentration of the compound with a retention time of 5.4 min reached a maximum of 15% of the volatiles after 5-hr irradiation and then decreased, whereas the concentration of the compound with a retention time of 15.5 min continued to increase as the photolysis was continued. After irradiation for 16 hr, vpc analysis of the photolysate indicated that the volatiles were composed of **20** (30%), a compound with a retention time of 5.4 min (7%), and a compound with a retention time of 15.5 min (63%). The photoproduct with a retention time of 15.5 min was purified by

(27) W. Cocker, L. O. Hopkins, L. Mabrouk, J. McCormick, and T. B. H. McMurry, *J. Chem. Soc.*, 2230 (1960).

vpc (above conditions) and was identified as 4-ethyl-3,4-dimethyl-1(4H)-naphthalenone (**22**). The spectroscopic properties of naphthalenone **22** are presented in Table I.

Irradiation of Naphthalenone 20 in Trifluoroethanol.—A solution of 50 mg of naphthalenone **20** in 5 ml of trifluoroethanol was irradiated through a uranium glass filter (short wavelength cutoff at *ca.* 360 mμ). Vapor phase chromatography (5 ft × 0.25 in. DEGS column, 180°, 100 ml/min of helium) of the photolysis solution after 15-min irradiation showed that the photolysate had components with the following retention times: 4.1 (naphthalenone **20**, 51%), 5.4 (11%), and 15.3 min (38%). Examination of the photolysate by vpc after irradiation for 1 hr indicated the presence of a single component with a retention time of 15.3 min. The photoproduct was purified by vpc and was identified by its infrared spectrum and retention time as naphthalenone **22**.

Similarly, irradiation of a solution of 110 mg of naphthalenone **20** in 11 ml of trifluoroethanol through a Pyrex filter for 2 hr proceeded with complete conversion and provided a 90% yield of naphthalenone **22**.

Registry No.—**7**, 23740-88-7; **9**, 23740-89-8; **13**, 23740-90-1; **14**, 2981-97-7; **20**, 23740-92-3; **22**, 23740-93-4; **24**, 23740-94-5.

Titanium Tetrachloride Promoted Condensations of Amines with Carboxamides and Similar Species

JAMES D. WILSON, CHARLES F. HOBBS, AND HAROLD WEINGARTEN

Central Research Department, Monsanto Company, St. Louis, Missouri 63166

Received October 8, 1969

Titanium tetrachloride–amine complexes aminate nonhindered carboxamides, β-dicarbonyl compounds, and vinylogous carboxylic acids. Amidinium and vinylogous amidinium salts are formed. In the presence of excess amine, certain amidinium ions are converted into their conjugate bases, enediamines.

Recently we have reported the titanium tetrachloride promoted amination of carbonyl compounds to give enamines,[1a] imines,[1b] and carboxamides.[2] We report here the further amination of carboxamides, which give amidinium salts,[3] and the amination of β diketones and tropolone, which can be regarded as vinylogous carboxylic acids and which give vinylogous amidinium salts as products. This reaction provides a very convenient route to symmetrically substituted amidinium salts and their derivatives.

Results and Discussion

Amination reactions were carried out on a number of representative carboxamides, acetylacetone, and tropolone, the results of which are collected in Table I. Dimethylamine was generally used as the amine component of the reagent to simplify nmr spectral analysis of the products, but other amines, *e.g.*, N,N′-dimethylethylenediamine and 1,2-dimethylhydrazine, proved equally effective. The reaction follows the stoichiometry of eq 1. The reactions were run in a solvent;

$$2R'CONR_2 + 4R_2NH + TiCl_4 \longrightarrow 2R'C(NR_2)_2{}^+Cl^- + 2R_2NH_2Cl + TiO_2 \quad (1)$$

THF or excess dimethylamine (under pressure) proved particularly convenient.

The amination of carboxamides is a significantly more difficult reaction to accomplish than the amination of ketones or carboxylic acids. While virtually any ketone can be converted into its corresponding enamine and any carboxylic acid into its amide by the complexes formed in the interaction of $TiCl_4$ with primary or secondary amines,[4] only nonsterically hindered amides undergo further amination. Thus the N,N-dimethylamides of formic, acetic, and propionic acids react (with decreasing rapidity) with the $TiCl_4$–$(CH_3)_2NH$ reagent to give good yields of tetramethylamidinium salts, but with the more highly substituted isobutyric amide the reaction stops at an intermediate stage, and N,N-dimethylpivalamide is inert. On the other hand, N,N-dimethyldichloracetamide and N,N-dimethylphenylacetamide react fairly readily, showing that there is a delicate balance among factors which determine the reactivity of these compounds.

Tropolone is about as reactive as carboxylic acids toward amination, but acetylacetone reacts very rapidly to give a high yield of vinylogous amidinium salt product.

The product isolated from each reaction is apparently dependent on the acidity of the initially formed amidinium ion. In general, compounds without a hydrogen atom α to the carboxyl group, alkyl derivatives of acetic acid, acetylacetone, and tropolone yield the amidinium (or vinylogous amidinium) salt, whereas electronegatively substituted acetic acids yield enediamines. With dimethylacetamide itself, the reaction can be run so as to yield either tetramethylacetamidinium chloride (**1**) or its conjugate base, vinylidenebis(dimethylamine) (**2**).[5] Evidently, the α-hydrogen-bearing amidinium ions are carbon acids of the same order of acid strength as dimethylammonium ion, and in the presence of excess dimethylamine (as these reactions are normally run) the stronger acids are converted into their conjugate bases.

However, N,N,N′,N′-tetramethylpropanamidinium chloride (**3**) is not so converted into its conjugate base, which implies that it must be a considerably weaker acid than **1**.[6] This is not the anticipated

(1) (a) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967). (b) H. Weingarten, J. P. Chupp, and W. A. White, *ibid.*, 3246 (1967).

(2) J. D. Wilson and H. Weingarten, *Can. J. Chem.*, **48**, 983 (1970).

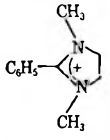
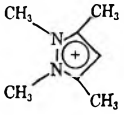
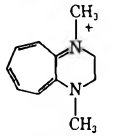
(3) After this work was completed, a brief report of the preparation of some complex cyclic amidinium ions by a similar procedure was published: R. Ian Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Stembach, *J. Org. Chem.*, **34**, 1143 (1969).

(4) R. T. Cowdell and G. W. A. Fowles, *J. Chem. Soc.*, 2522 (1960).

(5) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966); *J. Org. Chem.*, **31**, 2874 (1966).

(6) This was verified experimentally by observing the nmr spectra of mixtures of **1** with the conjugate base of **3**, propenylidenebis(dimethylamine), and of **3** with vinylidenebis(dimethylamine). The equilibrium mixture was found to consist almost entirely of **3** and vinylidenebis(dimethylamine), the other two components being undetectable by nmr; thus **3** is *at least* one order of magnitude weaker an acid than **1**.

TABLE I
PRODUCTS FORMED BY $TiCl_4$-PROMOTED AMINATIONS AND THEIR PHYSICAL CONSTANTS

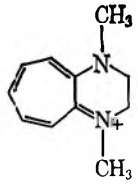
Product[a]	Registry no.	Yield, %	Mp or bp, °C (Torr)	Nmr, τ (rel area)	$\lambda_{max}^{CH_3CN}$, nm (log ϵ)
$HC[N(CH_3)_2]_2^+ PF_6^-$	23645-54-7	37	166–168	3.9 s (1), 7.1 s (12)[d]	*b*
$CH_2{=}C[N(CH_3)_2]_2$ (2)		39	115	6.6 s (2), 7.5 s (12)[e]	228 (3.36)
$CH_3CH_2C[N(CH_3)_2]_2^+ Cl^-$ (3)		70[c]	c	6.7 s (12), 7.1 q (2), 8.8 t (3), J = 7.5 Hz[f]	
$Cl_2C{=}C[N(CH_3)_2]_2$	10596-52-8	33	46 (2)	7.6 s[e]	272 (3.73)
$C_6H_5CH{=}C[N(CH_3)_2]_2$	10596-51-7	50	62 (0.2)	3.1 m (5), 5.5 s (1), 7.3 s (6), 7.4 s (6)[e]	233 (3.89), 242 sh, 317 (4.14)
 PF_6^-	23645-55-8	31	118.5–119.5	2.3 m (5), 5.9 s (4), 7.0 s (6)[d]	
$(CH_3)_2NC(CH_3){=}CHC(CH_3){=}N(CH_3)_2^+ BF_4^-$ (4)		78	230 dec	5.1 s (1), 6.9 s (12), 7.9 s (6)[d]	344 (4.58)[g]
 Cl^- (5)		23	255 dec	3.6 s (1), 6.2 s (6), 7.7 s (6)[d]	233 (3.39)
 PF_6^- (6)		27	217–218	2.6 m (5), 6.0 s (4), 6.4 s (6)[d]	268 (4.53), 362 (4.11) 440 (3.95)

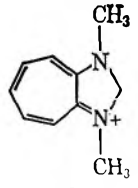
[a] Where salts with anions other than chloride are given, the halide was exchanged for the complex fluoro salt after the amination reaction. The chloride salts of these cations are not stable to storage, either because of hygroscopicity or photo- or oxidative degradation. Yield and physical data are for the complex fluoro salts except for **4** where the yield of the chloride salt is reported. [b] Literature λ_{max}^{EtOH} 224 nm (log ϵ 4.076): R. B. Lund, Ph.D. Thesis, University of Washington, 1960. [c] This salt was converted directly into its conjugate base for analysis. See Experimental Section. The nmr spectrum quoted was obtained by adding acid to a solution of the conjugate base. [d] CD_3CN solution, TMS internal standard. [e] Benzene solution, TMS internal standard. Agreed with data presented: H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966); *J. Org. Chem.*, **31**, 2874 (1966). [f] Agrees with spectrum of authentic compound reported: C. F. Hobbs and H. Weingarten, *J. Org. Chem.*, **33**, 2385 (1968). [g] Literature $\lambda_{max}^{CH_3CN}$ 345 nm (log ϵ 4.57): J. Kucera and Z. Arnold, *Collect. Czech. Chem. Commun.*, **32**, 1704 (1967).

result, for substitution of methyl for hydrogen on carbon normally *increases* the acidity; *e.g.*, CH_3NO_2 exhibits a pK_A of 10.2 and $CH_3CH_2NO_2$ a pK_A of 8.5.[7,8] In this case, however, the possibility exists for nonbonded interactions between the C- and N-methyl groups in the planar conjugate base, which would be relieved by rotation upon protonation. This would tend to destabilize the conjugate base and decrease the acidity of **3** compared with that of **1**.

The reaction of N,N-dimethylisobutyramide with dimethylamine and titanium tetrachloride was unusual in that it appeared to stop at an intermediate complex stage. Examination of the crude reaction mixture by nmr showed no evidence for either the tetramethylamidinium ion or its conjugate base; however, vacuum distillation, virtually under pyrolysis conditions, of the crude product gave a small yield of the conjugate base, 2-methylpropenylidenebis(dimethylamine).

The electronic spectrum of **6** merits some comment in that it differs considerably from that of its homolog **7**. Brasen, Holmquist, and Benson, who first prepared **7**, reported[10] the uv spectral values $\lambda_{max}^{CH_3CN}$ (log ϵ) 280 (4.95), 335 sh, 362 (4.04), and 375 nm (3.56), while we find **6** to exhibit the values $\lambda_{max}^{CH_3CN}$ (log ϵ) 268 (4.53), 362 (4.11), and 440 nm (3.95). However, **6** is bright yellow while **7** is reported to be red, indicating either that **7** possesses an undetected band above 450 nm or that it "tails" very strongly into the visible. No satisfactory rationale is at hand for these changes in spectra upon homologation, particularly the shift of the short-wavelength band to higher energy.


6


7

The nmr spectrum of **6** indicates that most of the charge in the system resides on the nitrogen atoms. The ring protons resonate at a rather higher field position (centered at τ 2.6) than typical tropenylium ions,[11] while the chemical shift of the N-methyl groups (τ 6.4) is at the low end of the range, where amidinium ion methyls are found.[12]

During the course of an extensive investigation into the electrochemistry of vinylamines,[13] **4** was

(7) F. C. Bordwell, W. J. Bogle, Jr., J. A. Hautala, R. H. Imes, and K. C. Yee, Preprints, Division of Petroleum Chemistry, American Chemical Society, Vol. 13, No. 2, p A25, 1968.

(8) From its reaction with dimethylamine, we can estimate that **1** exhibits a pK_A of 12 (dimethylammonium ion, pK_A = 10.7); it is thus almost as strong an acid as nitromethane. The tetramethylamidinium group must therefore be considered one of the most strongly acidifying methyl substituents.[9]

(9) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapters 1 and 3.

(10) W. R. Brasen, H. E. Holmquist, and R. E. Benson, *J. Amer. Chem. Soc.*, **83**, 3125 (1961).

(11) T. J. Pratt, R. B. Medz, W. R. Gresham, H. J. Dauben, Jr., and K. M. Harmon, to be published; K. M. Harmon, personal communication, 1968.

(12) *Cf.* the chemical-shift data in Table I.

(13) J. M. Fritsch and H. Weingarten, Abstracts, Midwest Regional Meeting of the American Chemical Society, Manhattan, Kan., Oct 31–Nov 1, 1968; *J. Amer. Chem. Soc.*, **90**, 763 (1968); **92**, in press.

studied and found to undergo in CH_3CN an irreversible one-electron reduction at -1.7 ± 0.1 V *vs.* sce,[14] and a *reversible* one-electron oxidation at +1.31 V. The product of the oxidation has a lifetime ($\tau_{1/2}$ = 0.6 sec[15]) too short for its structure easily to be proved, but it is probably the dication radical of **4**. It seems likely that other vinylogous amidinium ions will be found to undergo this kind of oxidation; perhaps in favorable circumstances dication radical salts will be isolated.

Derivatives of the products discussed in this paper bearing different substituents on nitrogen can be obtained simply by allowing the salt to react with an excess of an amine with the desired substituents. Thus **4** was converted into the pyrazolium ion **5** by allowing it to stand overnight at room temperature in a CH_3CN solution containing excess 1,2-dimethylhydrazine. Because of the reactivity, availability, and volatility of dimethylamine, the preferred method of preparing variously substituted amidinium and vinylogous amidinium salts should be first to prepare the tetramethyl compound by the method outlined here and then to exchange the amine groups.

Experimental Section

Except where otherwise noted, chemicals and solvents used in this investigation were the best grade available from Fisher Scientific, Matheson Coleman and Bell, or Aldrich Chemical Co. Melting points and boiling points were recorded uncorrected. Nmr spectra were obtained using a Varian Associates A-60 spectrometer, with TMS as an internal standard; ir spectra were obtained on KBr disks using a Beckman IR-4 spectrophotometer; ultraviolet spectra were obtained using a Cary 14 spectrophotometer.[16]

N,N-Dimethyl-4-dimethylamino-3-penten-2-immonium Fluoroborate (4). Method A.—Acetylacetone (10.0 g, 0.1 mol) and dimethylamine (45 g, 1 mol) were dissolved in cold pentane (400 ml) in a 1-l. round-bottom flask equipped with stirrer, N_2 inlet, and addition funnel. This mixture was cooled to −70° in a Dry Ice–acetone bath, and to it was added $TiCl_4$ (19 g, 0.1 mol), neat and in small portions. The resulting dark suspension was allowed to warm slowly to room temperature (25°) and to stir at that temperature for 12 hr. The now colorless mixture was filtered; the filter cake was washed with pentane and then dissolved in 200 ml of dry acetonitrile. Anhydrous K_2CO_3 (*ca.* 60 g) was added to this solution [to destroy $(CH_3)_2NH_2Cl$] and the resulting mixture was allowed to stand with occasional agitation for 0.5 hr. The solid was then filtered off and the resulting solution was evaporated to dryness, leaving crude **4**. Recrystallization from CH_2Cl_2–ether yielded 14.7 g (78%) of **4** (Cl^- salt) as hygroscopic, colorless crystals. The chloride was converted into the fluoroborate salt by shaking a CH_2Cl_2 solution of the salt with two successive 50-ml portions of saturated aqueous $NaBF_4$ and washing the aqueous layers with CH_2Cl_2 to recover **4**. The CH_2Cl_2 solutions were combined, dried, and evaporated under vacuum to leave 14.3 g (64%) of **4** BF_4^- salt, which was identified by its nmr and uv[17] spectra. The physical properties of **4** are given in Table I.

Amination of N,N-Dimethylpropanamide. Method B.—In a 250-ml pressure bottle were placed N,N-dimethylpropanamide (5.05 g, 0.05 mol) and $TiCl_4$ (5.3 g, 0.028 mol). The bottle and its contents were cooled in Dry Ice and anhydrous dimethylamine (18 g, 0.40 mol) was added carefully. The bottle was capped and allowed to warm to ambient temperature and stand for 24 hr with occasional shaking. It was then cooled again and opened, and cold, dry pentane (20 ml) was added. The resulting slurry was filtered and the filter cake was allowed to dry. Nmr analysis of the filter cake showed the presence of dimethylammonium ion and N,N,N′,N′-propanamidinium ion (**3**) only.

The amidinium salt was converted into its conjugate base by placing the filter cake in a distillation flask along with 1,5-diazobicyclo[4.3.0]non-5-ene (50 g) (a cyclic amidine) and heating the mixture to 100° until it completely liquefied. The pressure was reduced to 10 Torr, and the pot temperature was gradually raised to 140°. The distillate was caught in a Dry Ice cooled receiver. Redistillation afforded 4.5 g (70%) of propenylidenebis(dimethylamine), bp 52° (33 Torr), $n^{25}D$ 1.4567 [lit.[5] bp 74° (80 Torr), $n^{25}D$ 1.4552]. The nmr spectrum was identical with that reported previously.[5]

Tetramethylformamidinium Hexafluorophosphate.—Dimethylformamide (7.3 g, 0.10 mol) and dimethylamine (20 ml, 0.3 mol) were allowed to react with $TiCl_4$ (5.5 ml, 0.05 mol) for 8 hr by method A. The filtrate from the reaction mixture was extracted twice with 100-ml portions of CH_2Cl_2; the resulting solutions were combined and evaporated to dryness under vacuum. The residue was dissolved in a minimum quantity of methanol and added to a hot, saturated solution of $NaPF_6$ (25 g) (Ozark–Mahoning Corp.) in methanol. Anhydrous K_2CO_3 (*ca.* 10 g) was added, and the solution was warmed for a few minutes, filtered, and allowed to cool. The crystals which formed were filtered off and the filtrate was evaporated to dryness. The residue was extracted with several portions of CH_2Cl_2, which was in turn evaporated to dryness. This residue was recrystallized from CH_2Cl_2–Et_2O to give, when combined with the original crop, 18 g (73%) of tetramethylformamidinium hexafluorophosphate, which was identified by its nmr spectrum.[18] However, yields of the salt prepared by this method are highly variable, largely because it must be separated from by-product $(CH_3)_2NH_2Cl$. In fact, we have found the procedure of Arnold[19] to be the preferred method for preparing tetramethylformamidinium salts; CO_2 is the only by-product here [however, scrupulously dry $HCON(CH_3)_2$ must be employed as the starting material].

Vinylidenebis(dimethylamine) (2).—To a solution of N,N-dimethylacetamide (48.7 g, 0.56 mol) in dimethylamine (300 g, 6.67 mol) in a 50-ml round-bottom flask equipped with stirrer, Dry Ice reflux condenser, dropping funnel, and N_2 inlet, cooled in a Dry Ice–acetone bath, was added, dropwise with stirring, titanium tetrachloride (68.4 g, 0.36 mol) in pentane (100 ml). This mixture was allowed to warm to ambient temperature and stir at that temperature for 18 hr, by which time the original dark color had faded. The mixture was recooled and filtered under nitrogen, the filter cake being washed repeatedly with dry pentane. The filtrates and washings were combined and distilled to yield 24.8 g (37%) of vinylidenebis(dimethylamine), bp 115°, $n^{25}D$ 1.4500. The nmr spectrum (Table I) was identical with that of an authentic sample.

The dry filter cake was stirred with an additional 300 g of dimethylamine at reflux for 4 hr, and then filtered and washed as before. Distillation of the filtrate and washings gave an additional 6.9 g (11%, total 48%) of **2**.

2,2-Dichlorovinylidenebis(dimethylamine).—Using method A, N,N′-dimethyldichloroacetamide (15.6 g, 0.1 mol) and dimethylamine (41.0 g, 0.9 mol) were allowed to react with $TiCl_4$ (5.5 ml, 0.5 mol) in ether for 72 hr. A yield of 6.3 g (33%) of 2,2-dichlorovinylidenebis(dimethylamine) was isolated by distillation, bp 46° (2 Torr) [lit.[5] bp 55° (3 Torr)].

2-Phenylvinylidenebis(dimethylamine).—In a 250-ml pressure bottle, following method B, N,N-dimethylphenylacetamide (8.15 g, 0.05 mol) and $TiCl_4$ (3.1 ml, 0.028 mol) were allowed to react with dimethylamine (18 g, 0.40 mol) for 48 hr at 25°. Distillation gave 4.7 g (50%) of 2-phenylvinylidenebis(dimethylamine), bp 60–62° (0.2 Torr), $n^{25}D$ 1.5889 [lit.[5] bp 80° (0.9 Torr), $n^{25}D$ 1.5905]. The nmr spectrum was identical with that reported.[5]

1,2,3,5-Tetramethylpyrazolium Chloride.—By method A, 1,2-dimethylhydrazine dihydrochloride (2.66 g, 0.02 mol), acetylacetone (2.0 g, 0.02 mol), and triethylamine (10.1 g, (0.1 mol) were allowed to react with $TiCl_4$ (3.8 g, 0.02 mol) in THF solution for 4 days. The product was isolated by extracting the filtrate from the completed reaction with hot CH_3CN and recrystallizing the residue from evaporation of the resulting solution in CH_2Cl_2.

1,4-Dimethyl-1,2,3,4-tetrahydrocyclohepta[*b*]pyrazinium Hexafluorophosphate (6).—Method A was used. Tropolone (12.2 g,

(14) In DMF, $E_{1/2}$ (red) = −1.64 V: A. Holy, J. Krupicka, and Z. Arnold, *Collect. Czech. Chem. Commun.*, **30**, 4127 (1965).

(15) Estimated by cyclic voltammetry.

(16) We thank Mrs. N. K. Edelman and Mrs. J. S. Wager for making many of these measurements.

(17) J. Kucera and Z. Arnold, *Collect. Czech. Chem. Commun.*, **32**, 1704 (1967).

(18) R. B. Lund, Ph.D. Thesis, University of Washington, 1960.

(19) Z. Arnold, *Collect. Czech. Chem. Commun.*, **24**, 760 (1958).

0.1 mol), N,N'-dimethylethylenediamine (35.2 g, 0.4 mol), and $TiCl_4$ (19 g, 0.1 mol) were allowed to react for 6 days at 25° in ether. The reaction mixture was filtered and the precipitate was extracted with CH_2Cl_2 for 24 hr using a Soxhlet extractor. The resulting yellow solution was evaporated to dryness and the residue was treated with a solution of $NaPF_6$ (16.8 g, 0.1 mol) in hot methanol. On cooling, 1,4-dimethyl-1,2,3,4-tetrahydrocyclohepta[*b*]pyrazinium hexafluorophosphate crystallized out. The mother liquor was evaporated to dryness and the residue was extracted with hot CH_2Cl_2 to recover the remaining product. The two fractions were combined and recrystallized from CH_2Cl_2–Et_2O. Although it is apparently stable when crystalline, **6** decomposes quite rapidly in solution, possibly through oxidation; the chloride salt is quite sensitive in this respect.

Anal. Calcd for $C_{11}H_{15}N_2PF_6$: C, 41.26; H, 4.72; N, 8.75; F, 35.60. Found: C, 41.46; H, 4.58; N, 8.55; F, 35.69.

2-Phenyl-1,3-dimethylimidazolinium Hexafluorophosphate.—By method A, benzoic acid (6.1 g, 0.05 mol) and N,N'-dimethylethylenediamine (18 g, 0.2 mol) were allowed to react with $TiCl_4$ (5.6 ml, 0.051 mol) in THF for 48 hr. The filter cake from the reaction mixture was treated with CH_2Cl_2 to dissolve product, which was recovered by evaporation of the CH_2Cl_2. The chloride was exchanged for PF_6^- and the product was recrystallized from THF to yield 5.0 g (31%) of 2-phenyl-1,3-dimethylimidazolinium hexafluorophosphate, mp 118–120°.

Anal. Calcd for $C_{11}H_{15}N_2PF_6$: C, 41.26; H, 4.72; N, 8.75; F, 35.60. Found: C, 40.87; H, 4.75; N, 8.67; F, 35.61.

Registry No.—Titanium tetrachloride, 7550-45-0; **2**, 815-62-3; **4**, 23645-56-9; **5**, 23649-59-4; **6**, 23645-57-0.

Direct Fluorination of Amides[1]

VYTAUTAS GRAKAUSKAS AND KURT BAUM

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91702

Received September 8, 1969

The fluorination of secondary amides was shown to be a general method for the synthesis of difluoramino compounds and N-alkyl-N-fluoroamides. Formation of difluoramino compounds by the displacement of acylium ions was evidenced by the isolation difluoramino acids from lactams and 2-difluoraminoethanol esters from N-acylethanolamines. Some chemical properties of difluoramino acids are described. Alkylfluoroammonium salts were prepared by the reaction of N-alkyl-N-fluoroamides with sulfuric acid. The fluorination of cyclohexanecarboxamide gave cyclohexyl isocyanate and cyclohexylcarboxylic acid, apparently by hydrolysis of the difluoroamide. Oxidation of the fluorination product of acetamide gave tetrafluorohydrazine.

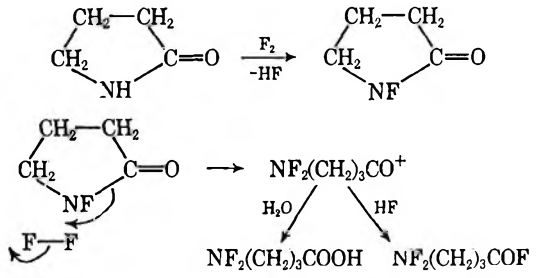
The direct fluorination of alkyl carbamates results in replacement of one or both hydrogens on nitrogen by fluorine,[2] whereas the fluorination of alkyl N-alkylcarbamates results in replacement of NH and subsequently acyl groups.[3] Fluorination studies of amides[4] have been limited to acetamide and N-methylacetamide. Aqueous fluorination of acetamide was reported to give only acetic acid, carbon dioxide, nitrous oxide, and a trace of tetrafluorohydrazine, and that of N-methylacetamide was reported to give acetic acid, carbon dioxide, and a 7% yield of difluoraminomethane. The present paper describes the fluorination of a variety of amides to give N-fluoroamides and difluoramino alkanes, as well as rearrangement products.

Products of the fluorination of secondary amides are shown in Table I. The fluorinations were generally conducted using solutions or suspensions of the substrates in water or acetonitrile, although in several cases no solvent was used. The reactions are similar to those of carbamates in that successive fluorination of NH and fluorinolysis of acyl groups takes place. The rates of the two reactions are of the same order of magnitude, and considerable amounts of difluoramino alkanes are formed, even at low fluorine to substrate ratios. The reactions, however, are characterized by high selectivity toward nitrogen and only two CH fluorination/products, 1,3-bis(difluoramino)-1-fluoropropane and 2-difluoraminoethyl fluoroacetate, were isolated in this work. As a practical synthesis method for difluoramino alkanes, the fluorination of secondary amides is comparable with that of carbamates, and therefore provides a more convenient choice of starting materials. The intermediates, N-fluoroamides, are isolated readily by conventional methods.

$$RNHCR' \xrightarrow{F_2} RNFCR' \xrightarrow{F_2} RNF_2$$

The products were characterized by elemental analysis and spectral data, or by comparison with authentic samples. Methyldifluoramine and ethyldifluoramine were prepared previously by reactions of N_2F_4 with alkyl iodides.[5] β-Difluoraminopropionic acid was prepared previously by the addition of difluoramine to acrylic acid,[6] and 1,3-bis(difluoramino)propane and 2-difluoraminoethanol, by the fluorination of the corresponding carbamates.[3]

The fluorinolysis of acyl groups can be rationalized as an electrophilic displacement of acylium ions by fluorine. In the case of lactams, the acyl fragment is retained in the product molecule. For example, 2-pyrrolidinone gave 3-difluoraminobutyric acid in aqueous solution, and 3-difluoraminobutyryl fluoride when no solvent was used in the fluorination.



(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) V. Grakauskas and K. Baum, *J. Amer. Chem. Soc.*, **91**, 1679 (1969).

(3) V. Grakauskas and K. Baum, *J. Org. Chem.*, **34**, 2840 (1969).

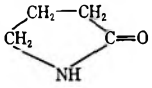
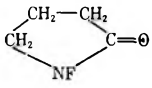
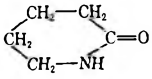
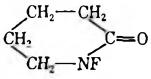
(4) R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *J. Chem. Soc., C*, 1514 (1966).

(5) J. W. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960).

(6) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

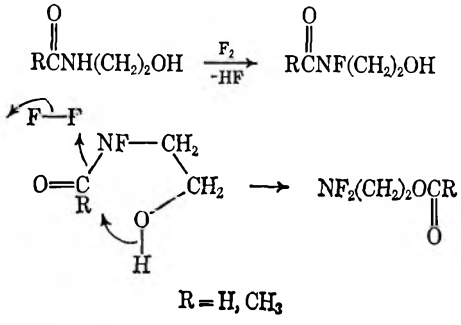
TABLE I

FLUORINATION OF SECONDARY AMIDES

Starting material	Products	Registry no.	Bp (mm), °C	Yield, %[a]
CH_3NHCHO	CH_3NFCHO	23649-62-9	76–77[b]	31
	CH_3NF_2		*c*	
C_2H_5NHCHO	C_2H_5NFCHO	23674-46-6	21–22 (25)	5.5
	$C_2H_5NF_2$		*c*	
$CH_3(CH_2)_3NHCOCH_3$	$CH_3(CH_2)_3NFCOCH_3$	23649-63-0	45–46 (25)[b]	1.5
$CH_3CONHCH_2CH_2CO_2H$	$NF_2CH_2CH_2CO_2H$	20955-66-2	60 (1)	36
		23649-65-2	37–38 (0.15)	16.5
	$NF_2(CH_2)_3COOH$	23649-66-3	52–54 (0.15)	11
	$NF_2(CH_2)_3COF$[d]	23649-67-4	<20 (0.2)[b]	
		23649-68-5	60–62 (0.2–0.3)	20
$HCONH(CH_2)_3NHCHO$	$NF_2(CH_2)_4COOH$		*e*	46
	$NF_2(CH_2)_3NF_2$	21298-22-6	26–30 (25)[b]	5.6
	$NF_2CHF(CH_2)_2NF_2$	23649-70-9		2.5
	$NF_2(CH_2)_3NFCHO$	23649-71-0	31–32 (0.2–0.3)[b]	2.5
$HCONHCH_2CH_2OH$	$NF_2CH_2CH_2OCHO$	23649-72-1	38–45 (25)	25
	$NF_2CH_2CH_2OH$	21298-33-9		3.7
$CH_3CONHCH_2CH_2OH$	$NF_2CH_2CH_2OCOCH_3$	23649-74-3	40–50 (25)[b]	13
	$NF_2CH_2CH_2OH$			3.6
	$NF_2CH_2CH_2OCOCH_2F$	23649-77-6	29–30 (0.1)[b]	0.8

[a] Yields were not optimized. [b] Impure distillate; analytical sample was isolated by gas chromatography. [c] Spectroscopic identification. [d] Nonhydrolytic fluorination conditions. [e] Purified through salt formation.

Further evidence for electrophilic acylium ion displacement is found in the fluorinations of N-acylethanolamines. The fluorinations of both the formyl and acetyl derivatives in aqueous solution gave 2-difluoraminoethanol and its corresponding esters. In the case of the acetyl compound, the fluoroacetate was also isolated. The alcohol function thus competes with the solvent to trap acylium ions.



$R = H, CH_3$

Simple N-fluoro-N-alkylamides were found to be hydrolytically stable in the presence of dilute aqueous acid. They underwent hydrolysis in concentrated sulfuric acid under the same conditions as the corresponding carbamates.[7] Thus methyl-N-fluoroformamide gave the previously identified[7] methylfluoroammonium ion. Ethyl-N-fluoroformamide gave ethylfluoroammonium ion. The fluorine nmr spectrum of the sulfuric acid solution, a triplet of triplets at −15.51 ppm from external trifluoroacetic acid (J_{NH_2-F} = 42.5 cps, J_{CH_2-F} = 28.7 cps), was consistent with previously reported fluoroammonium ion spectra.[7]

$$RNFCHO \xrightarrow[\Delta]{H_2SO_4} RNH_2F^+HSO_4^-$$

Although primary difluoramino compounds have been reported to undergo facile dehydrofluorination in the presence of bases,[8] it was found that analytically pure 6-difluoraminohexanoic acid could be isolated in 46% overall yield by extraction of the ϵ-caprolactam fluorination mixture with cold bicarbonate solution. On the other hand, aqueous sodium hydroxide at 0 to 3° reacted with the acid to give a 59% yield of 5-cyanovaleric acid in 15 min. Reactions of 6-difluoraminohexanoic acid and 4-difluoraminobutyric acid with alcohols in the presence of a trace of acid gave high yields of the corresponding esters.

3-Difluoraminobutyric acid reacted with thionyl chloride to give the acid chloride or the anhydride depending on the reactant ratio. The acid chloride reacted with sodium azide in benzene to give an 85% yield of the isocyanate. The isocyanate reacted with ethanol to give ethyl N-(3-difluoraminopropyl)carbamate, a compound previously obtained in impure form from the fluorination of ethyl trimethylenedicarbamate.[3]

$$NF_2(CH_2)_3COOH \xrightarrow{SOCl_2} NF_2(CH_2)_3COCl \xrightarrow[C_6H_6,\,\Delta]{NaN_3}$$

$$NF_2(CH_2)_3NCO \xrightarrow{EtOH} NF_2(CH_2)_3NHCO_2Et$$

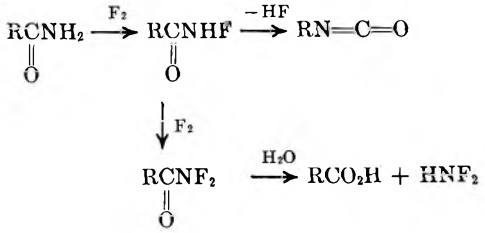
A more limited study was made of fluorinations of primary amides. The expected initial products, N-fluoroamides, could be expected to undergo further fluorination to give N,N-difluoroamides. Another possible reaction path of N-fluoroamides leads to isocyanates by the Hofmann rearrangement. Isocyanates

(7) V. Grakauskas, A. H. Remanick, and K. Baum, *J. Amer. Chem. Soc.*, **90**, 3839 (1968).

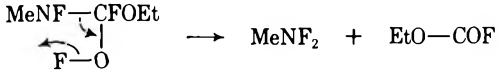
(8) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967); F. A. Johnson, C. Haney, and T. E. Stevens, *ibid.*, **32**, 466 (1967); G. N. Sausen and A. L. Logothetis, *ibid.*, **33**, 2330 (1968); A. L. Logothetis and G. N. Sausen, *ibid.*, **31**, 3689 (1966); S. K. Brauman and M. E. Hill, *J. Amer. Chem. Soc.*, **89**, 2127 (1967); A. S. Filatov and M. A. Englin, *Zh. Obshch. Khim.*, **38**, 1408 (1968).

have been isolated from reactions of primary amides with iodine pentafluoride,[9] and similar nucleophilic rearrangements were observed in reactions of fluoroammonium salts with carbonyl compounds. N,N-Difluoroamides were prepared previously from tetrafluorohydrazine and acyl radical sources[10] and were reported to react readily with hydroxylic compounds; reactions with HF, the fluorination by-product, would therefore be expected.

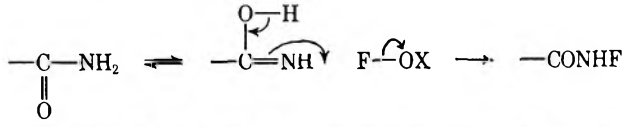
Fluorination of cyclohexanecarboxamide in acetonitrile with 2 mol of fluorine gave an 18% yield of cyclohexyl isocyanate and a 48% yield of cyclohexanecarboxylic acid (after aqueous bicarbonate extraction). The starting material was not hydrolyzed by HF under the fluorination conditions in a control experiment, indicating that the difluoroamide is a precursor to the acid. Additional evidence for a difluoroamide intermediate was obtained by fluorinating acetamide in acetonitrile and oxidizing the solution with chromic acid; a 50% yield of tetrafluorohydrazine was isolated. Tetrafluorohydrazine has been prepared from difluorocarbamates by this method.[11]



Banks, Haszeldine, and Laln[4] have proposed a mechanism for the formation of alkyldifluoramines from carbamates and amides in which fluorine adds to the carbonyl group of the N-fluoro intermediate, followed by intramolecular fluorination by the OF, *e.g.*,



For the first step of the fluorinations in aqueous solutions, they proposed the reaction of oxygen difluoride or hypofluorous acid with the enolic forms of the substrates, *e.g.*,



There now appears to be no reason to invoke oxygen difluoride or hypofluorous acid as intermediates, since similar results (aside from product hydrolysis) are obtained with water or acetonitrile as fluorination solvents. Enolization of the substrates is unnecessary since simple amines can be fluorinated in buffered aqueous solutions,[12] and weakly basic amines, in liquid HF.[13] There is no evidence of fluorine addition to carbonyl groups in the uncatalyzed fluorination of simple esters.[14] The displacement of acylium ions is well known with other electrophilic reagents. The simplest mechanism consistent with the available experimental data is the electrophilic displacement of hydrogen and acylium ions by molecular fluorine.

(9) T. E. Stevens, *J. Org. Chem.*, **31**, 2025 (1966).
(10) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).
(11) V. Grakauskas, U. S. Patent 3,350,172 (Oct 31, 1967).
(12) C. M. Sharts, *J. Org. Chem.*, **33**, 1008 (1968).
(13) C. L. Coon, M. E. Hill, and D. L. Ross, *ibid.*, **33**, 1387 (1968).
(14) V. Grakauskas, *ibid.*, **34**, 963 (1969).

Experimental Section

General.—Fluorinations were conducted in a glass standard taper three-necked flask fitted with a mechanical stirrer, a glass tube extending below the liquid level used as a gas inlet, and a standard taper thermometer well with an opening for gas exit. Standard fluorine-handling hardware[15] was used, and the fluorine was diluted fourfold to sixfold with nitrogen. Exit gases were vented through an aqueous potassium iodide trap. Safety shielding is required for the fluorinations and for handling NF compounds.

Methyl-N-fluoroformamide.—Methylformamide (100 g, 1.7 mol) was fluorinated without a solvent with 0.67 mol of fluorine at −30 to −40° over a 2.5-hr period. A mixture of methyldifluoramine[5] and hydrogen fluoride (12 g, ir identification) was removed at 10–15° (25 mm), and the remaining product was vacuum transferred at 25° (0.2 mm) into a −80° receiver. Distillation of the condensate gave 18.0 g (31% yield) of 93% pure (gc analysis) methyl-N-fluoroformamide, bp 76–77°. An analytical sample was isolated by gas chromatography (10 ft × 0.25 in. column of 25% butyl phthalate on Chromosorb P, 75°, 50-cc/min He flow), which showed four more volatile compounds.

Anal. Calcd for C_2H_4NFO: C, 31.17; H, 5.23; N, 18.18; F, 24.66. Found: C, 31.31; H, 5.39; N, 18.0; F, 24.1.

The proton nmr spectrum ($CDCl_3$ solution) showed a doublet (J = 26.2 cps) at δ 3.34 for the methyl and a doublet (J = 13 cps) at 8.58 for –CHO. The fluorine spectrum showed a broad signal at ϕ^* +67.1. The infrared spectrum showed the following peaks (μ): 3.45 (w), 5.86 (s), 6.74 (w), 7.0 (w), 7.60 (m), 8.70 (m), 9.0 (m), 9.69 (m), 9.9 (sh), and 12.2 (s).

When the fluorination was conducted in aqueous solution only methyldifluoramine was obtained.

Ethyl-N-fluoroformamide.—A solution of 73 g (1.0 mol) of ethylformamide in 350 ml of water was treated with 1 mol of fluorine at 0–5°. Ethyldifluoroamine (4.5 ml), identified by its infrared spectrum,[5] was collected in a −80° trap in series with the fluorination flask. The aqueous layer was extracted with three 100-ml portions of ether, dried, and distilled to give 5.0 g (5.5% yield) of ethyl-N-fluoroformamide, bp 20–21° (25 mm), $n^{25}D$ 1.3930.

Anal. Calcd for C_3H_6NFO: C, 39.55; H, 6.64; N, 15.38; F, 20.86. Found: C, 39.60; H, 6.81; N, 15.4; F, 21.1.

The proton nmr spectrum ($CDCl_3$ solution) consisted of a triplet (J = 7.5 cps) at δ 1.31 for the methyl, a doublet (J_{HF} = 31.2 cps) of quartets (J_{HH} = 7.5 cps) at 3.84 for the methylene, and a doublet (J_{HF} = 13.3 cps) at 8.53 for –CHO. The fluorine spectrum showed a broad unresolved signal at ϕ^* +81.7. The infrared spectrum showed a carbonyl band at 5.8 and an NF band at 10.5 μ.

The fluorination of 100 g (1.37 mol) of ethylformamide (no solvent) with 0.32 mol of diluted fluorine at −40 to −45° over a 2.5-hr period gave 4 ml of ethyldifluoramine and 12.0 g (41% yield based on fluorine) of ethyl-N-fluoroformamide.

Butyl-N-fluoroacetamide.—A solution of 86.5 g (0.75 mol) of butylacetamide in 450 ml of water was fluorinated with 0.75 mol of fluorine at 0–5°. The product was extracted with three 50-ml portions of methylene chloride, dried over sodium sulfate, and distilled to give 2.0 g (1.5% yield) of 75% pure butyl-N-fluoroacetamide, bp 45–46° (25 mm). An analytical sample was prepared by gas chromatography (6 ft × 0.25 in. column of 10% Ucon 50 HB100 on Fluoropak 80, 115°, 75-cc/min He flow, rention time 28 min).

Anal. Calcd for $C_6H_{12}NFO$: C, 54.12; H, 9.08; N, 10.52; F, 14.27. Found: C, 54.00; H, 9.11; N, 10.8; F, 14.6.

The proton nmr spectrum (CCl_4 solution) showed an irregular triplet at δ 0.95 for $-CH_2CH_3$, a doublet of triplets at 3.73 (J_{HF} = 33.8 cps) for $-NFCH_2CH_2-$, a multiplet at 1.5 for the other methylenes, and a doublet (J_{HF} = 7.6 cps) at 2.12 for CH_3CONF-. The fluorine spectrum consisted of a triplet (J = 33.8 cps) of quartets (J = 7.3 cps) at ϕ^* + 66.37. The infrared spectrum showed a carbonyl at 5.90 and relatively weak bands in the NF region at 10.01, 10.5, 11.0, and 11.4 μ.

β-Difluoraminopropionic Acid.—Fluorination of 26.2 g (0.20 mol) of N-acetyl-β-alanine in water (0.4 mol of fluorine, 5 hr),

(15) Allied Chemical Corp. Data Sheet PD-TA-85413A.

extraction with ether, drying over Drierite, and distillation gave 9.0 g (36% yield) of β-difluoraminopropionic acid, identical with that prepared previously.[6]

Fluorination of 2-Pyrrolidinone.—A solution of 85 g (1.0 mol) of 2-pyrrolidinone in 1 l. of water was treated with 1.0 mol of fluorine (0–5°, 1.5 hr). The product was extracted with five 75-ml portions of methylene chloride, dried, and distilled to give 17 g (16.5% yield) of N-fluoro-2-pyrrolidinone, bp 37–38° (0.15 mm), $n^{25}D$ 1.4390, and 15 g (11% yield) of 4-difluoraminobutyric acid, bp 52–54° (0.15 mm).

The infrared spectrum of N-fluoro-2-pyrrolidinone showed a carbonyl band at 5.73 and bands in the NF region at 10.0 (s), 10.85 (w), and 11.18 μ (w). The proton nmr spectrum (CCl_4 solution) consisted of a doublet (J_{HF} = 9.6 cps) of irregular triplets at δ 3.67 for $-CH_2NF-$ and a multiplet at 2.25 for the other methylenes. The fluorine spectrum consisted of a broad signal at ϕ^* +71.2.

Anal. Calcd for C_4H_6NFO: C, 46.60; H, 5.87; N, 13.57; F, 18.43. Found: C, 46.22; H, 5.70; N, 13.4; F, 18.9.

The proton nmr spectrum (CCl_4 solution) of 4-difluoraminobutyric acid consisted of a singlet at δ 12.37 for –COOH, a triplet of triplets (J_{HF} = 30 cps) for NF_2CH_2- at 3.63, a triplet at 2.58 for $-CH_2COOH$, and a quintet at 2.07 for the internal methylene. The fluorine spectrum consisted of a triplet (J = 30 cps) at ϕ^* −55.0.

Anal. Calcd for $C_4H_7NF_2O_2$: C, 34.54; H, 5.07; N, 10.07; F, 27.32. Found: 34.47; H, 5.13; N, 9.88; F, 27.0.

In another experiment, 140 g (1.65 mol) of 2-pyrrolidinone was fluorinated with no solvent (0.5 mol of fluorine, 2.5 hr, 0–5°). Some localized ignition at the inlet and charring took place. Volatile products were vacuum transferred at ambient temperature into a −80° receiver. Distillation of the condensate gave 12.5 g (24% yield) of N-fluoro-2-pyrrolidinone, bp 38–39° (0.2 mm). The forecut of this distillation, bp <20° (0.2 mm), 1.5 g, was found by gas chromatography (14 ft × 0.25 in. column of 10% 10% diethylene glycol adipate on Fluoropak 80, 80°, 50-cc/min He flow) to consist of 95% 3-difluoraminobutyryl fluoride. An analytical sample was isolated by gas chromatography.

Anal. Calcd for $C_4H_6NF_3O$: C, 34.05; H, 4.29; N, 9.93; F, 40.39. Found: C, 34.20; H, 4.23; N, 10.05; F, 39.2.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet of triplets at δ 3.58 (J_{HF} = 28.9 cps) for NF_2CH_2-, a quintet at 2.08 for $CH_2CH_2CH_2$, and a triplet at 2.68 for $-CH_2C(=O)-$. The fluorine spectrum consisted of a triplet at ϕ^* −54.16 for NF_2 and a singlet at −43.87 for –CF. The infrared spectrum

$$\begin{matrix} & \| \\ & O \end{matrix}$$

showed a carbonyl band at 5.48 and bands in the NF region at 9.85 (m), 10.3 (m), 11.0 (m), 11.37 (m), 11.6 (m), and 12.3 μ (s).

N-Fluoro-ε-caprolactam.—A solution of 113 g (1.0 mol) of ε-caprolactam in 1 l. of water was treated with 1.0 mol of fluorine (0–5°, 3 hr). The product was extracted with four 75-ml portions of methylene chloride, and the methylene chloride solution was extracted with cold aqueous sodium bicarbonate solution. The methylene chloride solution was dried and distilled to give 26 g (20% yield) of N-fluoro-ε-caprolactam, bp 60–62° (0.2–0.3 mm), $n^{25}D$ 1.4640.

Anal. Calcd for $C_6H_{10}NFO$: C, 54.94; H, 7.69; N, 10.68; F, 14.49. Found: C, 54.61; H, 7.52; N, 10.2; F, 15.0.

The proton nmr spectrum (CCl_4 solution) consisted of a doublet of triplets (J_{HF} = 28.5 cps) at δ 3.89 for CH_2NFCO-, a multiplet at 2.4 for $-CH_2CO-$, and a multiplet at 1.77 for the other methylenes. The fluorine spectrum consisted of a triplet (J = 29.6 cps) at ϕ^* +44.0. The infrared spectrum showed a carbonyl band at 5.88 and bands in the NF region at 9.8 (w), 10.18 (s), 10.42 (m), 10.70 (s), 11.82 (s), 12.4 (m), and 12.6 μ (s).

The distillation residue contained ε-caprolactam, and acidification of the bicarbonate solution gave 6-difluoraminohexanoic acid.

6-Difluoraminohexanoic Acid.—A solution of 56.5 g (0.50 mol) of ε-caprolactam in 650 ml of water was treated with 1.0 mol of fluorine at 0–5°. The product was extracted with ether and the ether solution was extracted with sodium bicarbonate solution at 0–5°. The sodium bicarbonate solution was acidified with sulfuric acid, and the product was extracted with methylene chloride, dried, and stripped of solvent to give 40 g (46% yield) of 6-difluoraminohexanoic acid. Unreacted ε-caprolactam was recovered from the ether layer.

Anal. Calcd for $C_6H_{11}NF_2O_2$: C, 43.12; H, 6.63; N, 8.4; F, 22.7. Found: C, 43.47; H, 6.24; N, 8.3; F, 21.9.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet of triplets (J_{HF} = 30 cps, J_{HH} = 8 cps) at δ 3.52 for NF_2CH_2-, multiplets at 1.75 and 2.4 for the other methylenes, and a singlet at 12.20 for –COOH. The fluorine spectrum consisted of a triplet (J = 30 cps) of doublets (J = 7 cps) at ϕ^* −55.7. The infrared spectrum showed broad OH–CH absorption at 3–4, carbonyl at 5.88, and bands in the NF region at 9.8, 10.75, 11.0, and 11.7 μ.

Fluorination of N,N′-Diformyl-1,3-diaminopropane.—Fluorination of 26 g (0.20 mol) of N,N′-diformyl-1,3-diaminopropane in 350 ml of water (0.8 mol of fluorine, 0–5°), extraction with methylene chloride, and distillation gave 2.5 g of colorless liquid, bp 26–30° (25 mm). Gas chromatography (6 ft × 0.25 in column of 10% dioctyl phthalate on Fluoropak 80, 70°) showed that the sample contained, in the order of elution, 33% (2.5% yield) 1,3-bis(difluoramino)-1-fluoropropane and 55% (5.6% yield) 1,3-bis(difluoramino)propane. The latter was identified by its spectra.[3]

The proton nmr spectrum of 1,3-bis(difluoramino)-1-fluoropropane (CCl_4 solution) consisted of a triplet of triplets (J_{HF} = 27.6 cps) at δ 3.73 for $NF_2CH_2CH_2-$, a broad multiplet at 5.45 for the methine, and a multiplet at 2.27 for the other methylene. The fluorine spectrum consisted of a poorly resolved triplet ($J \sim 25$ cps) at ϕ^* −53.37 for NF_2CH_2-, a broadened AB quartet [ϕ^*_A −29.2, ϕ^*_B −19.3 (J_{AB} = 610 cps)] for $CHFNF_2$, and a doublet (51 cps) of triplets (19 cps) at +173.41 for $-CH_2CHF-$. Lack of observable coupling between adjacent CF and NF_2 groups has been observed previously.[3]

Anal. Calcd for $C_3H_5N_2F_5$: C, 21.95; H, 3.05; N, 17.05; F, 57.9. Found: C, 21.67; H, 3.31; N, 16.2; F, 56.2.

In another experiment, the fluorination of 130 g (1.0 mol) of N,N′-diformyl-1,3-diaminopropane (no solvent, 1.5 mol of fluorine) was carried out at 10–20° over a 6.5-hr period. The mixture was washed with water, dried, and distilled to give 8 g of impure 1,3-bis(difluoramino)propane and 4.0 g of N,N,N′-trifluoro-N′-formyl-1,3-diaminopropane, bp 31–32° (0.2–0.3 mm), of approximately 95% purity. An analytical sample was obtained by gas chromatography.

Anal. Calcd for $C_4H_7N_2F_3O$: C, 30.77; H, 4.52; N, 17.94; F, 36.51. Found: C, 30.41; H, 4.60; N, 18.0; F, 36.6.

The proton nmr spectrum (CCl_4 solution) showed a quintet (J = 8 cps) at δ 2.14 for $CH_2CH_2CH_2$, a triplet of triplets (J_{HF} = 28.7, J_{HH} = 8 cps) at 3.61 for $NF_2CH_2CH_2$, a doublet (J_{HF} = 32.6 cps) of triplets at 3.92 for CH_2CH_2NF-, and a doublet (J = 11.3 cps) at 8.59 for CHO. The fluorine spectrum consisted of a triplet (J = 32 cps) of doublets (J = 11 cps) at ϕ^* +79.1 for CH_2NFCHO, and a triplet (J = 28 cps) at ϕ^* −54.6 for NF_2.

Fluorination of N-Formylethanolamine.—The product of fluorination of 44.5 g (0.5 mol) of N-formylethanolamine (350 ml of water, 1 mol of fluorine, 0–5°, 2 hr) was extracted with five 25-ml portions of methylene chloride, drie dover sodium sulfate, treated with solid sodium bicarbonate, and distilled to give 17.5 g of liquid, bp 38–45° (25 mm). Gas chromatography indicated a mixture consisting of 11% 2-difluoraminoethanol and 89% 2-difluoraminoethyl formate.

The infrared spectrum of the latter showed carbonyl at 5.85 and bands in the NF region at 9.77 (m), 10.34 (s), 11.22 (w), 11.9 (s), and 12.5 μ (s).

Anal. Calcd for $C_3H_5NF_2O_2$: C, 28.8; H, 4.03; N, 11.2; F, 30.4. Found: C, 28.7; H, 4.15; N, 11.2; F, 30.4.

A solution of 10.0 g of the above mixture in 15 ml of methanol containing 1 drop of sufuric acid was heated at 55–60° for 2 hr and then distilled to give 6.1 g of 90% 2-difluoraminoethanol.

Fluorination of N-Acetylethanolamine.—The product of fluorination of 103 g (1.0 mol) of N-acetylethanolamine (650 ml of water, 2 mol of fluorine, 0–5°) was extracted with five 40-ml portions of methylene chloride, dried over sodium sulfate, treated with solid sodium bicarbonate, and distilled to give 23 g of colorless liquid, bp 40–50° (2t mm), and 5.0 g, bp 29–30° (0.1 mm). Gas chromatography showed that the 23-g fraction contained 15% 2-difluoraminoethanol (3.6% yield) and 80% 2-difluoraminoethyl acetate (13% yield), and that the 5-g portion contained 69% unidentified nonfluorinated compound and 26% 2-difluoraminoethyl fluoroacetate (0.8% yield). Analytical samples were prepared by gas chromatography.

The proton nmr spectrum of 2-difluoraminoethanol ($CDCl_3$ solution) consisted of a singlet at δ 2.25 for the hydroxyl and multiplets for the methylenes. The fluorine spectrum consisted of a triplet (J = 26 cps) at ϕ^* −54.88. The infrared spectrum

showed prominent bands at 3.0, 9.28, 9.56, 10.43, 11.1, 11.9, and 12.61 μ.

Anal. Calcd for $C_2H_5NF_2O$: C, 24.75; H, 5.16; N, 14.44; F, 39.15. Found: C, 24.59; H, 5.30; N, 14.3; F, 38.5.

The proton nmr spectrum (CCl_4 solution) of 2-difluoraminoethyl acetate consisted of a singlet at δ 2.04 for $-\overset{\|}{C}-CH_3$, a triplet of triplets (J_{HF} = 28, J_{HH} = 7 cps) at 3.70 for $NF_2CH_2CH_2$, and a multiplet at 4.2 for the other methylene. The fluorine spectrum showed a triplet (J = 25 cps) at ϕ^* −54.57. The infrared spectrum showed carbonyl at 5.78 μ.

Anal. Calcd for $C_4H_7NF_2O_2$: C, 34.54; H, 5.07; N, 10.07; F, 27.3. Found: C, 34.40; H, 5.16; N, 9.87; F, 27.8.

The proton nmr spectrum of 2-difluoraminoethyl fluoroacetate (CCl_4 solution) consisted of a triplet of triplets (J_{HF} = 25, J_{HH} = 6 cps) at δ 3.78 for $NF_2CH_2CH_2$, a triplet (J = 7 cps) at 4.58 for $-CCH_2-$, and a doublet (J = 46.4 cps) at 4.83 for CH_2F-. The fluorine spectrum showed a triplet (J = 27 cps) at ϕ^* −54.2 for NF_2 and a triplet (J = 46.7 cps) at ϕ^* +231.7 for CF.

Anal. Calcd for $C_4H_6NF_3O_2$: C, 30.57; H, 3.85; N, 8.92; F, 36.3. Found: C, 30.96; H, 3.65; N, 9.07; F, 35.5.

Ethylfluoroammonium Bisulfate.—A solution of 0.4 g of ethyl-N-fluoroformamide in 2 g of concentrated sulfuric acid was heated at 65–70° for 45 min; gas evolution began at 45°. The fluorine nmr spectrum, which consisted of a triplet (J_{NH-F} = 42.5 cps) of triplets (J_{CH-F} = 28.7 cps) at −15.51 ppm from external trifluoroacetic acid, was consistent with those of previously reported fluoroammonium salts.[7]

Methylfluoroammonium Bisulfate.—The above procedure using methyl-N-fluoroformamide gave a methylfluoroammonium bisulfate solution in sulfuric acid identified by nmr spectra.[7]

5-Cyanovaleric Acid.—A solution of 5 g of sodium hydroxide in 20 ml of water was added dropwise over a 15-min period to a solution of 5.0 g (0.030 mol) of 6-difluoraminohexanoic acid in 25 ml of water at 0–3°. The solution was than allowed to stand at ambient temperature for 15 min and was acidified with sulfuric acid. The product was extracted with three 20-ml portions of methylene chloride, dried, and distilled to give 2.0 g (59% yield) of 5-cyanovaleric acid with the reported physical properties.[16]

Ethyl 6-Difluoraminohexanoate.—A solution of 3.8 g (0.023 mol) of 6-difluoraminohexanoic acid in ethanol containing 0.1 ml of sulfuric acid was refluxed for 8 hr. Ice (100 g) was added and the product was extracted with methylene chloride and distilled to give 3.5 g (78% yield) of ethyl 6-difluoraminohexanoate, bp 49–50° (0.2 mm), $n^{25}D$ 1.4060.

Anal. Calcd for $C_8H_{15}NF_2O_2$: C, 49.2; H, 7.74; N, 7.17; F, 19.5. Found: C, 48.9; H, 7.2; N, 7.10; F, 19.8.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet at δ 1.23 and a quartet at 4.05 for CH_3CH_2O-, a triplet of triplets (J_{HF} = 29, J_{HH} = 7 cps) at 3.43 for NF_2CH_2-, and multiplets at 1.57 and 2.25 for the other methylenes. The fluorine spectrum consisted of a triplet (J = 30 cps) at ϕ^* −55.8. The infrared spectrum showed carbonyl at 5.8 μ and weak bands in the NF region at 10.3, 10.8, 11.1, and 11.65 μ.

Similarly, **methyl 6-difluoraminohexanoate** and **ethyl γ-difluoraminobutyrate** were prepared, bp 45–46° (0.2 mm), $n^{25}D$ 1.4050, and bp 26–27° (0.2 mm), $n^{25}D$ 1.3932, respectively.

Anal. Calcd for $C_7H_{13}NF_2O_2$: C, 46.41; H, 7.20; N, 7.7; F, 21.0. Found: C, 46.1; H, 7.10; N, 7.4; F, 21.5.

Anal. Calcd for $C_6H_{11}NF_2O_2$: C, 43.10; H, 6.63; N, 8.38; F, 22.73. Found: C, 42.82; H, 6.41; N, 8.69; F, 23.0.

γ-Difluoraminobutyryl Chloride and γ-Difluoraminobutyric Anhydride.—Thionyl chloride (40 g, 0.33 mol) was added dropwise, with stirring, to a solution of 42 g (0.30 mol) of γ-difluoroaminobutyric acid in 220 ml of dry benzene. With a reflux condenser in place, the solution was heated at 60–65° for 45 min. Distillation gave 43 g (91% yield) of γ-difluoraminobutyryl chloride, bp 29° (0.2 mm), $n^{25}D$ 1.4145.

Anal. Calcd for $C_4H_6NF_2ClO$: C, 30.50; H, 3.84; N, 8.89; F, 24.12. Found: C, 30.48; H, 3.82; N, 9.12; F, 24.0.

The proton nmr spectrum (CCl_4 solution) showed a quintet for $CH_2CH_2CH_2$ at δ 2.53, a triplet of triplets (J_{HF} = 29, J_{HH} = 8 cps) at 3.57 for $NF_2CH_2CH_2$, and a triplet at 3.10 for $-CH_2-COCl$. The fluorine spectrum consisted of a triplet (J = 28 cps) at ϕ^* −54.6. The infrared spectrum showed carbonyl at 5.60 and bands in the NF region at 10.4 (s), 10.62 (m), 11.17 (m), 11.45 (s), and 11.92 μ (s).

A similar reaction using 15.3 g (0.11 mol) of γ-difluoraminobutyric acid and 12.0 g (0.10 mol) of thionyl chloride gave 9.0 g (57% yield) of γ-difluoraminobutyryl chloride and 4.0 g (30% yield) of γ-difluoraminobutyric anhydride, bp 105–106° (0.1–0.2 mm), $n^{25}D$ 1.4130.

Anal. Calcd for $C_8H_{12}N_2F_4O_3$: C, 36.93; H, 4.65; N, 10.77; F, 29.17. Found: C, 36.62; H, 4.56; N, 10.6; F, 30.5.

The infrared spectrum showed carbonyl bands at 5.50 and 5.71 μ.

γ-Difluoraminopropyl Isocyanate.—A stirred suspension of 13.7 g (0.21 mol) of recrystallized sodium azide in a solution of 31.5 g (0.20 mol) of γ-difluoraminobutyryl chloride in 360 ml of dry benzene was heated (using a reflux condenser) at 70–73° until nitrogen evolution ceased (50 min). The solution was filtered and distilled to give 23.0 g (85% yield) of γ-difluoraminopropyl isocyanate, bp 66–67° (45 mm), $n^{25}D$ 1.4028.

Anal. Calcd for $C_4H_6F_2N_2O$: C, 35.30; H, 4.44; N, 20.58; F, 27.92. Found: C, 35.11; H, 4.40; N, 20.2; F, 27.9.

The fluorine nmr spectrum (CCl_4 solution) consisted of a triplet (J = 28 cps) at ϕ^* −55.2. The infrared spectrum showed NCO at 4.42 and bands in the NF region at 10.17, 10.98, 11.27, and 11.7 μ.

Ethyl N-(3-Difluoraminopropyl)carbamate.—A solution of 1.36 g (0.010 mol) of γ-difluoraminopropyl isocyanate in 10 ml of ethanol was allowed to stand at ambient temperature for 18 hr. Distillation gave 1.64 g (90% yield) of ethyl N-(3-difluoraminopropyl)carbamate, bp 66–67° (0.1–0.2 mm), $n^{25}D$ 1.4190.

Anal. Calcd for $C_6H_{12}N_2F_2O_2$: C, 39.56; H, 6.64; N, 15.38; F, 20.86. Found: C, 39.89; H, 6.51; N, 15.1; F, 21.2.

Fluorination of Cyclohexanecarboxamide.—A suspension of 12.7 g (0.10 mol) of cyclohexanecarboxamide in 350 ml of acetonitrile was treated with 0.2 mol of fluorine at −15°. Half of the solution was stirred with solid sodium sulfate and distilled to give 1.1 g (18% yield) of cyclohexyl isocyanate, bp 28–30° (0.1 mm), identified by spectral comparison with an authentic sample. The remaining acetonitrile solution was concentrated to 10 ml under vacuum and the residue was added to 100 ml of aqueous 10% sodium bicarbonate. The aqueous phase was acidified and was extracted with 3–15-ml portions of methylene chloride. Removal of the solvent gave 3.1 g (48% yield) of cyclohexanecarboxylic acid, identical with an authentic sample.

Fluorination of 0.1 mol of the amide in 350 ml of water (0–5°, 0.2 mol of fluorine) gave, after extraction with hexane, 2.0 g (16% conversion, 43% yield) of cyclohexyl isocyanate and 8.0 g of the insoluble starting material.

Tetrafluorohydrazine.—A suspension of 23.6 g (0.40 mol) of acetamide in 25 ml of acetonitrile was fluorinated (0.8 mol of fluorine, 2 hr, −10 to −20°). A 10% aliquot of the resulting solution was added dropwise under a stream of helium to a stirred solution of 2.0 g of chromic anhydride in 40 ml of water at 5–7°. The reaction flask was connected, in series, to a 0° trap, a calcium sulfate drying tower, a −78° trap, and a −195° trap. After 20 min, the final trap contained 0.010 mol (50% yield by volumetric measurement) of tetrafluorohydrazine identified by its infrared spectrum.[17]

Registry No.—γ-Difluoraminobutyric anhydride, 236-49-82-3; γ-difluoraminopropyl isocyanate, 23649-83-4; ethyl N-(3-difluoraminopropyl)carbamate, 21298-39-5; N-fluoro-ϵ-caprolactam, 23649-75-4; 6-difluoraminohexanoic acid, 23649-76-5; ethyl 6-difluoraminohexanoate, 23649-78-7; methyl 6-difluoraminohexanoate, 23649-79-8; ethyl γ-difluoraminobutyrate, 23649-80-1; γ-difluoraminobutyryl chloride, 23649-81-2.

Acknowledgment.—The authors wish to thank Dr. H. M. Nelson and Mr. L. A. Maucieri for the nmr analysis and Mr. K. Inouye for the elemental analysis.

(16) W. Reppe, *et al.*, *Ann. Chem.*, **596**, 93 (1955).

(17) C. B. Colburn, *Advan. Fluorine Chem.*, **3**, 113 (1963).

Bicyclic Enamines. V. Cumulated Cyclopropylenamines[1,2]

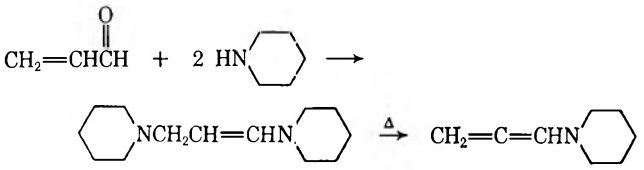
A. GILBERT COOK, SUSAN B. HERSCHER, DIANA J. SCHULTZ, AND JONATHAN A. BURKE

Department of Chemistry, Valparaiso University, Valparaiso, Indiana 46383

Received September 16, 1969

Cyclopropylcarbinylaminals were studied. Certain of these aminals possess double bonds in such a steric position that they aid in the formation of cumulated cyclopropylenamines. These cumulated cyclopropylenamines show uv maxima of high intensity in the 300-nm region. The origins of these observed phenomena are discussed. The basicities of various cyclopropyl methyl ketones are reported and compared with those of other methyl ketones. The basicity of the tricyclic 2-acetyltricyclene is much stronger than that of other reported cyclopropyl ketones, with a pK_{BH^+} of -4.06.

One of the earliest reports of the formation of enamines[3] describes the formation of what is probably a cumulated dienamine.[4] This synthesis is carried out by treating an α,β-unsaturated aldehyde such as acrolein with 2 mol of a secondary amine such as piperidine

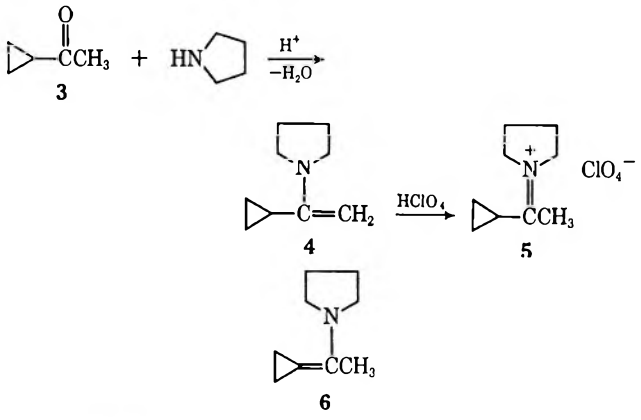


to form amino enamine **1** (a vinylogous aminal). Vacuum distillation of **1** produced cumulated dienamine **2**. This type of compound has been virtually ignored since this early report.[5]

The cyclopropyl group has many chemical and physical properties which are analogous to those observed in alkene groups.[6] This would lead one to suspect that tertiary cyclopropylamines behave like enamines in such typical reactions as alkylation and acylation. However, this similarity in chemical behavior between cyclopropylamines and enamines has not been observed.[7]

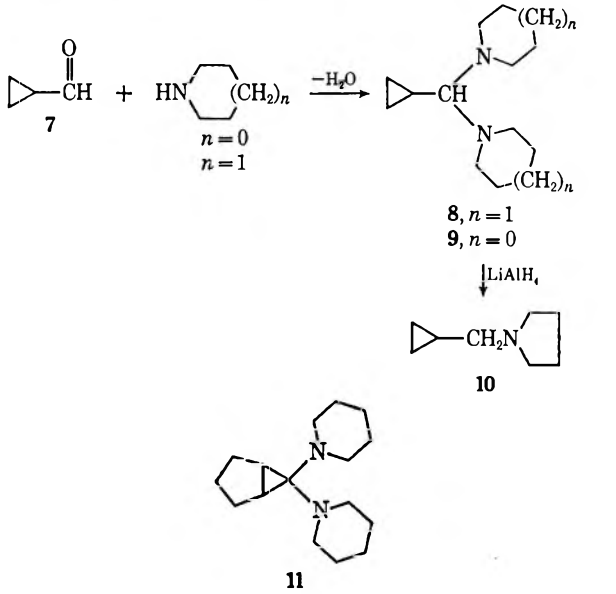
Although cyclopropylamines themselves do not show any of the typical enamine properties, the properties of cumulated cyclopropylenamines is a significant area for investigation. The problem of constructing such a system for investigation then arises. The reaction of secondary amines with ketones or aldehydes is the most widely used method of synthesizing enamines,[3] so the reaction of secondary amines with cyclopropyl ketones or aldehydes should be a fruitful approach.

The treatment of methyl cyclopropyl ketone (**3**) with pyrrolidine in the presence of an acid catalyst produced, beside ring-fission products,[8] a small amount of enamine **4**. Identification of **4** was made through its ir spectrum and spectral and elemental analysis of its perchlorate salt **5**.[9] The ir spectrum of the enamine



product indicated that a trace of cumulated cyclopropyl enamine **6** might also be present, but it was very unstable and was not positively identified.

The reaction of cyclopropanecarboxaldehyde (**7**) with piperidine results in the formation of aminal **8**.[10] In a similar manner aminal **9** is produced when **7** is



treated with pyrrolidine. These aminals are thermally stable, and hence they are distillable and not readily converted into "cumulated" enamines, as was vinylogous aminal **1**, which was studied by Mannich and coworkers.[4] Aminals are commonly produced by the reaction of a secondary amine with an aldehyde,[3,11-13]

(1) For the previous article in the series, see A. G. Cook and W. M. Kosman, *Tetrahedron Lett.*, 5847 [1966].

(2) Support of this work by a grant from the Petroleum Research Fund of the American Chemical Society and by a Valparaiso University Grant is gratefully acknowledged.

(3) For a comprehensive review of enamines, see "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1969.

(4) C. Mannich, K. Handke, and K. Roth, *Chem. Ber.*, **69**, 2112 (1936).

(5) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967).

(6) M. Yu Lukina, *Usp. Khim.*, **31**, 419 (1962).

(7) R. A. Fouty, Ph.D. Dissertation, University of Pennsylvania, 1962.

(8) A. G. Cook and K. E. Ungrodt, unpublished data.

(9) J. V. Paukstelis, Ph.D. Dissertation, University of Illinois, 1964. He made this ternary iminium salt by the direct reaction of ketone **3** with pyrrolidium perchlorate.

(10) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

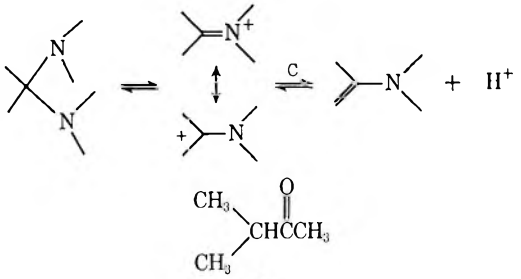
(11) C. Mannich and H. Davidsen, *Chem. Ber.*, **69**, 2106 (1936).

(12) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).

(13) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).

but upon distillation 1 mol of the amine is usually eliminated and an enamine is formed. It has been shown that aminals and enamines are in equilibrium in some cases.[14] Aminal **9** is reduced to amine **10** by treatment with lithium aluminum hydride, a reaction parallel to the borohydride reduction of aminal **11** to the monoamine reported by Szmuszkovicz.[15]

Stable aminals are formed from aldehydes with no α hydrogens such as benzaldehyde,[16] from cyclopropanones,[15,17,18] and from cyclopropylcarboxaldehydes such as **7**. Apparently, cyclopropanones form stable aminals rather than enamines because of the excessive ring strain that would be introduced by the formation of an enamine, but the question remains as to the reluctance of aminals formed from cyclopropylcarboxaldehydes to yield enamines under the normal conditions. There are three steps which together determine the overall rate of enamine formation,[3,19] and the last of



13

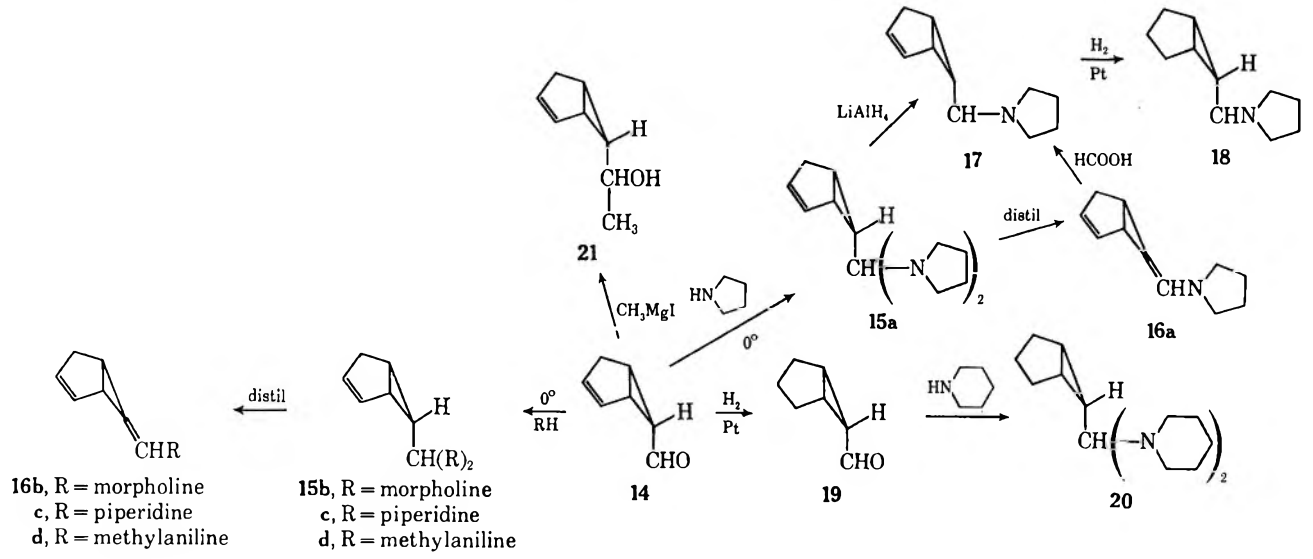
these steps (step C) has direct bearing on the question at hand. Step C depends upon the ease of losing a proton from the β-carbon atom of the ternary iminium ion.

The base-catalyzed exchange of deuterium for the methine hydrogen in isopropyl methyl ketone (**13**) is much more rapid than that for the methine hydrogen in cyclopropyl methyl ketone (**3**).[20,21] In fact, the base-catalyzed exchange of deuterium for cyclopropyl methine hydrogens is essentially nonexistent[22] in spite of the s character of the exocyclic bonding orbitals.[23] The endocyclic carbon–carbon bonds in cyclopropane are $sp^{4.12}$ hybridized[24–27] and can have pseudoconjugation with an adjacent π-electron system when the plane of the cyclopropane ring is parallel to the axis of the p orbital.[28–35] The exocyclic carbon–carbon bonds are $sp^{2.28}$ hybridized. Any change in the endocyclic carbon–carbon bonds toward sp^3 hybridization causes increased strain in the ring. Thus the orbital geometry of the carbanionlike transition states in this base-catalyzed hydrogen exchange makes meaningful delocalization of charge impossible; *i.e.*, because of the cyclopropane ring the unshared electron pair is in an orbital with a smaller amount of p character than would be desirable for maximum overlap with the carbonyl p orbital. The formation of an enamine from an hemiaminal or an aminal is an analogous situation, since the transition state in step C in going from the ternary iminium ion to the enamine would be very similar to the carbanion-like transition states in the base-catalyzed hydrogen exchange, and for similar reasons the enamine does not readily form. It has been shown from heats of hydrogenation studies that a double bond exocyclic to a cyclopropane ring is very highly strained,[36] as would be expected from the theoretical model, since this would mean the use of a p orbital in the cyclopropyl carbon and sp^x would have $x < 4.12$. Thus it would take some special type of stabilization to cause aminals such as **8** or **9** to form their respective enamines.

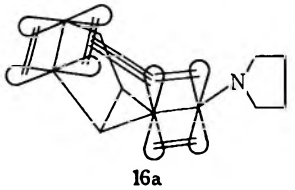
Bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde[37] (**14**) possesses within its structure the potential for such stabilization. Treatment of **14** with pyrrolidine and anhydrous potassium carbonate at 0° causes a very exothermic reaction to take place with the production of aminal **15a**, which, upon slow distillation, gives enamine **16a** in an overall 70% yield. This cumulated cyclopropylenamine can be reduced with 98% formic acid[38] to produce amine **17**. The exact stereochemistry of the reduction product was not determined, but it is probably a mixture of *endo* and *exo* isomers. The pure *endo* isomer of amine **17** was synthesized by the reduction of aminal **15a** with lithium aluminum hydride. This in turn was catalytically hydrogenated to saturated amine **18**. Similar sequences of aminal formation followed by enamine production upon distillation were carried out using morpholine, piperidine, and N-methylaniline as the secondary amines. These enamines are typically very unstable in the presence of air. Treatment of these cumulated cyclopropylenamines with strong acid such as perchloric acid resulted in immediate decomposition of the enamine and formation of dark, gummy tar. Allowing enamine **16a** to stand with a large excess of pyrrolidine for an extended period of time both at room temperature and elevated temperatures did not cause the formation of any noticeable amount of aminal **15a**. Aldehyde **14** underwent normal addition with methylmagnesium iodide to form alcohol **21**.

The source of the stabilization for this system which allows it to form cumulated cyclopropylenamines,

(14) P. Ferruti, D. Pocar, and G. Bianchetti, *Gazz. Chim. Ital.*, **97**, 109 (1967).
(15) J. Szmuszkovicz, E. Cerda, M. F. Grostic, and J. F. Zieserl, Jr., *Tetrahedron Lett.*, 3969 (1967).
(16) R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, **71**, 227 (1949).
(17) W. J. M. Van Tilborg, S. E. Schaafsma, H. Steinberg, and T. J. DeBoer, *Rec. Trav. Chim. Pays-Bas*, **86**, 417 (1967).
(18) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).
(19) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(20) C. Rappe and W. H. Sachs, *Tetrahedron*, **24**, 6287 (1968).
(21) W. T. Van Wijnen, H. Steinberg, and T. J. DeBoer, *Rec. Trav. Chim. Pays-Bas*, **87**, 844 (1968).
(22) H. W. Amburn, K. C. Kauffman, and H. Shechter, *J. Amer. Chem. Soc.*, **91**, 530 (1969).
(23) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 23 and 49–52.
(24) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949).
(25) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).
(26) L. L. Ingrahm, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 479.
(27) W. A. Bernett, *J. Chem. Educ.*, **44**, 17 (1967).
(28) N. C. Deno, H. G. Richey, Jr., J. S. Lui, D. N. Lincoln, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 4533 (1965).
(29) H. C. Brown and J. D. Cleveland, *ibid.*, **88**, 2051 (1966).
(30) (a) P. von Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966); (b) P. von R. Schleyer and V. Buss, *ibid.*, **91**, 5880 (1969).
(31) L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647 (1965).
(32) A. P. Krapcho and R. C. H. Peters, *Tetrahedron Lett.*, 4827 (1968).
(33) (a) C. U. Pittman, Jr., and G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 5123 (1965); (b) G. A. Olah and J. M. Bollinger, *ibid.*, **90**, 6082 (1968).
(34) J. E. Baldwin and W. D. Foglesong, *ibid.*, **90**, 4303, 4311 (1968).
(35) J. C. Martin and B. R. Ree, *ibid.*, **91**, 5882 (1969).
(36) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *ibid.*, **90**, 4315 (1968).
(37) J. Meinwald, S. S. Labana, and M. S. Chadha, *ibid.*, **85**, 582 (1963).
(38) (a) P. L. deBenneville and J. H. Macartney, *ibid.*, **72**, 3073 (1950); (b) P. L. de Benneville, U. S. Patent 2,578,787 (1951); (c) N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, **79**, 6210 (1957).



whereas other cyclopropyl systems such as cyclopropanecarboxaldehyde (7) will not, lies with the orientation of the carbon–carbon double bond in the fused five-membered ring relative to the cyclopropane ring and relative to the developing enamine double bond. The reaction of bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde (**19**) with piperidine yields only distillable aminal **20**, which demonstrates that the source of stabilization must be the cyclopentene double bond, since it is the only element missing in aldehyde **19**.



16a

Direct conjugation between the enamine double bond and the cyclopropane ring in **16a** is not possible because of their orthogonal geometry. However, the cyclopropane ring is pivital in the conjugation of this system in two ways. First, it is situated in such a manner that the axis of the π bond in the five-membered ring and the plane of the cyclopropane ring are nearly parallel, a situation allowing almost maximum overlap and pseudoconjugation. The conjugation of an olefin with cyclopropane has minimal conformational requirements[39] compared with those systems which have a greater electron demand and hence require a "bisected" geometry.[40-42] Second, the cyclopropane ring rigidly holds the enamine double bond in a position such that one of its p orbitals overlaps the π-electron cloud of the cyclopentene double bond in a homoconjugative manner.

The conjugative interaction of the cyclopentene double bond with both the enamine double bond and the cyclopropane ring (even though the enamine double bond and cyclopropane ring cannot be directly conjugated with each other) is shown by the ultraviolet maximum of 302 nm (ϵ 39,000) for enamine **16a**.

(39) C. H. Heathcock and S. R. Poulter, *J. Amer. Chem. Soc.*, **90**, 3766 (1968).
(40) W. G. Dauben and G. H. Berezin, *ibid.*, **89**, 3449 (1967).
(41) M. J. Jorgenson and T. Leung, *ibid.*, **90**, 3769 (1968).
(42) R. C. Hahn, P. H. Howard, S. M. Kong, G. A. Lorenzo, and N. L. Miller, *ibid.*, **91**, 3558 (1969).

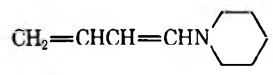
Similar maxima are exhibited by the other enamines, **16c** and **16d** (see Table I). This maximum cannot be due to the cumulated enamine double bond–cyclopropane ring alone, because similar compounds have shown no ultraviolet maxima above 200 nm,[43] nor can it be due to conjugation between the cyclopentene double bond and the cyclopropane ring alone, because vinyl cyclopropanes show maxima only below 200 nm[39] (see Table I). The rigid bicyclic configuration of systems such as enamine **16a** is necessary for the interaction of the three groups (*i.e.*, cyclopropane ring, cyclopentene, and enamine double bond). This is demonstrated by another compound which possesses these three groups in the same relative positions, but without the rigidity of the bicyclic system, namely vinylmethylenecyclopropane (**22**).[44] This compound possesses only a shoulder just past 200 nm in its ultraviolet spectrum.[45]

TABLE I
ULTRAVIOLET MAXIMA

Compd	λ_{max}^{EtOH}, nm (ϵ)
14	205 (4,350)[a]
16a	302 (39,000)
	237 (23,000)
	220 (28,000)
16c	293 (21,000)
16d	329 (32,000)
17	205 (2500)
22	Below 200[b]
23	273 (34,200)[c]
	193.5 (11,200)[d]

[a] Reference 37. [b] T. C. Shields, personal communication. [c] G. Opitz and W. Merz, *Justus Liebigs Ann. Chem.*, **652**, 139 1962). [d] Reference 39.

22



23

The ultraviolet spectrum of enamine **16a** can be best accounted for by considering it as a dienamine whose

(43) E. F. Ullman and W. J. Fanshawe, *ibid.*, **83**, 2379 (1961).
(44) T. C. Shields, W. E. Billups, and A. R. Lepley, *ibid.*, **90**, 4749 (1968).
(45) See Table I, footnote *b*.

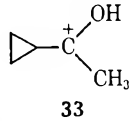
conjugation is *extended* by a cyclopropyl group.[39-42,46,47] For example, dienamine **23** (possessing a piperidine moiety) shows a uv maximum at 273 nm (ϵ 34,200).[48] A cyclopropyl group imparts a bathochromic shift of from 8 to more than 15 nm to the transition of an olefin.[39] Therefore, a cyclopropyl extended dienamine would show a uv maximum of *ca.* 288 nm, which corresponds well with the uv maximum of enamine **16c** (also possessing a piperidine moiety) of 293 nm.

Since cyclopropyl ketones and aldehydes were of great interest to us in this study, a study of the basicity of several methyl ketones was carried out, comparing the influence of a cyclopropyl ring with that of other groups. The method used to determine the basicity of these ketones is that described by Haake.[49] This method involves the measurements of the chemical shift of acetyl methyl groups as a function of sulfuric acid concentration, using the equation

$$\log \frac{\delta_B - \delta_{obsd}}{\delta_{obsd} - \delta_{BH^+}} = \log \frac{[BH^+]}{[B]} = m(pK_{BH^+} - H_0)$$

Since the H_0[50,51] scale is used to determine effective sulfuric acid concentration, the m value is a measure of the protonation behavior of the base relative to Hammett bases; *i.e.*, if $m = 1$, the base is a Hammett base. The chemical shifts were found using the methyl protons in trimethylammonium chloride as reference, and the slope (m) and intercept ($c = mpK_{BH^+}$) were determined by least squares. A summary of the results is found in Table II. The cyclopropane rings were not ruptured in the cold sulfuric acid solutions,[33a,52] as shown by comparison of the nmr spectra of the compounds both in concentrated sulfuric acid and in pure water.

A cyclopropyl ketone or aldehyde possesses greater s character in its exocyclic carbon–carbonyl carbon bond ($sp^{2.28}$–sp^2) than the isomeric acyclic ketone or aldehyde (sp^3–sp^2).[6,24-27] Therefore the cyclopropyl group is electron attracting in its inductive effect (s-character effect)[23] in a manner analogous to unsaturated groups.[53] On the other hand its mesomeric effect is similar to that of an aromatic system or an unsaturated group because of its ability to delocalize the positive charge of a cyclopropylcarbinyl cation.[54] Cyclopropylamines are weaker bases than their acyclic counterparts because of the inductive effect of the cyclopropyl group.[55,56] Cyclopropyl methyl ketone (**3**) is a stronger base than the corresponding acyclic isopropyl methyl ketone (**13**) owing to the greater importance of delocalization of positive charge in planar carbonium ion **33** than the cyclopropyl inductive effect. The base strength of **3**

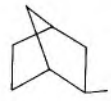


33

corresponds well with that of acetophenone (**25**), and substitution of an α methyl group into **3** to give **29** increases the basicity by *ca.* one pK unit just as a *para* methyl group does to acetophenone (**26**). Whether this is due strictly to an inductive effect, a mesomeric effect, a steric effect, or some combination of these in the cyclopropyl case is not known, although it is interesting to note that in the acyclic series of ketone **13**, introduction of a methyl group does not have this pronounced effect, as illustrated by the pK of *t*-butyl methyl ketone (**24**). Both the *endo* and *exo* isomers of the bicyclo[2.2.1]heptyl ketone **31** had identical basicities of about the same order of magnitude as the bicyclo[2.2.2] acetyl ketone **32** and the cyclohexyl ketone **27**. When the cyclopropane ring was placed in the rigid and strained tricyclic system of nortricyclyl ketone **30**, the basicity was greatly enhanced. This correlates well with the observation that a cyclopropane ring in bicyclic compounds is more basic toward hydrogen bonding and charge-transfer agents than when it is in a monocyclic compound.[57] This is attributed to an increase in the π character of the bicyclic compounds.

TABLE II

BASICITIES OF SOME METHYL KETONES[a]

Compd	R	pK_{BH^+}[b]	c[b]	m[b]	No. of points[c]
3		−6.52	−3.30 ± 0.10	0.505	10
13	$(CH_3)_2CH$	−7.42	−3.84 ± 0.05	0.518	9
24[d]	$(CH_3)_3C$	−7.1[d]			
25[e]	Phenyl	−6.51[e]		0.52	
26[f]	*p*-Tolyl	−5.47[f]			
27	Cyclohexyl	−7.03	−2.93 ± 0.013	0.416	11
28	Cyclobutyl	−6.86	−2.24 ± 0.010	0.326	9
29		−5.47	−2.55 ± 0.007	0.466	9
30		−4.06	−1.49 ± 0.002	0.367	11
31	 [g]	−7.04	−3.06 ± 0.014	0.435	11
32		−7.03	−2.85 ± 0.015	0.406	8

[a] Used nmr chemical-shift method described in ref 49 with $(CH_3)_3NH^+Cl^-$ as reference compound and H_0 values from ref 50 and 51. [b] By least squares using $\log [BH^+]/[B] = m(pK - H_0)$ with c = intercept = mpK and m = slope. Standard deviations are also given. [c] Number of points between 5 and 95% protonation used in the least-squares determination. [d] Reference 49. [e] Reference 50. [f] H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960). [g] *exo* and *endo*.

(46) J. P. Pete, *Bull. Soc. Chim. Fr.*, 357 (1967).
(47) S. Nishida, I. Moritani, E. Tsuda, and T. Teraji, *Chem. Commun.*, 781 (1969).
(48) See Table I, footnote *c*.
(49) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).
(50) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 1 (1957).
(51) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).
(52) C. U. Pittman, Jr., and S. P. McManus, *ibid.*, **91**, 5915 (1969).
(53) M. J. S. Dewar and J. M. Harris, *ibid.*, **90**, 4468 (1968).
(54) (a) R. Breslow, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, Chapter 4; (b) N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 129 (1964); (c) M. Hanack and H. J. Schneider, *Angew. Chem. Int. Ed. Engl.*, **6**, 666 (1967); (d) D. Bethell and V. Gold, "Carbonium Ions," Academic Press, London, 1967, Chapter 7.
(55) A. G. Cook, W. C. Meyer, K. E. Ungrodt, and R. H. Mueller, *J. Org. Chem.*, **31**, 14 (1966).
(56) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5030 (1951).
(57) Z. Yoshida, N. Ishibe, and H. Kusumoto, *ibid.*, **91**, 2279 (1969).

Experimental Section

The instruments used in this work were the Beckman DK-2A recording spectrophotometer, the JEOL C-60HL high-resolution nuclear magnetic resonance spectrometer, and a Perkin-Elmer Model 137 infrared spectrometer. The analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Methyl Ketones.—Cyclopropyl methyl ketone and methylcyclopropyl methyl ketone were obtained from Aldrich Chemical Co., Milwaukee, Wis. 3-Methyl-2-butanone was obtained from Distillation Products Inc., Rochester, N. Y. Cyclohexyl and cyclobutyl methyl ketones were prepared by the method of Walker and Hauser.[58] Bicyclo[2.2.2]octyl methyl ketone was prepared by the method of Ouellette and Booth.[59] A mixture of *exo*- and *endo*-bicyclo[2.2.1]heptyl methyl ketone was prepared by catalytic hyrogenation of *exo*- and *endo*-bicyclo[2.2.1]hept-2-enyl methyl ketone,[60] and pure *exo*-bicyclo[2.2.1]heptyl methyl ketone was synthesized by the method of Stockmann.[61] 2-Acetylnortricyclene was prepared by the acetylation of nortricyclene.[62]

General Procedure for Aminal and Enamine Formation from Aldehydes.—To a mixture of 1 mol of aldehyde and some anhydrous potassium carbonate was added 2 mol of secondary amine. The mixture was allowed to stand overnight under nitrogen at 0°. The reaction mixture was filtered and excess reactants were removed at room temperature *in vacuo*. The resultant aminal was purified by recrystallization or distillation. Distillation also produces enamine in some cases.

A. Cyclopropanecarboxaldehyde[63] (7) and Pyrrolidine.—1,1-Di(N-pyrrolidino)cyclopropylmethane (9) was obtained as a colorless liquid: yield 27%; bp 126–127° (15 mm); n^{20}D 1.4952; ν_{max}^{film} 3060 cm^{-1} (cyclopropyl hydrogen).

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.21; H, 11.53; N, 14.25.

B. Bicyclo[3.1.0]hex-2-ene-*endo*-carboxaldehyde (14)[37] and Pyrrolidine.—6-*endo*-[1,1-Di(N-pyrrolidino)methylbicyclo[3.1.0]hex-2-ene (15a) was produced with no enamines present (by ir analysis) at room temperature prior to distillation. Upon distillation this aminal partially decomposed to an enamine, but some of the aminal was obtained as a colorless liquid: bp 122° (1.2 mm); n^{19}D 1.5290; nmr (neat) τ 4.57 ppm (=CH).

Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.55; H, 10.41; N, 11.94.

The corresponding enamine, 6-N-pyrrolidinomethylenebicyclo[3.1.0]hex-2-ene (16a), was produced in a 70% overall yield upon slow distillation of the product: bp 81.5–83° (0.4 mm); n^{31}D 1.5804; ν_{max}^{film} 1650 cm^{-1} (C=CN); nmr (neat τ 4.50 (cyclopentene =CH) and 4.10 ppm [=C(N)H]; λ_{max}^{EtOH} 302 nm (ϵ 39,000), 237 (23,000), and 220 (28,000).

C. Aldehyde 14 and Morpholine.—6-*endo*-1,1-Di(N-morpholino)methylbicyclo[3.1.0]hex-2-ene (15b) was obtained in the form of colorless plates in quantitative yield: mp 71–73°; ν_{max}^{Nujol} 3050 cm^{-1} (cyclopropyl hydrogen); nmr (neat) τ 4.68 ppm (cyclopentene=CH).

Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.11; H, 8.90; N, 10.43.

Slow distillation of aminal **15b** gave 6-N-morpholinomethylenebicyclo[3.1.0]hex-2-ene (16b) as a colorless liquid: yield 56%; bp 81° (0.12 mm); n^{24}D 1.5783; ν_{max}^{film} 1650 cm^{-1} (C=CN); nmr (neat) τ 4.40 (cyclopentene =CH) and 4.00 ppm [=C(N)H].

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.38; H, 9.77.

D. Aldehyde 14 and Piperidine.—Distillation of the product resulted in the formation of 6-N-piperidinomethylenebicyclo[3.1.0]hex-2-ene (16c) as a colorless liquid: yield 45%; bp 89° (0.4 mm); ν_{max}^{film} 1650 cm^{-1} (C=CN); λ_{max}^{EtOH} 293 mn (ϵ 21,000).

E. Aldehyde 14 and N-Methylaniline.—6-*endo*-1,1-Di(N-methylanilino)methylbicyclo[3.1.0]hex-2-ene (15d), bp 193–194° (0.6 mm), and 6-N-methylanilinomethylenebicyclo[3.1.0]hex-2-ene (16d), bp 99° (0.15 mm), n^{20}D 1.6355, λ_{max}^{EtOH} 329 nm (ϵ 32,000), ν_{max}^{film} 1650 cm^{-1}, were obtained as light yellow liquids upon distillation of the reaction mixture in yields of 11 and 13%, respectively.

F. Bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde (19)[64] and Piperidine.—6-*endo*-1,1-Di(N-piperidino)methylbicyclo[3.1.0]-hexane (20) was obtained as a stable, distillable product: yield 23%; bp 125° (0.53 mm); n^{26}D 1.5078.

Anal. Calcd for $C_{17}H_{30}N_2$: C, 77.80; H, 11.52. Found: C, 77.76; H, 11.39.

Reaction with Lithium Aluminum Hydride. A. 1,1-Di(N-pyrrolidino)cyclopropylmethane (9).—A stirred slurry of 1.03 g (0.027 mol) of lithium aluminum hydride, 6.98 g (0.027 mol) of aminal 9, and 150 ml of ether was refluxed for 68 hr. The reaction mixture was hydrolyzed with saturated aqueous sodium sulfate, filtered, and distilled to give 2.36 g (47%) of N-cyclopropylmethylpyrrolidine (10): bp 51° (15 mm); n^{24}D 1.4593; ν_{max}^{film} 3050 cm^{-1} (cyclopropyl hydrogen); nmr (neat) τ 2.31 ppm (d, J = 6.0 Hz, $\triangleright CH_2$).

Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.08. Found: C, 76.63; H, 11.93.

B. 6-*endo*-1,1-Di(N-pyrrolidino)methylbicyclo[3.1.0]hex-2-ene (15a).—A slurry of 3.7 g of lithium aluminum hydride, 8.15 g (0.03 mol) of aminal 15a, and 200 ml of ether was refluxed overnight, and the product, 6-*endo*-N-pyrrolidinomethylbicyclo[3.1.0]hex-2-ene (17), was isolated in the usual manner: yield 90%; bp 50° (0.26 mm); n^{25}D 1.5014.

Reduction of 6-N-Pyrrolidinomethylenebicyclo[3.1.0]hex-2-ene (16a) with Formic Acid.—Reduction of 4.08 g (0.025 mol) of enamine 16a with 98–100% formic acid in the usual manner[38] resulted in the formation of 1.3 g (32%) of 6-N-pyrrolidinomethylbicyclol[3.1.0]hex-2-ene (17) (probably a mixture of *endo* and *exo* isomers): bp 53° (0.2 mm); n^{35}D 1.4990, λ_{max}^{EtOH} 205 nm (ϵ 2500).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50. Found: C, 81.10; H, 10.51.

Hydrogenation of 6-*endo*-N-Pyrrolidinomethylbicyclo[3.1.0]hex-2-ene (17).—A solution of 2.86 g (0.018 mol) of amine 17 in 95% ethanol was shaken with 0.1 g of PtO_2 and 40 psi of hydrogen. After the hydrogenation was complete, the catalyst and solvent were removed, and a total of 2.00 g (67%) of 6-*endo*-N-pyrrolidinomethylbicyclo[3.1.0]hexane (18) was obtained: bp 58° (0.45 mm); n^{25}D 1.4920; λ_{max}^{film} 3030 cm^{-1} (cyclopropyl hydrogen).

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.48. Found: C, 79.89; H, 11.49; N, 8.36.

Reaction of Bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (14) with Methylmagnesium Iodide.—To a stirred solution of 0.14 mol of methylmagnesium iodide in 200 ml of ether was added 13.56 g (0.125 mol) of aldehyde 14 in 50 ml of ether. The stirred solution was refluxed for 1 hr, decomposed with saturated aqueous ammonium chloride, filtered, removed of solvent, and distilled. A total of 8.2 g (53%) of 1-hydroxy-1-bicyclo[3.1.0]hex-2-ene-6-*endo*-ethane (21) was obtained: bp 74° (15 mm); n^{24}D 1.4895; ν_{max}^{film} 3350 cm^{-1} (OH); nmr (DMSO) τ 4.50 (cyclopentene C=CH) and 5.90 ppm ($-CH_3$).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.42; H, 9.92.

Reaction of Cyclopropyl Methyl Ketone (3) with Pyrrolidine.—A stirred solution of 8.41 g (0.1 mol) of **3**, 14.22 g (0.2 mol) of pyrrolidine, 0.1 g of *p*-toluenesulfonate, and 300 ml of benzene was refluxed with continuous removal of water for 72 hr. The solvent was removed and the residual oil was distilled to give 1.69 g (12%) of a mixture of enamines **4** and **6**, bp 55° (1.5 mm). Treatment of an ether solution of this reaction product with ethanolic perchloric acid resulted in the formation of ternary iminium perchlorate salt **5**,[9] colorless plates from isopropyl alcohol, mp 173–174°, ν_{max}^{Nujol} 1649 cm^{-1}.

Anal. Calcd for $C_9H_{16}ClNO_4$: C, 45.48; H, 6.79. Found: C, 45.53; H, 6.93.

Registry No.—**3**, 765-43-5; **4**, 23735-64-0; **5**, 23735-65-1; **6**, 23735-66-2; **7**, 1489-69-6; **9**, 23735-68-4; **10**, 23735-69-5; **13**, 563-80-4; **15a**, 23735-71-9; **15b**, 23735-72-0; **15d**, 23735-73-1; **16a**, 23735-74-2; **16b**, 23735-75-3; **16c**, 23735-76-4; **16d**, 23735-77-5; **17**, 23735-78-6; **18**, 23809-48-5; **19**, 4729-42-4; **20**, 23735-80-0; **21**, 23735-81-1; **22**, 19995-92-7; **26**, 122-00-9; **27**, 823-76-7; **28**, 3019-25-8; **29**, 1567-75-5; **30**, 22482-71-9; *exo*-**31**, 824-59-9; *endo*-**31**, 824-58-8; **32**, 23735-46-8.

(58) H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1386 (1946).
(59) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **31**, 3065 (1966).
(60) J. G. Dinwiddie, Jr., and S. P. McManus, *ibid.*, **30**, 766 (1965).
(61) H. Stockmann, *ibid.*, **29**, 245 (1964).
(62) H. Hart and R. A. Martin, *ibid.*, **24**, 1267 (1959).
(63) L. B. Young and W. S. Trahanovsky, *ibid.*, **32**, 2349 (1967).
(64) Prepared by low-pressure hydrogenation of bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde with platinum oxide catalyst.

Relative Reactivities of Enamines in Alkylation Reactions

MARTIN E. KUEHNE AND THEODORE GARBACIK

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

Received July 14, 1969

Competitions of enamines with varied amine and olefinic moieties in the reactions with methyl acrylate, acrylonitrile, benzyl bromide, methyl iodide, and ethyl iodide gave relative reactivities for substitution on carbon. A correlation with the nmr chemical shift of the enamine β proton was shown for the first three. The C to N alkylation ratios of these enamines with methyl iodide, ethyl iodide, *sec*-butyl bromide, and benzyl bromide (before and after possible rearrangement) were determined.

The use of enamines for electrophilic α substitution of ketones and aldehydes has resulted in a formidable collection of examples.[1] Yet little quantitative information has been advanced, which would help in choosing the optimum enamine system for a desired reaction. It has been suggested that morpholine enamines are preferable for acylation reactions[2] but pyrrolidine and hexamethylene imine enamines for alkylations.[3] In reactions of cyclohexanone derived enamines with cyanogen chloride[4] highest yields were obtained with the pyrrolidine enamine in the presence of triethylamine but the piperidine enamine was better in absence of triethylamine and the morpholine enamine poor in either case. While arylations with reactive nitro aryl halides require pyrrolidine or piperidine enamines[5] one obtained higher yields with morpholine enamines in reactions with nitro olefins.[6] In alkylations of enamines derived from aldehydes, branched secondary amines have shown an advantage in preventing the otherwise prevalent nitrogen alkylation[7,8] also found in the ethylation of pyrrolidine enamines of 7-(53%), 8-(95%) and 9-(88%) membered ring ketones.[9] The relative facility for rearrangement of N to C protonated enamines[10] and the relative yields of alkylidene derivatives obtained by condensing aldehydes with enamines[11,12] are other examples which have been used as analogs in planning synthetic reactions.

In the present study we have determined the relative reactivities of a variety of enamines with several electrophiles in enamine alkylation reactions. Competitions between enamines in Michael additions to acrylonitrile and methyl acrylate established reactivities with dependence on structure and basicity of the cyclic amine and the olefinic portions of the enamine. In these reactions N alkylation, if present, is expected to be readily reversible[3] and should thus not affect the relative rates of competing carbon alkylations, unless large and different concentrations of intermediate zwitterionic N alkylation products arise from competing pairs of enamines. A parallel reactivity series was found on alkylation of the enamines with benzyl bromide in refluxing dioxane. Under these conditions rearrangement[13] of N to C benzylation products could be demonstrated (Table I) and final amounts of N alkylation were found to be small (2–8% for eight cyclic enamines).

With a notation for the enamines of amine ring size/olefin ring size, with h representing the 4-substituted 3-heptene moiety and m for morpholine, *one finds reactivity orders of 5/5 > 5/6 > 5/7 + 5/h and 5/6 > 7/6 > 6/6 > m/6 in both Michael addition reactions and on benzylation.* While the relative reactivity orders are the same in these reactions, individual reactivity differences between enamines were not the same in the three series. In general they were smaller in the reactions of benzyl bromide than in the Michael addition reactions.

Electrophilic attack of an enamine at carbon leads to an imonium salt through a transition state which could, in principle, look like the starting enamine or the product. Thus, in either case, one would expect a correlation of reactivity with the amount of charge delocalization in the enamine (negative charge density on carbon or ease of obtaining imonium structure). If steric hindrance to attack of the enamine is present, however, a relative decrease in reactivity is expected and the correlation may then not be possible.

A measure of the amount of charge delocalization in enamines can be obtained from the nmr chemical shift of a β-vinyl proton, which becomes more shielded by increasing electron density on the β carbon.[14] Thus a correlation of enamine reactivity and the chemical shift of the β proton is expected if steric factors are held constant and spatial direct shielding effects from nitrogen to β proton are negligible or constant.

In the series of eight cyclic enamines studied, this correlation was found, with inversions observed only where the chemical shifts of the enamine β protons came close to each other (about 1-cps difference). *Thus nmr shielding of the β proton decreased in the order of 5/5 > 5/6 > 7/6 > 6/5 > m/5 > 5/7 > m/6 > 6/6 and the relative reactivities decreased as 5/5 > 5/6 > 6/5 > 7/6 > m/5, 5/7 > 6/6 > m/6.* The inverted reactivities of the 7/6 and 6/5 systems are in line with the more favorable C to N benzylation ratio of the latter and may thus be due to relative steric shielding at carbon. Inversion of the m/6 and 6/6 systems, however, requires a different explanation and could be due to decreased relative nucleophilicity of the morpholine system, thus demonstrating the fallibility of equating negative charge density on carbon with reactivity, even

(1) For a summary of enamine chemistry with 731 references, see M. E. Kuehne in "Enamines: Their Synthesis, Structure and Reactions," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1969.

(2) S. Hünig, E. Benzing, and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

(3) G. Stork, A. Brizzolara, H. K. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(4) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).

(5) M. E. Kuehne, *ibid.*, **84**, 837 (1962).

(6) M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).

(7) G. Opitz, *Angew. Chem.*, **73**, 542 (1961).

(8) T. L. Curphey and J. Chao-Yu Hung, *Chem. Commun.*, 510 (1967).

(9) G. Opitz, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 47 (1961).

(10) G. Opitz and A. Griesinger, *ibid.*, **665**, 101 (1963).

(11) L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, **95**, 1495 (1962).

(12) K. C. Brannock, R. D. Burpitt, H. E. Davis, H. S. Pridgen, and J. G. Thweatt, *J. Org. Chem.*, **29**, 2579 (1964).

(13) K. C. Brannock and R. D. Burpitt, *ibid.*, **26**, 3576 (1961).

(14) W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).

TABLE I

RELATIVE REACTIVITIES OF COMPOUNDS LISTED HORIZONTALLY WITH RESPECT TO COMPOUNDS LISTED VERTICALLY

	5/5	5/6	7/6	6/5	5/h	m/5	5/7	m/6	6/6
5/5	1.0[a]	0.37[a]	0.20[a]		0.14[a]		*a*	0.018[a]	0.076[a]
	1.0[b]	0.42[b]	0.20[b]		*b*		0.12[b]	0.066[b]	0.077[b]
	1.0[c]	0.83[c]	0.67[c]		0.27[c]		0.63[c]	0.10[c]	0.15[c]
6/5		1.3[a]	0.26[a]	1.0[a]	0.32[a]		0.43[a]	<0.067[a]	0.11[a]
		1.1[b]	0.77[b]	1.0[b]	*b*		*b*	0.11[b]	0.30[b]
		1.4[c]	0.95[c]	1.0[c]	0.77[c]		*c*	0.32[c]	0.83[c]
m/5		2.9[a]	1.5[a]		0.90[a]	1.0[a]	1.0[a]	0.13[a]	0.30[a]
		3.5[b]	1.1[b]		*b*	1.0[b]	*b*	0.11[b]	0.22[b]
		1.5[c]	1.1[c]		1.2[c]	1.0[c]	*c*	0.29[c]	0.67[c]
5/7	*a*	*a*	*a*	2.3[a]	*a*	1.0[a]	1.0[a]	*a*	*a*
	8.1[b]	2.5[b]	*b*	*b*	*b*	*b*	1.0[b]	*b*	*b*
	1.6[c]	*c*	*c*	*c*	*c*	*c*	1.0[c]	*c*	*c*
5/h	6.9[a]	3.6[a]	*a*	3.1[a]	1.0[a]	1.1[a]	*a*	0.72[a]	0.75[a]
			b	*b*	1.0[b]	*b*	*b*	*b*	*b*
	3.7[c]	*c*	*c*	1.3[c]	1.0[c]	0.83[c]	*c*	*c*	0.45[c]

[a] With methyl acrylate. [b] With acrylonitrile. [c] With benzylbromide.

with constant steric hindrance to electrophilic attack. In this connection it should be noted that we found the rates of quaternization of corresponding simple tertiary amines with methyl iodide to decrease in the order of N-methylpyrrolidine > N-methylpiperidine > N-methylmorpholine. An alternative interpretation is that the close nmr chemical shifts of the m/6 and 6/6 systems are inverted relative to charge densities on carbon, by a small difference in spatial proton–nitrogen interaction. This receives support from the expected 6/5 > m/5 ratios of reactivity and shielding.[15]

The acyclic 5/h enamine showed a more shielded β proton than any of the cyclic enamines. However, its reactivity in Michael addition reactions and on benzylation fell near the bottom of the sequence between the m/5 and 6/6 systems. The decreased reactivity is due to increased steric shielding of the enamine β carbon by the rotating alkyl chains. This is also reflected by the relatively low C to N benzylation ratio, which decreases even further on branching of the alkyl chains, in the pyrrolidine enamine of di-*sec*-butyl ketone, even though the vinyl proton is still more shielded here.

Methylations and ethylations of the same cyclic enamines led to a different sequence of reactivity at carbon: 7/6 > 5/6 ≃ 5/7 ≃ 5/5 > 6/5 > m/5 > 6/6 ≃ m/6. Here, a more difficult reversal of alkylation on nitrogen was expected to alter the order of competitive C alkylation found with the previous three reactions. The most remarkable change occurred by interchanging the 5/5 and 7/6 compounds from the top and middle of the series, even though these compounds still showed high and similar carbon to nitrogen alkylation ratios. These results suggest the synthetic advantage of using hexamethylene imine in enamine methylations of cyclohexanones.

While relatively high reactivity on carbon is desirable for an enamine substitution reaction, selection of a favorable C to N alkylation ratio may be more significant. Examination of the ratios listed in Table II shows no correlation of data for alkylations of nine enamines with methyl iodide, ethyl iodide, *sec*-butyl bromide, or benzyl bromide, nor any correlation of the C to N alkylation ratios with the electron density at the β carbon, as estimated from nmr spectra. Since no predictive rules can be established here, the data should be especially helpful in selection of optimum enamine systems for desired alkylation systems.

The methylation reactions of the nine enamines shown in Table II were found to be 95–100% completed at room temperature after 24 hr. A small excess of enamine was used in these reactions. When the reaction mixtures were then heated to 100° for 18 hr, the C to N alkylation ratio was found to increase drastically. This increase was followed in the 7/6 methylation by comparison of the relative intensities of the N-methyl amonium singlet at δ 3.12 with the C-methyl imonium doublet at δ 1.08. It was also found that the absolute intensity of the methyl doublet of 2-methylcyclohexanone, obtained from these mixtures by hydrolysis, increases correspondingly when compared with a known absolute standard (0.33 equiv of added *t*-butyl alcohol). These increases of C methylation products seen by nmr also compared quantitatively with the titration values given in Table II.

The increased ratio of C to N methylation products found on heating the alkylation reactions, which contained excess enamine, should be due to intermolecular N to C methyl transfer. However, with an excess of alkylating agent in reaction mixtures stored at room temperature for ten days, one did not observe values equal to or lower than those obtained with excess enamine at room temperature in 24 hr in all cases. Heating of one such reaction mixture still showed an increase of the C to N alkylation ratio. The facility of the N alkylated enamines to act as carbon methylating agents was also found to vary with the structure of the heterocyclic and olefinic moieties of the enamines. On this basis morpholine enamines are particularly poor and the hexamethylene imine enamine system best for the methylation reaction.

Experimental Section

Preparation of Enamines.—The following enamines were prepared by reported procedures: pyrrolidine enamine of cyclopentanone,[3] cyclohexanone,[3] cycloheptanone;[4] piperidine enamine of cyclopentanone,[16] cyclohexanone;[2] morpholine enamine of cyclopentanone,[3] cyclohexanone;[2] hexamethylene imine enamine

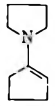
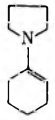
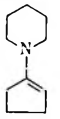
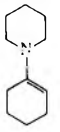
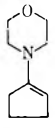
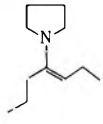
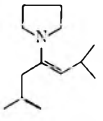
(15) After submission of this manuscript, K. Nagarajan and S. Rajappa, *Tetrahedron Lett.*, 2293 (1969), reported similar nmr data for these enamines. Their measurements in carbon tetrachloride showed equivalence of the 7/6 and 6/5 systems and 6/6 > m/6 by 2 cps.

(16) A. Rieche, E. Schmitz, and E. Beyer, *Chem. Ber.*, **92**, 1212 (1959).

TABLE II

C TO N ALKYLATION RATIOS

(EQUIVALENTS ON C PER EQUIVALENT ON N)[a]

	Code	Benzyl bromide Rt	Benzyl bromide 100°	Methyl iodide[b] Rt	Methyl iodide[b] 100°	Ethyl iodide 100°	sec-Butyl bromide 100°
	5/5	13	53	4.3	20	6.6	5.7
	5/6	3.8	78	2.6	3.2	1.9	11
	6/5	3.9	80	1.8	17	2.3	8.4
	6/6	0.67	12	0.45 (0.33)	1.5	1.3	20
	7/6	4.2	28	2.9 (4.9)	26	5.6	8.7
	m/5	15	20	2.4 (3.0)	4.6	12	7.4
	m/6	6.6	28	1.7 (0.63)	5.5 (2.0)	11	12
	5/h	16	16	4.3	5.9	3.9	6.8
	5/n	2.9	5.4	1.2	4.1		

[a] Reaction conditions: 24 hr at room temperature, 18 hr at 100°, with excess enamine. [b] Values in parentheses: 10 days at room temperature, 24 hr at 100°, with 2 equiv of methyl iodide.

of cyclohexanone.[2] The pyrrolidine enamine of 2,6-dimethyl-4-heptanone was prepared by refluxing a solution of 42 g (0.29 mol) of the ketone, 25 g (0.35 mol) of pyrrolidine, and a crystal of *p*-toluenesulfonic acid in 100 ml of benzene for 30 hr, under nitrogen, passing the condensate through a Soxhlet extractor filled with Linde, type 4A Molecular Sieve. Distillation gave 9.8 g (17% yield) of the enamine, bp 112–115° (12 mm). The pyrrolidine enamine of 4-heptanone was prepared by the same procedure in 40% yield and distilled at 97–100° (13 mm). These enamines showed the usual ir enamine absorptions[1] and nmr spectra with the expected proton integration ratios.

Nmr Chemical Shifts of β Protons.—All measurements were made with a Varian A-60 instrument on samples dissolved in deuteriochloroform with internal TMS standard. The listed downfield shifts from TMS are average values of three measurements. The enamines are listed as amine ring size/olefin ring size, with m for morpholine, h for 4-substituted 3-heptene, and n for 2,6-dimethyl-4-substituted-3-heptene: 5/n (238.0 cps), 5/h (239.5 cps), 5/5 (241.7 cps), 5/6 (256.8 cps), 7/6 (261.0 cps), 6/5 (262.3 cps), m/5 (265.9 cps), 5/7 (269.5 cps), m/6 (278.7 cps), 6/6 (279.7 cps).

Competition Reactions.—One equivalent (0.01 mol) each of two different enamines was added to 25 ml of dry dioxane. One equivalent of the alkylating agent was added and the mixture refluxed for about 15 hr under nitrogen. After cooling, 5 ml of water was added, the mixture refluxed for 1 hr, cooled and concentrated under vacuum to about 10 ml. The concentrate was extracted with 75 ml of ether, the extract dried over magnesium sulfate and filtered, and the volume reduced to about 5 ml under vacuum. Ratios of ketone products were measured with an Aerograph A-90-P thermal conductivity gas chromatograph. Conditions for separations, with retention times in parentheses, were as follows: a, 2-methylcyclopentanone (12 min) and 2-methylcyclohexanone (38 min), 20 psi, column 9-ft 10% Apiezon L, 80°, injector 150°, detector 190°; b, 2-ethylcyclopentanone (30 min) and 2-ethylcyclohexanone (63 min), 20 psi, column 9 ft 10% Apiezon L, 90°, injector 170°, detector 180°; c, 2-benzylcyclopentanone (25 min) and 2-benzylcyclohexanone (45 min), 35 psi, column 9 ft 10% Apiezon L, 170°, injector 210°, detector 195°; d, 2-(2-cyanoethyl)cyclopentanone (11 min) and 2-(2-cyanoethyl)cyclohexanone (16 min), 60 psi, column 5 ft 20% Apiezon L, 175°, injector 200°, detector 247°; e, 2-(2-carbomethoxyethyl)cyclopentanone (12 min) and 2-(2-carbomethoxyethyl)cyclohexanone (19 min), 30 psi, column 9 ft 10% Apiezon L, 180°, injector 200°, detector 200°; f, cyclohexanone (9 min) and 2-(2-butyl)cyclohexanone (21 min), 20 psi, column 9 ft 10% Apiezon L, 120°, injector 180°, detector 200°; g, 2-benzylcyclopentanone (28 min) and 3-benzyl-4-heptanone (22 min), 60 psi, column 30 ft 20% Apiezon L, 224°, injector 270°, detector 290°; i, 2-(2-carbomethoxyethyl)cyclopentanone (14 min) and 2-(2-carbomethoxyethyl)-4-heptanone (9 min), 20 psi, column 6 ft 10% ethylene glycol adipate, 133°, injector 240°, detector 254°; j, 2-benzylcyclohexanone (28 min) and 3-benzyl-4-heptanone (15 min), 60 psi, column 9 ft 10% Apiezon L, 170°, injector 200°, detector 200°; k, 2-(2-carbomethoxyethyl)cyclohexanone (22 min) and 2-(2-carbomethoxyethyl)-4-heptanone (13 min), 30 psi, column 9 ft 10% Apiezon L, 170°, injector 200°, detector 200°.

Using the 5/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (0.37), 6/6 (0.076), m/6 (0.018), 7/6 (0.20); with acrylonitrile, 5/6 (0.42), 6/6 (0.077), m/6 (0.066), 7/6 (0.20); with benzyl bromide, 5/6 (0.83), 6/6 (0.15), m/6 (0.10), 7/6 (0.67); with ethyl iodide, 5/6 (1.1), 6/6 (0.22), m/6 (0.24); with methyl iodide, 5/6 (1.1), 6/6 (0.25), m/6 (0.12), 7/6 (6.7).

Using the 6/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (1.3), 6/6 (0.11), m/6 (less than 0.067), 7/6 (0.26); with acrylonitrile, 5/6 (1.1), 6/6 (0.30), m/6 (0.11), 7/6 (0.77); with benzyl bromide, 5/6 (1.4), 6/6 (0.83), m/6 (0.32), 7/6 (0.95); with ethyl iodide, 5/6 (1.2), 6/6 (0.17), m/6 (0.11), 7/6 (2.1), with methyl iodide, 5/6 (3.2), 6/6 (0.26), m/6 (0.38), 7/6 (8.2).

Using the m/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (2.9), 6/6 (0.30), m/6 (0.13), 7/6 (1.5); with acrylonitrile, 5/6 (3.5), 6/6 (0.22), m/6 (0.11), 7/6 (1.1); with benzyl bromide, 5/6 (1.5), 6/6 (0.67), m/6 (0.29), 7/6 (1.1); with ethyl iodide, 5/6 (1.4), 6/6 (0.38), m/6 (0.10), 7/6 (2.0); with methyl iodide, 5/6 (1.6), 6/6 (0.53), m/6 (0.53), 7/6 (7.0).

Using the 5/7 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 6/5 (2.3), m/5 (1.0); with acrylonitrile, 5/5 (8.1), 5/6 (2.5); with benzyl bromide, 5/5 (1.6); with methyl iodide m/5 (0.53).

Using the 5/h enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (3.6), 6/6 (0.75), m/6 (0.72), m/5 (1.1), 6/5 (3.1), 5/5 (6.9); with benzyl bromide 6/6 (0.45), m/5 (0.83), 6/5 (1.3), 5/5 (3.7).

Quaternization of Tertiary Amines.—To 50 ml of 50% aqueous dioxane was added 0.02 ml of N-methylpyrrolidine or N-methylpiperidine, or N-methylmorpholine. The solution was stirred and the pH measured with a Fisher Accumet pH meter equipped with a Beckman glass electrode and a calomel reference electrode. Methyl iodide, 5.0 g (0.035 mol), was added and the pH mea-

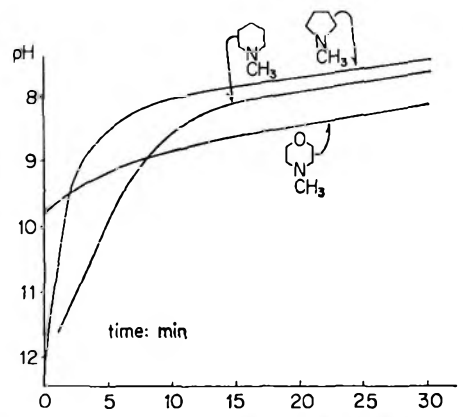


Figure 1.—Quarternization of tertiary amines with methyl iodide.

sured at 1-min intervals for 15 min and after 20, 25, and 30 min. A plot of the data is shown in Figure 1.

C to N Alkylation Ratios.—An enamine (6–7 ml) from Table I was added to about 80 ml of dry dioxane. From this mixture three 25-ml samples were drawn. One sample was diluted with 50 ml of dioxane and enough water to increase the volume to 100 ml. From this 10-ml aliquots were drawn, diluted with water, and titrated with standard hydrochloric acid to determine the total enamine per 25-ml sample. Each of the other 25-ml samples was refluxed for 18 hr, or cooled in ice, and then stored for 24 hr at 25° with <1 equiv of a different alkylating agent, under nitrogen. After cooling, 5 ml of water was added and the mixture refluxed for 1 hr. The cooled reaction mixtures were diluted with 50 ml of dioxane in volumetric flasks and diluted with water to 100 ml. The amount of unreacted enamine was determined by titrating 10-ml aliquots, dissolved in water, with standard hydrochloric acid. The amount of amine acid salt, which equals the amount of C alkylated products, was determined by titrating 10-ml aliquots, dissolved in 50 ml of alcohol, with standard sodium hydroxide. Amount of N alkylated product = total enamine − unreacted enamine − C alkylated product. Titrations were carried out with the pH meter described above and end points determined[17,18] from the following equation: endpoint volume = maximum volume + $0.05\Delta(\Delta pH/\Delta V)_{max}/[\Delta(\Delta pH/\Delta V)_{max-1} + \Delta(\Delta pH/\Delta V)_{max+1}]$. The results are listed in Table I.

Registry No.—5/5, 7148-07-4; 5/6, 1125-99-1; 5/7, 14092-11-6; 5/h, 23516-90-7; 5/n, 3494-04-0; 6/5, 1614-92-2; 6/6, 2981-10-4; 7/6, 23430-63-9; m/5, 936-52-7; m/6, 670-80-4; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; *sec*-butyl bromide, 78-76-2.

(17) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1963, p 556.

(18) J. J. Lingane, "Electroanalytical Chemistry," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p 93.

Alkylation of Amines. A New Method for the Synthesis of Quaternary Ammonium Compounds from Primary and Secondary Amines

HAROLD Z. SOMMER AND LARRY L. JACKSON

Chemical Research Laboratory, Research Laboratories, Edgewood Arsenal, Maryland 21010

Received June 30, 1969

Primary and secondary amines have been exhaustively alkylated to their quaternary stage in a one-step procedure. The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, has been synthetically utilized. An organic base of greater base strength than the reactant amines has been employed to bind the acid generated in alkylation reactions. Aniline and aniline derivatives with pK_a values of 3.86–5.34 have been completely methylated in the presence of the stronger, but sterically hindered base, 2,6-lutidine (pK_a = 6.77). The mild and homogeneous reaction conditions resulted in good yields with minimal laboratory manipulations and effort. As an example of the applicability of the method to amines that possess labile functions, the bisquaternary carbamate, 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide), has been prepared from 3,5-diaminophenyl dimethylcarbamate in a one-step procedure.

Quaternary ammonium compounds are prepared in most cases from tertiary amines, primary or secondary amines being used only occasionally as the starting materials.[1-3] The methods previously available for direct alkylation of primary and secondary amines to the quaternary stage require relatively harsh reaction conditions and give rise to undesirable side reactions, and, hence, are limited to stable amines and alkylating agents. These methods were developed by A. W. Hofmann in the nineteenth century and are still employed without significant changes. The reaction of a primary or secondary amine with an alkylating agent, such as an alkyl halide, involves the liberation of a hydrohalic acid which combines with the reactant amines to form a mixture of amine hydrohalide salts. Consequently, very low concentrations of free amines remain for subsequent alkylation. To increase the concentration of the free amines, inorganic bases are utilized as the proton acceptors.

The general procedure for the direct alkylation of primary or secondary amines to their quaternary ammonium salts is to reflux a mixture of the amine, an excess of the alkyl halide, and sodium carbonate or sodium hydroxide in water or alcohol. Under these heterogenous reaction conditions prolonged heating is needed leading to numerous side reactions and low yields. Consequently, this method is of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases. Further complications arise from the fact that the physical properties of quaternary ammonium salts closely resemble those of inorganic salts. Thus, the purification of quaternary compounds in the presence of inorganic salts can be very laborius, since their solubilities in most common solvents are very similar. In view of the above difficulties and in spite of the addi-

(1) For a review, see J. Goerdeler in "Methoden Der Organishen Chemie, Stickestoffverbindugen" (Houben-Weyl), Eugen Muller, Ed., Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp 587–640.

(2) W. Krucker, "Synthese de Sels d'Ammonium quaternaires derives d'Aminophenols et Etude de leur Action sur la Transmission neuromusculaire," J. Peyronnet, Paris, 1951, pp 11–60.

(3) M. M. Markowitz, *J. Org. Chem.*, **22**, 983 (1957).

tional steps involved, the route usually chosen is the synthesis and isolation of the appropriate tertiary amine prior to quaternization.

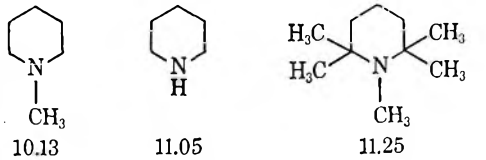
When primary amines react with alkylating agents a sequence of reactions occurs resulting in the formation of a mixture of products.[4] The composition of the product mixture depends on the molar concentration of the reactants, the temperature, the basicities of the starting and alkylated amines, the steric configuration of all the reacting species, and their solubilities in the various solvent media. In the complex series of equilibria the most readily controllable step is the final alkylation of the tertiary amine to the quaternary salt. The preparation of secondary and tertiary amines by this procedure is generally impractical because of the competing reactions and difficulty of separation. The equilibria can be shifted toward complete alkylation by the introduction of strong inorganic bases, but the disadvantages mentioned previously limit the scope of this approach.

In principle, the alkylation of a primary or secondary amine to the quaternary stage could be greatly simplified if an organic base could be used to bind the acid that is generated as the reaction proceeds. The organic base should have solubilities similar to those of the starting amines to attain homogeneous reaction conditions, it must be a stronger base (larger pK_a) than the reacting amines to combine preferentially with the acid produced, it must alkylate at a significantly slower rate than the reacting amines, and it should be readily available. Preferably, the acid salt of the organic base and the quaternary ammonium salt should be separable on the basis of solubility.

The seemingly contradictory requirement, that the organic base have a larger pK_a, yet react at a slower rate than the amines to be alkylated, led us to examine more closely the relationship between basicity and nucleophilicity.

Correlations between basicity and nucleophilicity in amines have been extensively explored in the literature.[5-23] Even though a direct relationship has been demonstrated in most studies, the exceptions, attributable to steric hindrance, are of special interest.[7,11,13,14]

Hall[18] determined the basicities of the following piperidine compounds which are shown in the order of increasing pK_a values.



10.13 11.05 11.25

1-Methylpiperidine is a weaker base than piperidine, while 1,2,2,6,6-pentamethylpiperidine is the strongest of the three, in spite of the five methyl groups surrounding the nitrogen. These examples indicate that, whereas steric factors can weaken basicity, polar effects, however, overcome severe steric hindrance.

Such compensation is not encountered when the parameters that govern nucleophilicity are evaluated. Clarke and Rothwell,[7] studying the effects of substituents on the rate of formation of alkylpyridinium halides, showed that the basicity of the pyridine nitrogen is enhanced by the inductive effects of alkyl substituents on the aromatic ring and that the influence of steric hindrance is insignificant. The pK_a values of the monosubstituted 2- and 4-methylpyridines (5.97 and 6.02) are essentially identical and greater by approximately 0.8 pK_a unit than pyridine (5.17). Dimethyl substitution, both in the 2, 4 and 2,6 positions, likewise results in very similar pK_a values (6.72 and 6.77). The pK_a of collidine, the 2,4,6-trimethylpyridine derivative, rises to a value of 7.48. The additive effect of the methyl groups on base strength, an increase of about 0.8 pK_a unit/methyl group from mono- to di- to trimethyl substitution, clearly demonstrates the electron-donor feature and rules out steric hindrance as a significant factor in protonation.[11,13,14]

In sharp contrast, steric hindrance greatly affects nucleophilicity in these alkyl-substituted pyridines. Of the cases cited by Clarke and Rothwell, only 4-methyl- and 4-ethylpyridine quaternize faster than pyridine. Regardless of base strength, the amines with *ortho* substituents alkylate more slowly than pyridine. 2,6-Lutidine (pK_a = 6.77) quaternizes with methyl iodide 18.6 times and 2,4,6-collidine (pK_a = 7.48) 9.1 times as slowly as pyridine (pK_a = 5.17). With allyl bromide the differences in alkylation rates are 260 and 150, respectively.

When both steric and electrical effects have to be considered, it seems evident that the latter is the dominant contributor in the determination of base strength, exemplified by the extremely hindered 1,2,2,6,6-pentamethylpiperidine, which is 13 times as strong a base as 1-methylpiperidine.[18] Steric effects, however, play the major role in the determination of nucleophilicity, strikingly demonstrated by the comparison of base strengths and alkylation rates of 2,6-lutidine and pyridine. 2,6-Lutidine is about 40 times as strong as pyridine in base strength, yet reacts with methyl iodide approximately 19 times as slowly.[7] Thus, competing strong electron donor and pronounced steric effects result in an increase of basicity and decrease of nucleophilicity.

In light of these observations the interaction between a proton and a hindered amine and the interaction of the same amine with an alkylating agent must be substantially different. The proton, owing to its small size and its electron deficiency, appears to be able to approach the nitrogen of an amine and form a chemical bond in spite of steric hindrance. On the other hand, a sterically hindered nucleophile is hampered or even completely blocked in its attack on the alkylating agent.

(4) P. Karrer "Organic Chemistry," 4th English ed, Elsevier, Amsterdam, 1950, p 128.
(5) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(6) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956); **79**, 5441 (1957).
(7) K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(8) D. P. Evans, *et al.*, *ibid.*, 1345 (1939).
(9) A. I. Biggs and R. A. Robinson, *ibid.*, 388 (1961).
(10) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(11) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).
(12) H. C. Brown and R. R. Holmes, *ibid.*, **77**, 1727 (1955).
(13) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).
(14) H. C. Brown, *et al.*, *ibid.*, **78**, 5375 (1956).
(15) G. W. Ceska and E. Grunwald, *ibid.*, **89**, 1371, 1377 (1967).
(16) M. M. Fickling, *et al.*, *ibid.*, **81**, 4226 (1959).
(17) A. Fischer, *et al.*, *J. Chem. Soc.*, 3591, 3596 (1964).
(18) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5444 (1957).
(19) H. P. Crocker and B. Jones, *J. Chem. Soc.*, 1808 (1959).
(20) D. P. Evans, *et al.*, *ibid.*, 1348 (1939).
(21) W. G. Brown, *et al.*, *J. Amer. Chem. Soc.*, **61**, 2597 (1939).
(22) W. G. Brown and S. Fried, *ibid.*, **65**, 1841 (1943).
(23) D. H. McDaniel and H. C. Brown, *ibid.*, **77**, 3756 (1955).

Whereas electron-donating groups favor the protonation of the amine, the inherent bulk of these groups retards alkylation. Severely hindered amines, it can be concluded, exhibit an inverse relationship between basicity and nucleophilicity.

In the search for an organic base that is readily protonated, yet is a relatively poor nucleophile, an appropriate hindered amine can now be chosen which can successfully serve as the proton acceptor in direct alkylation reactions of primary or secondary amines to their quaternary stage. The quaternization of aniline and its substituted derivatives with methyl iodide in the presence of 2,6-lutidine has been selected in the present study to test the validity and practical implementation of the above concept. 2,6-Lutidine fulfills the requirements outlined for the organic base. Its pK_a (6.77)[7] is greater than that of aniline (4.65),[10] N-methylaniline (4.89),[10] *and N,N-dimethylaniline (5.07),[10] and is alkylated at a slower rate.*[24] It is soluble in most common organic solvents and commercially available, and the separation of trimethylphenylammonium iodide and 2,6-lutidine hydroiodide is feasible on the basis of solubility differences, as shown in Table I.

TABLE I[a]

SOLUBILITIES OF $C_6H_5\overset{+}{N}(CH_3)_3I^-$ AND 2,6-LUTIDINE SALTS

Compound	DMF, 25°, g/100 ml	Acetone, 25°, g/100 ml	Acetone, 56° g/100 ml
$C_6H_5\overset{+}{N}(CH_3)_3I^-$	13	0.15	0.5
2,6-Lutidine HI	60	2.5	7.0
2,6-Lutidine MeI	6	0.16	0.4

[a] The data were obtained by saturating the solvent with a known quantity of the salt and weighing the undissolved material.

The concentrations of the reactants and the selection of the solvent are important for separation and purification of the quaternary ammonium salt. Table II lists the yields of trimethylphenylammonium iodide obtained at various concentrations in several solvents. A solution of aniline (1 equiv), 2,6-lutidine (2 equiv), and methyl iodide (excess) was allowed to stand at room temperature until precipitation of the product was complete. The product was collected and its purity was determined by its melting point and its mixture melting point with lutidine methiodide and lutidine hydriodide.

Aniline generates 2 equiv of hydriodic acid when it is alkylated to the quaternary state with methyl iodide. Therefore, 2 equiv of 2,6-lutidine are required to free the intermediate secondary and tertiary amines from their hydroiodides. While an excess of the alkylating agent is desirable, an excess of the proton acceptor should be avoided to minimize the formation of 2,6-lutidine methiodide.

The above method has been successfully applied to aromatic amines in the pK_a range from 3.86 (4-bromoaniline)[9] to 5.34 (4-methoxyaniline),[9] as shown in Table II. The reaction with 3-nitroaniline (pK_a of 2.45)[25] resulted in a mixture of the desired product, together with significant amounts of 2,6-lutidine methiodide. Hence, the lower limit of the usefulness of 2,6-lutidine in this quaternization method appears to be for amines with pK_a values between 2.45 and 3.86. The upper limit is determined by the basicity of 2,6-lutidine, *i.e.*, pK_a of 6.77.

TABLE II

YIELDS OF $C_6H_5\overset{+}{N}(CH_3)_3I^-$ AS A FUNCTION OF CONCENTRATION IN VARIOUS SOLVENTS AT 25°

Solvent	Molar concentration of aniline	Yield, %
Acetone	0.054	0
Acetone	0.108	76
Acetone	0.215	Mixture[a]
DMF[b]	0.54	0
DMF[b]	0.90	28
DMF[b]	1.28	49
DMF[b]	1.54	59
DMF[b]	2.69	Mixture[a]
MeOH	0.54	22
MeOH	0.72	29
MeOH	2.15	49
MeOH	3.58	52
MeOH	10.0	Mixture[a]
CH_3CN	0.54	29
CH_3CN	0.67	29
CH_3CN	0.90	Mixture[a]
EtOAc	0.108	Mixture[a]
EtOAc	0.215	Mixture[a]
Benzene	0.154	Mixture[a]

[a] The mixture consists of $C_6H_5\overset{+}{N}(CH_3)_3I^-$ and 2,6-lutidine HI. [b] N,N-Dimethylformamide.

At the concentrations indicated in Table III the quaternary ammonium product precipitates from the reaction solution. Higher concentrations often lead to mixtures and lower concentrations allow a substantial portion of the product to remain in solution.

Amines can also be employed in the form of their salts, in which case 3 equiv of 2,6-lutidine is used. The additional equivalent liberates the amine before alkylation proceeds. (4-Bromophenyl)trimethylammonium iodide has been prepared in this manner from 4-bromoaniline hydrochloride.

When N-phenylbenzylamine (pK_a of 4.04) was alkylated to form benzyldimethylphenylammonium iodide a mixture containing 25% 2,6-lutidine methiodide was obtained. In this instance, the steric hindrance of the starting secondary amine apparently is sufficient to decrease the alkylation rate to a level where 2,6-lutidine methiodide formation becomes significant. However, the mixture is easily separated on the basis of the relatively low solubility of 2,6-lutidine methiodide in methanol.

As examples for direct quaternization of amines possessing labile functions, 3-(dimethylcarbamoyloxy)-phenyltrimethylammonium iodide (Prostigmine iodide) and the bisquaternary carbamate 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide) (IV) were synthesized. The former was prepared from the dimethylcarbamate ester of 2-aminophenol and the latter as shown in Scheme I.

(24) K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938); K. J. Laidler, *ibid.*, 1786 (1938).

(25) P. Pascal, *Compt. Rend.*, **262C**, 1196 (1966).

TABLE III

ANILINE DERIVATIVES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF 2,6-LUTIDINE

R_1	R_2	R_3	pK_a	Solvent	Molar concentration of aniline derivatives	Product R_1	Product R_2	Product R_3	Yield,[a] %
H	H	H	4.65[b]	Acetone	0.054	H	H	Me	76
4-Me	H	H	5.08[c]	Methanol	2.16	4-Me	H	Me	53
4-OMe	H	H	5.34[d]	DMF[e]	1.53	4-OMe	H	Me	87
4-Br	H	H, HCl		Acetone	0.108	4-Br	H	Me	76
4-Br	H	H	3.86[d]	DMF	2.09	4-Br	H	Me	97
4-OH	H	H	5.31[f]	DMF	2.18	4-OH	H	Me	60
3-OH	H	H	4.31[c]	DMF	2.18	3-OH	H	Me	66
H	H	Me	4.89[b]	Methanol	2.70	H	H	Me	67
H	H	Benzyl	4.04[b]	Methanol	2.20	H	H	Benzyl	71
$3\text{-}NH_2$	H	H	4.88[g]	DMF	2.15	$3\text{-}\overset{+}{N}Me_3I^-$	H	Me	67
$3\text{-}NH_2$	5-OCONMe$_2$	H		DMF	0.40	$3\text{-}\overset{+}{N}Me_2I^-$	5-OCONMe$_2$	Me	63
3-OCONMe$_2$	H	H		Methanol	0.58	3-OCONMe$_2$	H	Me	94

[a] Analytically pure material. [b] Reference 10. [c] Reference 25. [d] Reference 9. [e] N,N-Dimethylformamide. [f] M. Gillois and P. Rumpf, *Bull. Soc. Chim. Fr.*, 112 (1954). [g] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Van Nostrand-Reinhold Co., New York, N. Y., 1961, p 709.

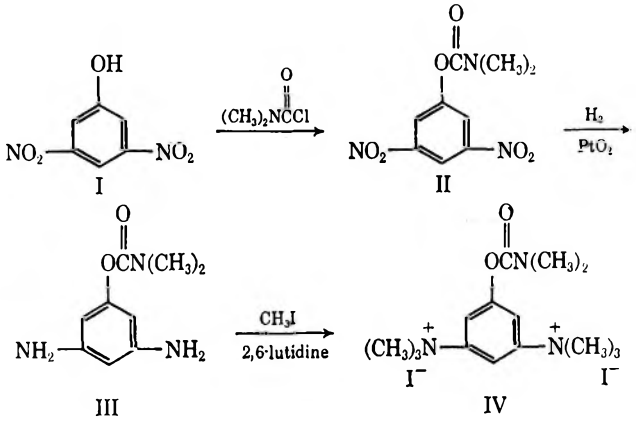
TABLE IV

ANALYTICAL DATA

R_1	R_2	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % I	Calcd, % N	Found, % C	Found, % H	Found, % I	Found, % N
4-OMe	H	228–229	$C_{10}H_{16}INO$[b]	41.0	5.5	43.3	4.8	41.2	5.6	43.2	4.9
$3\text{-}\overset{+}{N}Me_3I^-$	H	182–183	$C_{12}H_{22}I_2N_2$[c]	32.2	5.0	56.6	6.2	32.0	5.2	56.6	6.3
$3\text{-}\overset{+}{N}Me_3I^-$	5-OCONMe$_2$	183–184	$C_{15}H_{27}I_2N_3O_2$	33.7	5.1	47.4	...	33.7	5.3	47.0	...

[a] Melting points are uncorrected. [b] Registry no. 17310-99-5. [c] Registry no. 23649-60-7.

SCHEME I



If an anion other than iodide is desired, the quaternary ammonium iodide is easily exchanged by conventional ion-exchange procedures.[3]

This study is being continued to extend the applicability of the method described herein to a wider range of amines and alkylating agents.

Experimental Section

Materials.—The aniline derivatives were distilled or recrystallized as required. 2,6-Lutidine and the solvents were dried and distilled before use.

General Procedure.—Methyl iodide (excess) is added to a solution of equimolar quantities of aniline or the aniline derivative and 2,6-lutidine in an appropriate solvent (see Table II). Since the reactions are exothermic and are generally completed in a few minutes, gradual addition of methyl iodide or external cooling of the reaction mixture is advisable. After the reaction has taken place, the mixture is allowed to stand at room temperature for a few hours to ensure complete precipitation of the quaternary product. The product is collected on a filter, washed with acetone, and vacuum dried. To obtain analytically pure materials the quaternary ammonium salts are stirred with additional acetone to remove any remaining 2,6-lutidine hydriodide or are recrystallized from acetone or a methanol–ether mixture. Dry solvents are essential since the presence of water greatly increases the solubility of quaternary ammonium compounds in organic solvents.

The known quaternary ammonium iodides were identified by their elemental analyses and melting points.[26,27] Analytical data and melting points of compounds not found in the literature are given in Table IV.

4-(Methoxyphenyl)trimethylammonium Iodide.—4-Methoxyaniline (2.8 g) was dissolved in 15 ml of N,N-dimethylformamide and cooled in an ice–water bath. 1,6-Lutidine (4.9 g) and methyl iodide (16 g) were added and the reaction mixture was allowed to stand in the cooling bath for approximately 0.5 hr. After additional standing at room temperature for 1.5 hr, the precipitate that formed was collected on a filter. The crude product thus obtained melting between 219 and 220° was stirred in 150

(26) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, pp 335–337; "Tables for Identification of Organic Compounds," C. D. Hodgman, Editor-in-Chief, Chemical Rubber Publishing Co. Cleveland, Ohio, 1960, pp 183–188.

(27) A. Deutsch and O. Fernö (Aktiebolaget Leo), Swedish Patent, 128,292 (1950); *Chem. Abstr.*, **44**, 9477 (1950).

ml of acetone for 10 min at room temperature. After filtration and drying, 5.8 g (87% yield) of white crystalline product was obtained, mp 228–229°.

For analysis, see Table IV.

5-(Dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium Iodide) (IV).—A solution of 3.95 g of 3,5-dinitrophenol (I), 2.33 g of dimethylcarbamoyl chloride, and 4 ml of triethylamine in 100 ml of benzene was refluxed for 4 hr. Triethylamine hydrochloride was removed by filtration and the filtrate washed with 0.1 *N* sodium hydroxide and dried (Na_2SO_4). Addition of 20 ml of ethanol precipitated crude 3,5-dinitrophenyl dimethylcarbamate (II). Recrystallization from ethanol–water gave 2.83 g (52%) of yellow crystals, mp 78–79°.

Anal. Calcd for $C_9H_9N_3O_6$: C, 42.4; H, 3.5; N, 16.5. Found: C, 42.7; H, 3.5; N, 16.3.

A mixture of 510 mg of 3,5-dinitrophenyl dimethylcarbamate (II) and 200 mg of platinum oxide in 20 ml of absolute ethanol was hydrogenated in a Parr apparatus (Parr Instrument Co., Inc., Moline, Ill.). Absorption of 6 mol of hydrogen was complete in 20 min. The catalyst was removed by filtration and the filtrate was evaporated to give 3,5-diaminophenyl dimethylcarbamate (III) as a residue. The residue was dissolved in 5 ml of N,N-dimethylformamide. 2,6-Lutidine (0.9 ml) and methyl iodide (3 g) were added and the solution was allowed to stand at room temperature for 12 hr. The precipitate that formed was collected on a filter. Recrystallization from methanol–ether gave 670 mg (63%) of 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide) (IV).

For analysis, see Table IV.

Registry No.—Trimethylphenylammonium iodide, 98-04-4; II, 15925-97-0; IV, 23649-61-8.

Acknowledgment.—The authors are indebted to Mr. Ronald D. Deibel for his valuable assistance in the experimental work.

Studies of Benzonorbornene and Derivatives. II. The *ac*-Bromobenzonorbornenes and -dienes[1]

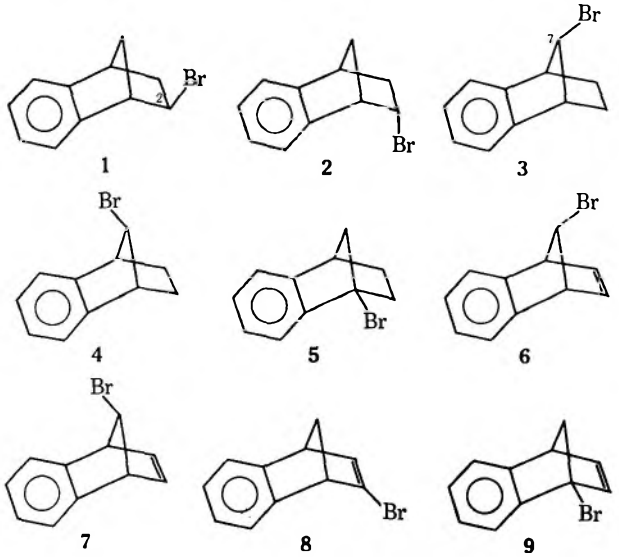
JAMES W. WILT AND PHILIP J. CHENIER[2]

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

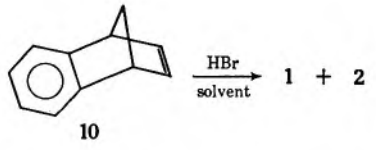
Received July 14, 1969

The synthesis and properties of the nine *ac*-bromobenzonorbornenes and -dienes are described. Addition of hydrobromic acid to benzonorbornadiene (**10**) produced the *exo*-2 bromide **1**. Its *endo* epimer **2** was prepared by diimide reduction of the vinylic bromide **8**. The *anti*-7 bromide **3** was obtained most simply by hydrogenolysis of the *exo*-2,*anti*-7 dibromide **13**, itself the addition product of **10** and bromine. Reaction of 1,2-dibromotetrachloroethane with **10** added bromine to afford the *trans*-2,3 dibromide **15** predominantly. Its rearrangement in hydrobromic acid produced some *exo*-2,*syn*-7 dibromide **17**, which was treated with zinc in ethanol to form the *syn*-7 bromide **4**. Application of the Hunsdiecker reaction on the corresponding acid afforded the bridgehead bromide **5**. The olefinic *anti*-7 bromide **6** resulted from **13** upon dehydrobromination. The highly reactive olefinic *syn*-7 bromide **7** was difficult to obtain, finally being synthesized *via* the tosylhydrazone of the *syn*-7-bromo ketone **24**. The vinylic bromide **8** was made from **15** by dehydrobromination. Treatment of **8** with hydrobromic acid produced some 1,*exo*-2 dibromide **27**, which could be dehydrobrominated to the bridgehead olefinic bromide **9**. The spectra of these compounds are tabulated and discussed briefly. Certain miscellaneous transformations in this system are mentioned as well.

There are nine *ac*-bromobenzonorbornenes and -dienes as shown (**1**–**9**), numbered according to Bartlett and Giddings.[3] Certain of them have been previously reported. Wiley and Barstow[4] have reported the preparation of **1** and **2** as mixtures. An earlier paper of this series[1a] has described the synthesis of **3** and **6**. Bromides **6** and **7** have also been prepared by Cristol and coworkers.[1d] The bridgehead bromide **5** was part of another study[5] and it is included here for completeness. Likewise, a preliminary report[1c] mentioning the sequence leading to **7** is here given in detail.



exo-2-**Bromobenzonorbornene** (**1**).—Wiley and Barstow[4] reported that the reaction of benzonorbornadiene (**10**) with hydrogen bromide in various solvents led to mixtures of **1** and the *endo* epimer **2**. Independently,



(1) (a) Paper I of this series: J. W. Wilt, G. Gutman, W. J. Ranus, Jr., and A. R. Zigman, *J. Org. Chem.*, **32**, 893 (1967). (b) The present paper is taken from the dissertation of P. J. C., Loyola University of Chicago, 1969. (c) Certain portions have appeared in preliminary form: J. W. Wilt and P. J. Chenier, *J. Amer. Chem. Soc.*, **90**, 7366 (1968), and the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968, Abstracts of Papers, p 36. (d) For related work, *cf.* S. J. Cristol and G. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967); S. J. Cristol and A. L. Noreen, *J. Amer. Chem. Soc.*, **91**, 3969 (1969).

(2) National Science Foundation Trainee, 1965–1968; University Fellow, 1968–1969.

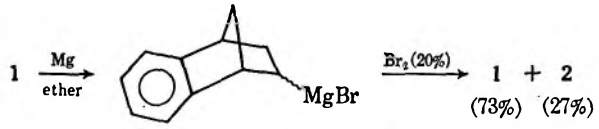
(3) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(4) G. A. Wiley and L. E. Barstow, Abstracts of the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, paper 5K; L. E. Barstow, *Tetrahedron Lett.*, 6309 (1968).

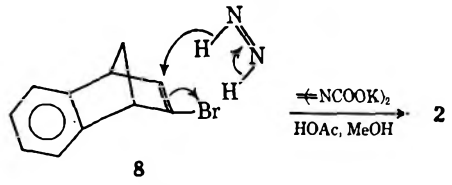
(5) H. F. Dabek, Jr., dissertation, Loyola University of Chicago, Chicago, Ill., 1969.

we found that the addition in ether led to both isomers also, **1** and **2** in an 86:14 ratio by nmr spectroscopy. When hydroquinone was added, only the *exo* epimer **1** resulted.

endo-**2-Bromobenzonorbornene** (**2**).—Treatment of the Grignard reagent from **1** with bromine produced both **2** and **1**, but the preferred method was to reduce

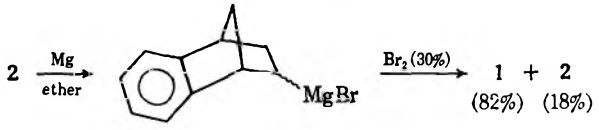


2-bromobenzonorbornadiene (**8**) with diimide (76% yield, no **1**). *exo* addition of hydrogen from diimide was previously used[1a] to prepare the *endo*-2 chloride.

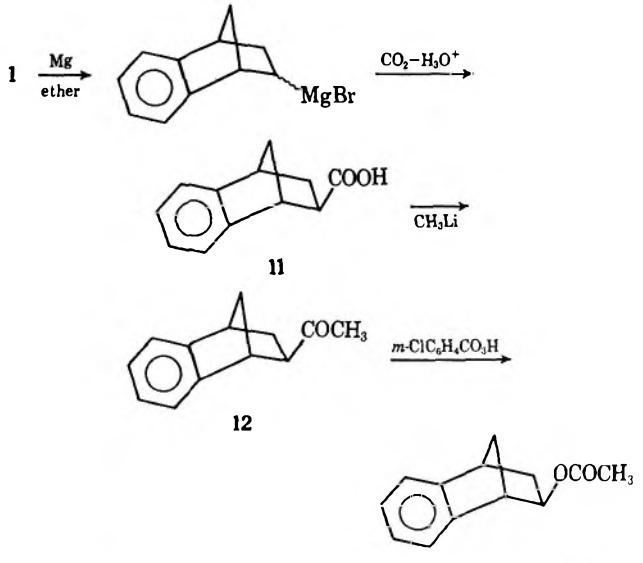


8

Treatment of the Grignard reagent of **2** with bromine again give a mixture of **1** and **2**. Although the low



yield of bromides from each of these reactions precludes discussion of the mechanistic implications, it would appear that electrophilic substitution at C-2 in this system shows an *exo* preference. In this connection, the reaction of carbon dioxide with the Grignard reagent from **1** is interesting. Only the *exo* acid **11** was isolated



11

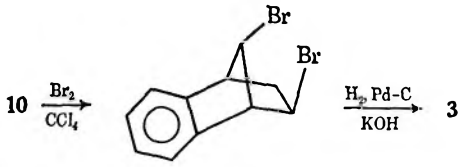
12

(17%) yield). This acid could not be obtained from **1** with sodium cyanide in dimethyl sulfoxide or by hydrolysis of *exo*-2-trichloromethylbenzonorbornene.[6]

(6) L. H. Barstow and G. A. Wiley, *Tetrahedron Lett.*, 865 (1968). See also, E. Tobler and D. J. Foster, *J. Org. Chem.*, **29**, 2839 (1964).

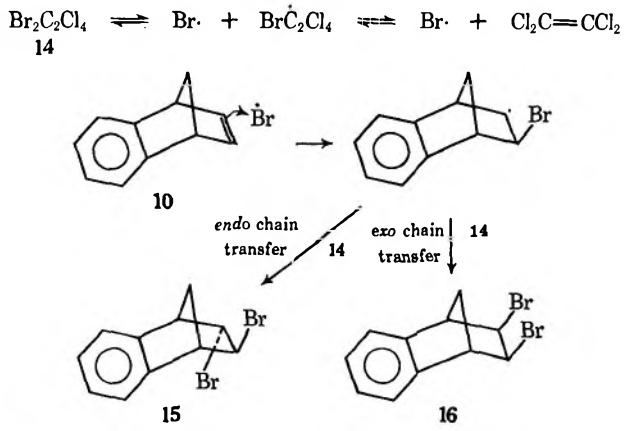
Its structure and stereochemistry were therefore established as shown. The final step[7] led to only *exo*-2-benzonorbornenyl acetate, identical with that prepared from the known[3] *exo*-2 alcohol. The isolation of *only* **11** reinforces the view that *exo* attack on the organometallic is favored.

anti-**7-Bromobenzonorbornene** (**3**).—A more convenient procedure than an earlier one[1a] was to hydrogenolyze *exo*-2,*anti*-7-dibromobenzonorbornene (**13**).[1a,d] The yield (36%) is poorer, but a difficult step is avoided.



13

syn-**7-Bromobenzonorbornene** (**4**).—It was clear from earlier experience that functionalization of the *syn*-7 position required a new approach to synthesis in this area. If a *trans* addition of the proper sort could be achieved with benzonorbornadiene (**10**), a subsequent Wagner–Meerwein shift could realize the goal. Because ionic additions invariably give some (and often mostly) rearranged adducts,[1a,d] witness **13** above, a radical addition of bromine was required. We chose 1,2-dibromotetrachloroethane (**14**), an interesting bromine carrier first used by Huyser and DeMott,[8] to brominate allylic positions. The pathways they suggested for the process led us to believe that *in the absence* of easily brominated allylic positions the reagent would *add* bromine to the double bond of an olefin. Indeed, quantitative addition of bromine to **10** *via* this reagent gave *trans*-2,3-dibromobenzonorbornene (**15**) and *exo*,*cis*-2,3-dibromobenzonorbornene (**16**) in a ratio of 89:11. No rearranged **13** was observed, the only other product being tetrachloroethylene.[9]

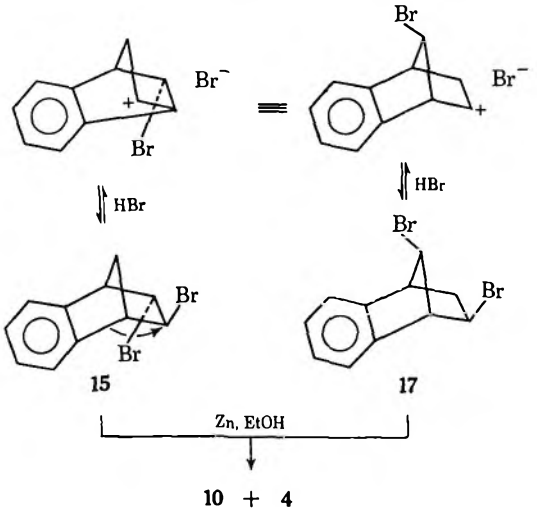


(7) This oxidation is stereospecific. Witness the formation of optically active *exo* acetate from active *exo*-norbornyl methyl ketone by J. A. Berson and S. Suzuki, *J. Amer. Chem. Soc.*, **81**, 4088 (1959).

(8) E. S. Huyser and D. N. DeMott, *Chem. Ind.* (London), 1954 (1963).

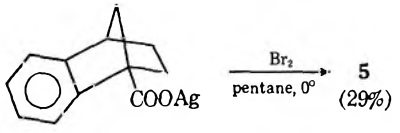
(9) This reaction should be valuable for skeletally retentive additions of bromine to those olefins where rearrangement under ionic conditions is serious, provided that allylic bromination is obviated structurally. For example, the reagent converts *anti*-7 bromide **6** into the *trans*-2,3,*anti*-7 tribromide (unpublished work) and norbornene into the *trans*-2,3 dibromide. The latter result was communicated to us by Professor A. J. Fry and coworkers (Wesleyan University) in a preprint of their forthcoming publication, for which we thank them.

Partial rearrangement of the unseparated **15** was then achieved with little loss (93% recovery) in refluxing hydrobromic acid.[10,11]



The fate of the *exo,cis* isomer **16** in this reaction is unclear. Its Wagner–Meerwein rearrangement should lead to the *exo,anti* dibromide **13**. In any event, the simple expedient of zinc dust in ethanol converted the rearranged dibromide mixture into benzonorbornadiene (**10**) and the desired *syn*-7 bromide **4** (27%).

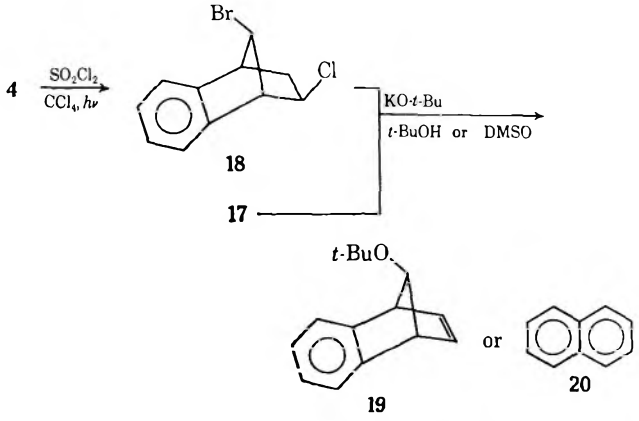
1-Bromobenzonorbornene (5).—This preparation involved Hunsdiecker degradation of the bridgehead acid as shown.[12] Use of carbon tetrachloride as solvent



gave considerable 1-chlorobenzonorbornene. The reaction will be discussed in detail elsewhere.

***anti*-7-Bromobenzonorbornadiene (6).**—Its preparation and properties have been described.[1a,d] The data for **6** in Tables I–III are included for completeness.

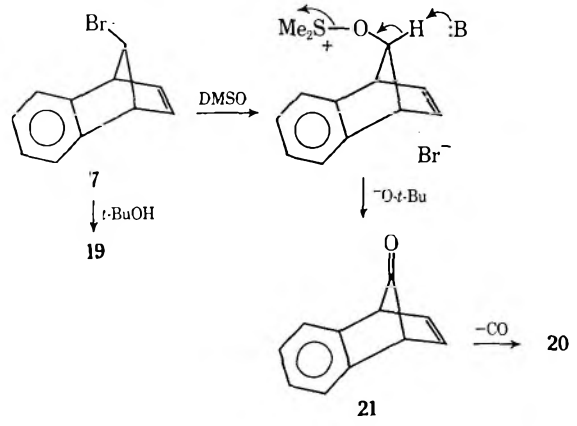
***syn*-7-Bromobenzonorbornadiene (7).**—The synthesis of this elusive, highly reactive compound proved to be quite a challenge. Vigorous dehydrohalogenation of either *exo*-2-chloro-*syn*-7-bromobenzonorbornene (**18**) or the *exo,syn* dibromide **17** led to the ether **19** or to naphthalene (**20**) depending on the solvent used.



(10) *Cf.* H. Kwart and L. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4072 (1954).

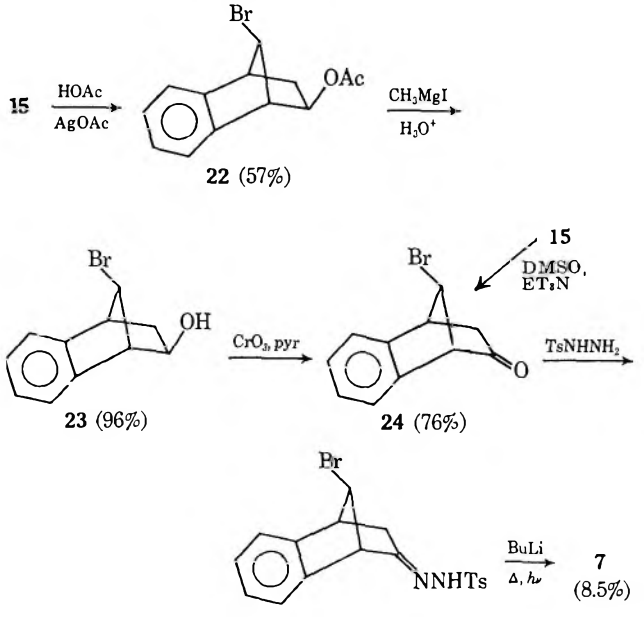
(11) In the depiction of the rearrangement below the intermediate ions have been shown as classical species (they are undoubtedly delocalized) and the attendant inversion of the bicyclic ring system with rearrangement has been omitted, both for reasons of simplicity in formulation.

Other, more mild, elimination attempts gave no reaction (see Experimental Section). Clearly the desired **7** was produced in some of the attempts, but its very high solvolytic reactivity allowed ether formation in *t*-butyl alcohol or oxidation[13] in dimethyl sulfoxide. In this



latter solvent, the anticipated dienone **21** produced led to naphthalene.[14]

The successful synthesis of **7** proceeded from the *trans* dibromide **15**. Solvolytic rearrangement of **15** (with *ca.* 11% **16** also present) in acetic acid containing silver acetate readily afforded *exo*-2-acetoxy-*syn*-7-bromobenzonorbornene (**22**). Since alkaline hydrolysis of **22** was disappointing, the alcohol **23** was prepared by treatment of **22** with methyl Grignard reagent. *syn*-7-Bromobenzonorbornen-2-one (**24**) resulted upon oxidation of **23** with chromium trioxide in pyridine.



(12) The acid has been described: J. W. Wilt, C. A. Schneider, J. P. Berliner, and H. F. Dabek, Jr., *Tetrahedron Lett.*, 4073 (1966).

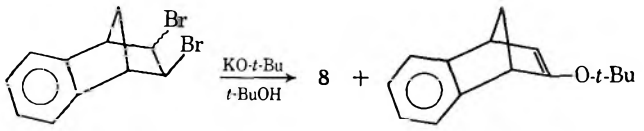
(13) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, **79**, 6562 (1957); H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(14) Ketone **21** has never been isolated. Its ready decarbonylation to naphthalene has been documented.[3] The general instability of 7-norbornadienone and its analogs has been ascribed to an unfavorable interaction of the filled π orbitals of the olefinic and carbonyl systems by S. Yankelevich and B. Fuchs, *Tetrahedron Lett.*, 4945 (1967). The decarbonylation of such compounds to aromatic molecules and carbon monoxide is an orbitally allowed sigmasymmetric transformation; *cf.* D. M. Lemal and S. D. McGregor, *J. Amer. Chem. Soc.*, **88**, 1335 (1966). Stabilization of 7-norbornadienone as its iron tricarbonyl has recently been reported by J. M. Landesberg and J. Sieczkowski *ibid.*, **90**, 1655 (1968).

The ketone could also be prepared directly from dibromide **15** with silver fluoroborate and triethylamine in dimethyl sulfoxide.[15] However, this direct route was not extensively explored. After several other unsuccessful procedures, pure *syn*-7 bromide was obtained by irradiation of the lithium tosylhydrazone salt of **24**, rotating as a thin film.[16]

When **7** was heated in dimethyl sulfoxide with potassium t-butoxide, it yielded naphthalene (**20**), implicating the presence of **7** in the earlier attempts at its synthesis described above.

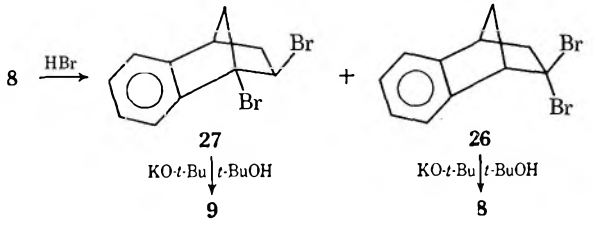
2-Bromobenzonorbornadiene (8).—Dehydrobromination of the mixture of *trans* dibromide **15** and the *exo,cis* dibromide **16** readily produced **8** (52%), along with a small amount (2%) of the vinyl ether **25**. The vinyl



15 + 16 25

ether was removed by hydrolysis to 2-benzonorbornenone with 15% sulfuric acid. Bromide **8** could also be converted into this ketone in concentrated sulfuric acid.

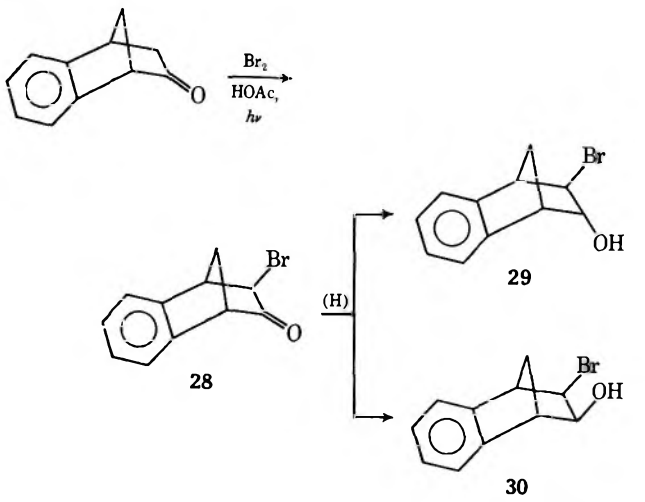
1-Bromobenzonorbornadiene (9).—Addition of hydrobromic acid to the vinyl bromide **8** was attended by partial Wagner–Meerwein rearrangement to the desired 1,*exo*-2-dibromobenzonorbornene (**27**)[17] (72%



yield, **27** and **26** in a 60:40 ratio by nmr spectroscopy). Dehydrobromination of the mixture then produced **8** (38%) and the bridgehead isomer **9** (54%). Separation was simple by chromatography.

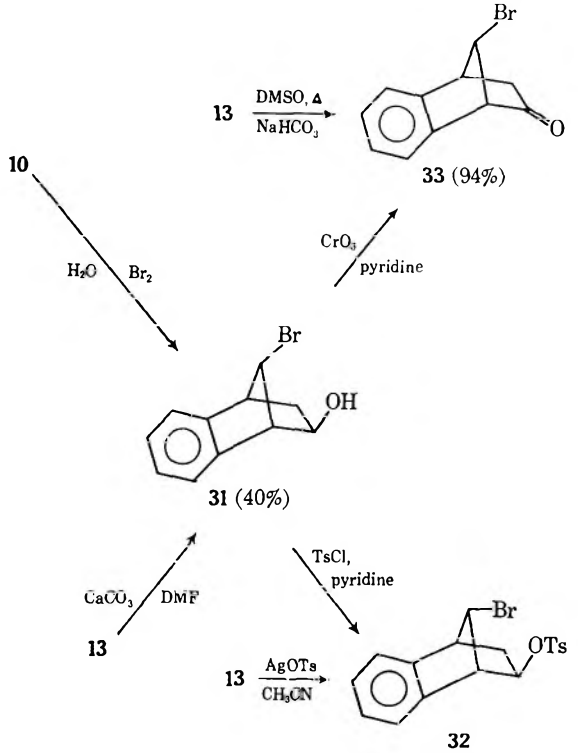
Miscellaneous.—The synthesis of bromo ketones **28** and **33** and a few of their transformations are mentioned briefly here.

2-Benzonorbornenone was brominated readily to the *exo*-3-bromo ketone **28**. No evidence for any *endo* epimer was found.[18] Reduction to the bromohydrins **29** and **30** was achieved with three different reagents. Diborane in tetrahydrofuran gave a mixture of **29** and **30** in the ratio of 80:20, respectively, while



sodium borohydride in methanol–water and lithium aluminum hydride in ether gave ratios of 45:55 and 37:63. It appears that an *exo*-3 bromine provides less steric hindrance than an *anti*-7 bromine because ketone **33** is reported to yield only *exo* alcohol (*endo* attack) with lithium aluminum hydride.[19] All attempts to rearrange **29** to a *syn*-7 alcohol derivative (see the conversion of **15** into **17**) were fruitless.

Conversion of olefin **10** into the bromohydrin **31** was accomplished with bromine water. Dibromide **13** also gave **31** upon solvolysis, and its tosylate upon treatment with silver tosylate in acetonitrile. The identity of this tosylate **32** with that from **31** confirmed the reaction pathway. The *anti*-7-bromo ketone **33** was produced from **31** by oxidation or from **13** by treatment with base in dimethyl sulfoxide.[13] Reac-



tion of the tosylhydrazone of **33** with butyllithium[20] failed to produce the *anti*-7 bromide **6**, as did attempts

(15) *Cf.* D. M. Lemal and A. J. Fry, *J. Org. Chem.*, **29**, 1673 (1964).

(16) (a) This "dry" method for carbenoid decomposition is similar to that described by G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 935 (1965). See also, R. R. Sauers and R. J. Kiesel, *ibid.*, **89**, 4695 (1967). (b) S. J. Cristol and A. L. Noreen (University of Colorado) have independently synthesized bromide **7** from the corresponding acetate. We thank Professor Cristol for a preprint of their work.[1d]

(17) For similar reactions, see J. W. Wilt, C. F. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968), and A. J. Fry and W. B. Farnham, *Tetrahedron Lett.*, 3345 (1968).

(18) Only *exo* bromination is observed with 2-norbornanone also. *Cf.* H. Krieger, *Suomen Kemistilehti*, **31B**, 320 (1958). As the enols are the intermediates, these brominations again show the *exo* preference for addition reactions in these systems.

(19) R. Caple, F. M. Hsu, and C. S. Ilenda, *J. Org. Chem.*, **33**, 4111 (1968).

(20) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); G. Kaufman, F. Cook, H. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89**, 5736 (1967).

to invert **33** to *syn*-7 derivatives using lithium chloride in N,N-dimethylformamide or silver acetate in acetic acid. These last reactions do invert other substituted norbornanones.[21]

Tables.—Table I is self-explanatory. As for Table II, the nmr spectra of substituted benzonorbornenes

TABLE I

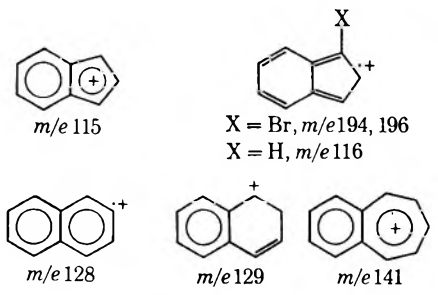
PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR BROMIDES 1–9

	Mp or bp (mm), °C	Found, % C	Found, % H
Bromobenzonorbornene			
exo-2- (**1**)[a]	76.5–77 (0.1)	59.25[b]	5.27
endo-2- (**2**)[c]	92–94 (1)	59.70[d]	5.07
anti-7- (**3**)[e]	33–34	59.22	4.97
syn-7- (**4**)	122.5–123	59.26	4.97
1- (**5**)[f]	68–70 (0.1)	59.42	5.13
Bromobenzonorbornadiene			
anti-7- (**6**)[e]	53–54	59.64[g]	4.32
syn-7- (**7**)	61.1–61.7	59.87	4.29
2- (**8**)[h]	80.5–81 (0.9)	59.75	4.10
1- (**9**)	*i*	59.95	4.27

[a] $n^{15}D$ 1.5950, d^{27}_4 1.405. [b] Calcd for $C_{11}H_{11}Br$ (**1**–**5**): C, 59.22; H, 4.97. [c] $n^{13.5}D$ 1.5927, d^{25}_4 1.437. [d] The bromide contained by glpc 1.45% *endo*-2-*t*-butoxybenzonorbornene. Calcd for this mixture: C, 59.55; H, 5.04. [e] Data taken from ref 1a. [f] Data taken from ref 5. [g] Calcd for $C_{11}H_9Br$ (**6**–**9**): C, 59.75; H, 4.10. [h] $n^{15}D$ 1.5958, d^{27}_4 1.444. [i] Collected as an oil by glpc.

have been discussed at length in the literature.[1a,d] No further elaboration is given here with the exception that certain features of the 7-proton resonances might be mentioned. Cristol and Nachtigall reported[1d] that the 7-chlorobenzonorbornadienes showed the *syn*-7 proton (δ 4.15) in the *anti*-7 chloride upfield from the *anti*-7 proton (δ 4.42) in the *syn*-7 chloride. Likewise, we find the *syn*-7 proton in **6** (δ 4.35) is upfield from the *anti*-7 proton in **7** (δ 4.64). Also, the *syn*-7 proton in **3** (δ 3.95) is upfield from the *anti*-7 proton in **4** (δ 4.12). These chemical shifts conform to the long-held view that protons *syn* to an aromatic ring resonate upfield relative to their epimeric *anti* protons.[22]

The general pattern of the mass spectra for some selected bromides (Table III) agrees with that of similar compounds reported by Cristol and Nachtigall.[1d] Some major fragments are shown below. The *m/e*



value 143 is a P − Br fragment while the *m/e* values of 220, 222, and 222 and 224 are the parent molecular ions for the bromides **5**, **7**, and **2**, **4**, and **5**, respectively. The base peak *m/e* 115 or 116 for **2**, **4**, and **5** reflects a retro Diels–Alder fragmentation, which eliminates CH_2CHBr in **2** but CH_2CH_2 *and* Br in **4** and **5**. Only the bridgehead bromide **5** shows a bromine-containing fragment, *m/e* 194 and 196, probably as a consequence of the difficult formation of a bridgehead cation by bromine loss (*m/e* 143). Note the difference in this respect of bromide **4**. Presumably a hydrogen shift in the fragment *m/e* 194 and 196 and bromine loss then occur to afford the base peak *m/e* 115 from **5**.

The base peak *m/e* 141 for bromides **6** and **7** is benzotropylium ion. It is interesting to note the great difference between **6** and **7** in the percentages of the naphthalene radical-cation fragment (*m/e* 128). The analogous chlorides to **6** and **7** show only slight fragmentation of this sort, though again the *syn*-7 chloride shows more.[1d]

Experimental Section

Melting points and boiling points are uncorrected for stem exposure. The former were taken on a Fisher-Johns block. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. For nmr spectra, see Table II. Infrared (ir) spectra were obtained on a Beckman IR-5A spectrophotometer. Only strong or structurally significant absorptions are given (in μ). Italicized absorptions were useful in contrasting isomers with one another. Ultraviolet spectra, given as λ_{max}, were taken on a Unicam SP 800 instrument. For mass spectra, see Table III. Gas–liquid partition chromatography (glpc) was performed on a Wilkens (Varian) Aerograph Model A-90P with helium gas carrier.

exo-**2-Bromobenzonorbornene** (**1**).—Benzonorbornadiene (**10**, 13 g, 0.091 mol) was mixed with hydrobromic acid (48%, 70 ml) in a pressure bottle, sealed, and heated at 60–70° in a water bath with shaking for 3 hr. After 3 hr of further shaking, water was added and the mixture was extracted with ether. The ether extracts were made neutral, dried, and distilled. Bromide **1** was collected as an oil [17.5 g, 86%, bp 95–100° (1.0–1.3 mm)]. The redistilled material had the properties given in the tables and ir λ^{neat} 6.87, 6.96, *8.11*, *8.33*, *10.31*, 10.75, and 13.30 μ. The bromide decomposed on both Reoplex 400 (polypropylene glycol adipate) and SE-30 columns at 187–190°, but no *endo* isomer was ever observed. It gave an immediate reaction with alcoholic silver nitrate.

The stirred addition of dry hydrogen bromide to **10** (8.6 g, 0.06 mol) was carried out in anhydrous ether at 0°. The saturated solution was allowed to stand at 25° overnight. Isolation of the product as above yielded bromides **1** and **2** [7.0 g, 52%, bp 96–99° (1.2 mm), 86% **1** and 14% **2** by nmr]. Addition of hydroquinone (0.2 g) to the ether used in the above reaction on a one-quarter scale gave only *exo* bromide **1** (81% crude yield).

endo-**2-Bromobenzonorbornene** (**2**).—2-Bromobenzonorbornadiene (**8**, see later text, 5.0 g, 0.023 mol) was dissolved in methanol (20 ml) and to it was added potassium azodicarboxylate[23] (5.24 g, 0.027 mol). The solution was stirred while glacial acetic (3.68 g, 0.061 mol) in additional methanol (20 ml) was added dropwise over a period of 1.5 hr, followed by further stirring for 1.5 hr. Water was added and the mixture extracted with hexane. The extracts were washed, dried, and freed of solvent. The remaining oil was distilled to give, after a small forecut of benzonorbornene and **8**, the *endo* bromide **2** [3.85 g, 76%, bp 92–98° (1.2 mm)]. Redistilled material possessed the properties in the tables and ir λ^{neat} 6.87, 6.95, *7.80*, *8.28*, *8.50*, *11.58*, and 13.2–13.4 μ. The bromide showed trace contamination on Reoplex 400 at 197° but no decomposition and no exo bromide. The contaminant was *endo*-2-*t*-butoxybenzonorbornene.[24] The bromide gave a faint cloudiness with alcoholic silver nitrate after 15–30 sec at 25° and a definite reaction on warming.

Reaction of the Grignard Reagents of 1 and 2 with Bromine.—Bromide **1** (3.02 g, 14 mmol) was slowly converted into its Gri-

(21) J. T. Lumb and G. H. Whitham, *Chem. Commun.*, 400 (1966); P. G. Gassman, J. M. Hornback, and J. L. Marshall, Abstracts of the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, paper 93 (Organic). See also H. Krieger,[18] and E. Tobler, D. E. Battin, and D. J. Foster, *J. Org. Chem.*, **29**, 2834 (1964).

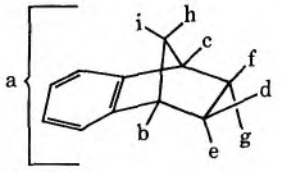
(22) The prediction of chemical shifts for bridge protons in norbornene and its derivatives is a complicated matter. *Cf.* B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *J. Amer. Chem. Soc.*, **90**, 3721 (1968), and A. P. Marchand and J. E. Rose, *ibid.*, **99**, 3724 (1968).

(23) J. Thiele, *Justus Liebigs Ann. Chem.*, **271**, 127 (1892). The crude salt was used as purification was unprofitable.

(24) Bromide **8**, as prepared in this work, contains a slight amount of 2-butoxybenzonorbornadiene. Diimide converts this latter substance into the *endo*-2 ether.

Table II

Nmr Spectra of Various Benzonorbornenes[a]



	Proton resonance, δ							
	b	c	d	e	f	g	h	i
Bromide								
1[b]	3.5 (m)	3.2 (m)	Br	3.75 (m)	1.6–2.5 (m)			
2	3.4 (m)	3.25 (m)	4.45 (dt)	Br	2.5 (ddd)	1.3 (dt)	1.55 (dt)	1.87 (ddt)
3[c]	3.37 (dd)	3.37 (dd)	2.33 (m)	1.23 (m)	2.33 (m)	1.23 (m)	Br	3.95 (p)
4	3.43 (dd)	3.43 (dd)	2.0 (m)	1.2 (m)	2.0 (m)	1.2 (m)	4.12 (t)	Br
5[d]	Br							
6[c]	4.05 (dd)	4.05 (dd)	Vinyl, 6.7 (dt)				Br	4.35(m)
7[e]	3.99 (q)	3.99 (q)	Vinyl, 6.85 (t)				4.64 (t)	Br
8	3.75 (m)	3.75 (m)	Vinyl 6.63 (dt?)				2.49 (dt)	2.18 (m)
9	Br	3.8 (m)	Vinyl, 6.73 (d)				2.83 (dd)	2.62 (m)
Dihalide								
13[c]	3.85 (d)	3.49 (dd)	Br	3.7 (ddd)	2.85 (dt)	2.15 (dd)	Br	4.1 (m)
15	3.45 (m)	3.45 (m)	Br	3.76 (t)	4.61 (t)	Br	2.33 (dt)	2.03 (m)
16	3.45 (m)	3.45 (m)	Br	4.01 (d)	Br	4.01 (d)	2.33 (dt)	2.03 (m)
17	3.65 (m)	3.65 (m)	Br	2.3 (cm)	2.2 (cm)	1.2 (m)	4.12 (t)	Br
18	3.55 (m)	3.55 (m)	Cl	3.89 (dd)	2.2 (m)	2.2 (m)	4.77 (t)	Br
Bromo ketone								
24[e]	3.85 (m)	3.85 (m)	CO		2.55 (dd)	2.2 (d)	4.74 (t)	Br
28	3.7 (m)	3.7 (m)	CO		Br	3.94 (d)	2.80 (dt)	2.45 (m)
33	3.7 (m)	3.7 (m)	CO		2.75 (dd)	1.82 (dd)	Br	4.4 (m)
Bromohydrin								
23[e]	3.4 (m)	3.4 (m)	OH[f]	3.97 (dd)	1.85 (m)	1.85 (m)	4.76 (t)	Br
29	3.3 (m)	3.3 (m)	4.61 (dd)	OH[f]	Br	3.3 (m)	2.35 (dt)	1.95 (m)
30	3.3 (m)	3.3 (m)	OH[f]	3.6 (dd)	Br	4.08 (dd)	2.35 (dt)	1.95 (m)
31	3.5 (m)	3.5 (m)	OH[f]	3.8 (m)	2.05 (m)	2.05 (m)	Br	4.15 (m)
Miscellaneous								
11[e]	3.65 (m)	3.65 (m)	COOH[g]	1.9 (cm)				
12	3.45 (m)	3.45 (m)	$COCH_3$[h]	2.45 (m)	1.75 (cm)			
22	3.5 (m)	3.5 (m)	$OCOCH_3$,[i]	4.68 (ddd)	1.95 (m)		4.51 (t)	Br
32[e]	3.65 (m)	3.65 (m)	OTs[j]	4.58 (ddd)	2.50 (dt)	1.90 (ddd)	Br	4.05 (m)

[a] The spectra were determined on a Varian A-60A spectrometer. The solutions were *ca.* 15% solutions in carbon tetrachloride with 1% TMS (δ 0.0) added unless otherwise indicated. The δ values for multiplets are the centers. The usual abbreviations for splittings are used; cm is a broad, complex multiplet. The aromatic protons a were found in the range of δ 6.8–7.5 and are not given. The integrations for all resonances were within 10% of the proper values. [b] Neat sample. [c] From ref 1a. [d] From ref 5. [e] $CDCl_3$ solvent (1% TMS). [f] OH resonance variable. [g] COOH, δ 11.7 (s). [h] $COCH_3$, δ 2.17 (s). [i] $OCOCH_3$, δ 2.03 (s). [j] OTs (CH_3), δ 2.45 (s).

Table III

Partial Mass Spectra of Selected Bromides[a]

Bromide	Fragment ions, *m/e*, % base peak										
	115	116	128	129	141	143	194	196	220[b]	222[b]	224[b]
2	37	100[c]	18	9	10	22				7	7
4	100[c]	12	31	28		94				13	13
5	100[c]	11	20		10	41	16	15		10	9
6	36		4		100[c]				4	4	
7[d]			96		100[c]				25	22	

[a] All spectra except that of 7 were determined on a Perkin-Elmer Model 270 mass spectrometer at 70 eV with the samples introduced directly upon elution from an SE-30 glpc column at *ca.* 160°. [b] Parent molecular ions. [c] Base peak. [d] This spectrum was obtained on a Bendix time-of-flight mass spectrometer, Model 12-107, at 70 eV with the bromide introduced at ambient temperature from a Kel-F vacuum line. The spectrum was scanned from 125 to 250 amu only.

gnard reagent in ether in the usual way, though heating was required. Dry bromine (2.16 g, 14 mmol) was then added dropwise at 0°. After 30 min, the excess bromine was destroyed. Work-up afforded bromides 1 and 2 (20%, nmr analysis indicated a 73:27 ratio of 1 and 2). The same reaction applied in scale to bromide 2 (1.51 g, 7 mmol) gave *ca.* 30% 1 and 2 in the ratio (by nmr) of 82:18. Again Grignard formation was slow and difficult, even with heating.

Reaction of the Grignard Reagent of 1 with Carbon Dioxide. Benzonorbornene-*exo*-2-carboxylic Acid (11).—Under nitrogen, bromide 1 (10.05 g, 0.045 mol) and ethylene bromide (8.46 g, 0.045 mol) were added in dry ether to magnesium (0.09 g-atom) in further ether. Grignard formation was complete in 1 hr. The solution was then forced into a saturated solution of carbon dioxide in ether at −5°. After 30 min, Dry Ice chunks were added. Sulfuric acid (10%) was next slowly added, followed by water. The ether layer was separated and treated with sodium hydroxide solution (10%). The alkaline material was then acidified with 1:1 hydrochloric acid to precipitate acid 11 (1.46 g, 17%, mp 108–11°). Recrystallization from petroleum ether (bp 30–60°) gave the analytical sample: mp 112–113.5°; nmr in Table II; ir λ^{KBR} 3.0–4.0, 5.93, 8.10, 8.24, and 13.31 μ.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.76; H, 6.46.

Another preparation that omitted the ethylene bromide and the nitrogen gave only 5% 11. Some benzonorbornene and *exo*-benzonorbornenol (air oxidation) were also detected, along with a solid, probably a dimeric coupling product,[25] which was not studied further. The *exo* nature of 11 was demonstrated by transformations described later.

***anti*-7-Bromobenzonorbornene (3).**—This more convenient synthesis was used. *exo*-2,*anti*-7-Dibromobenzonorbornene[1a] (13, 13.6 g, 0.045 mol) was dissolved in warm 95% alcohol (250 ml). To this was added potassium hydroxide (2.52 g) in a little alcohol

(25) Bromide 3 coupled to a dimer under similar conditions.[1a]

and palladium on charcoal (5%, 0.35 g). The mixture was hydrogenolyzed in a Parr apparatus for 4 hr at 30 psig (ambient temperature). The catalyst was filtered away and the solvent was evaporated. Pentane and water were added and the pentane layer was separated, dried, and distilled free of solvent. After a small forecut of benzonorbornene, bromide **3** was obtained [3.65 g, 36%, bp 93–135° (overheated) (1 mm), lit.[1a] bp 107–108° (2.5 mm)]. The material solidified on standing, mp 30–35°, lit.[1a] mp 33–34°. Its spectra agreed with those reported. It was homogeneous on an SE-30 column at 172°.

syn-7-**Bromobenzonorbornene** (**4**).—Olefin **10** (19.5 g, 0.137 mol) and 1,2-dibromotetrachloroethane[26] (22.1 g, 0.069 mol) were dissolved in carbon tetrachloride (50 ml) and irradiated with a General Electric 275-W sun lamp under a reflux condenser. The solution became yellow, then red. After 1.75 hr the solvent and tetrachloroethylene (ir λ 11.0 μ) were removed on a rotary evaporator and the residue was distilled to 100° (1 mm) to remove excess **10** (75% recovery of excess). The remaining material was taken up in ether and decolorized and the solvent was removed. The oily, pale red residue (20.6 g, 100%) consisted of 89% *trans*-**2,3-dibromobenzonorbornene** (**15**) and 11% *exo,cis*-**2,3-dibromobenzonorbornene** (**16**) by nmr: ir λ^{neat} 6.84, 7.84, 8.55, 13.1–*13.3*, and *14.09* μ. No *exo-2,anti-7* dibromide **13** was observed. All attempts to purify the material were unsuccessful, although it could be made colorless by repeated treatments with decolorizing carbon.

No dibromides were observed upon attempted bromination of mixtures of **1** and **2** using either a 22-W light bulb or a low pressure uv apparatus. Similarly, an attempt to rearrange dibromide **13** to either **15** and/or **16** with aluminum bromide in carbon disulfide (25°, 2 weeks) failed to change the material.

The mixed dibromides **15** and **16** (51.5 g) were then refluxed with stirring in hydrobromic acid (48%, 200 ml) for 8 hr. The solution was diluted with water and extracted with hexane. The hexane extracts were washed, dried, and evaporated to yield an oil (48 g, 93%). *Via* nmr analysis this oil contained 57% *exo*-**2,*syn*-7-dibromobenzonorbornene** (**17**) and 43% starting **15**. *What happened to 16* was not determined. At reflux times of 4 and 65 hr, this same ratio was found, whereas only a 1-hr reflux gave a product, containing less **17** (44%). For the nmr, see Table II; the ir spectrum consists of λ^{neat} *8.33*, *10.56*, and *12.89* μ (for **17**). The mixture of **15** and **16** was also treated with aluminum bromide in carbon disulfide, but *ca.* 67% of the material was unchanged after 12 hr at 25° and dark insoluble material was formed as well.

To a warm slurry of fresh zinc dust (23 g, 0.352 g-atom) in ethanol (absolute, 200 ml) was added the above mixture of dibromides **17** and **15** (30.8 g, 0.102 mol). After the material was heated under reflux for 4 hr, water was added to the cooled mixture, followed by ether. The ether extracts were washed well, dried, and distilled to afford olefin **10** [5.3 g, 36%, bp up to 80° (1.2 mm)]. The residual *syn*-**7** bromide (6.2 g, 27%) solidified on cooling and scratching. *Recrystallization from a petroleum* ether (bp 30–60°) and ether mixture gave white platelets with the properties given in the tables and ir λ^{KBr} 8.20, 9.00, *10.2*, *11.67*, 12.3, and 13.0–13.2 μ; bp 96° (0.9 mm); homogeneous on a Reoplex 400 column at 190°. The bromide gave only a faint cloud with alcoholic silver nitrate upon boiling 2 min.

1-Bromobenzonorbornene (**5**).—The bromide was prepared in another study[5] by reaction of silver benzonorbornene-1-carboxylate in pure, *dry* petroleum ether (bp 30–60°) with bromine under nitrogen. Bromide **5** was obtained in 29% yield along with a substantial amount of ester (?) material. The analytical sample was obtained by glpc from Reoplex 400 at 188° (see the tables): ir λ^{neat} 6.90, 7.80, 10.10, and 13.3 μ. Use of carbon tetrachloride as solvent gave a mixture of **5** and the 1-chloro analog.

anti-**7-Bromobenzonorbornadiene** (**6**).—The compound was available from an earlier study.[1a]

syn-**7-Bromobenzonorbornadiene** (**7**).—Silver oxide (22.8 g, 0.098 mol) and acetic anhydride (10 g, 0.098 mol) were added to glacial acetic acid (200 ml) and the mixture (warm) was shaken until the solid was white (*ca.* 15 min). The mixture of dibromides **15** and **16** (58.9 g, 0.195 mol) was added and the material then was refluxed with stirring for 13 hr. The silver bromide was filtered off and washed well with ether. Water was added to the filtrate, followed by ether. The ether extracts were combined with the silver bromide washings, made neutral, dried, and evaporated. The residual solid was taken up in hot hexane, decolorized, and chilled for 36 hr to produce *exo*-**2-acetoxy-*syn*-7-bromobenzonorbornene** (**22**, 31.6 g, 57%, mp 86–95°). Recrystallization was effected from petroleum ether (bp 30–60°) to give **22** as a white, microcrystalline solid: mp 101–102°; for the nmr, see Table II; ir λ^{KBr} 5.79, 7.30, 8.0–8.2, 9.68, and 9.86 μ.

Anal. Calcd for $C_{13}H_{13}O_2Br$: C, 55.53; H, 4.66. Found: C, 55.70; H, 4.63.

The bromoacetate **22** (29.1 g, 0.103 mol, once recrystallized) in dry ether (200 ml) was added in portions to methylmagnesium iodide (0.309 mol) in dry ether (430 ml) over a 30-min period at −5°. The material was refluxed for 2 hr, cooled, and treated with sulfuric acid (10%) cautiously over a 15-min period, followed by water. The layers were separated and the ether phase was combined with some washes of the aqueous phase. The ether was then removed from the dried extracts to yield *syn*-**7-bromo-*exo*-2-benzonorbornenol** (**23**, 23.7 g, 96%) which was recrystallized from petroleum ether (bp 30–60°) and ether mixtures as a white solid: mp 126–128° subl; for the nmr, see Table II; ir λ^{KBr} 2.97, *7.25*, 8.20, 8.46, *9.59*, 9.9–10.2, *10.79*, *11.09*, *13.00* and 13.37 μ.

Anal. Calcd for $C_{11}H_{11}OBr$: C, 55.25; H, 4.64. Found: C, 55.28; H, 4.87.

Attempted saponification of **22** with potassium hydroxide in aqueous methanol produced dark red, nondescript material which could not be profitably purified.

Chromium trioxide (29.1 g) was *carefully* added with stirring to pyridine (290 ml) at 15°. To this suspension was added crude alcohol **23** (9.7 g, 0.041 mol) in further pyridine (10 ml). The material was stirred at 25° for 55 hr, diluted with water, and extracted with ether. The extracts were made neutral, rinsed, and dried. Removal of the ether left *syn*-**7-bromobenzonorbornene-2-one** (**24**, 7.3 g, 76%). Upon recrystallization from hexane–ether, the material formed white flakes: mp 133.5–135°; for the nmr, see Table II; ir λ^{KBr} 5.77, *7.83*, 9.22, 9.36, *11.06*, *12.44*, *12.95*, and *13.36* μ.

Anal. Calcd for $C_{11}H_9OBr$: C, 55.72; H, 3.83. Found: C, 55.76; H, 4.11.

The **2,4-dinitrophenylhydrazone** was recrystallized from ethyl acetate–ethanol as a light orange solid, mp 177.5–180.5°, uv λ^{max} (EtOAc) 359 mμ (ε 26,000).[27]

Anal. Calcd for $C_{17}H_{13}O_4BrN_4$: N, 13.43. Found: N, 13.54.

Bromo ketone **24** was inert to boiling silver nitrate. Attempted formation of **24** by Oppenauer oxidation of **23** (quinone, aluminum *t*-butoxide in benzene) gave only traces of neutral products. Use of chromium trioxide in pyridine for 25 hr above gave a 6:1 ratio of **24** to **23**. Reaction of dibromide **15** (20 mmol) with silver fluoroborate in dimethyl sulfoxide followed by triethylamine[21] gave 0.6 g (13%) of **24**.

The tosylhydrazone of *24* was made in the usual fashion from equimolar proportions of **24** and tosylhydrazine in methanol containing a few drops of glacial acetic acid. After a reflux period of 1.5 hr, the material stood overnight. The precipitated solid (10.61 g, 76%) was recrystallized from ethyl acetate to yield a white, crystalline solid, mp 221.5–222.5° dec; ir λ^{KBr} 7.52 and 8.61 μ.

Anal. Calcd for $C_{18}H_{17}O_2BrN_2S$: C, 53.34; H, 4.23. Found: C, 53.48; H, 4.24.

Finely crushed tosylhydrazone (crude, 4.05 g, 10 mmol) was converted into the lithium salt by treatment in suspension with *n*-butyllithium in hexane (1.6 *M*, 12.5 ml, 20 mmol), under nitrogen with rapid stirring for 45 min. Water was added cautiously. The aqueous layer was separated and the water was removed by rotary evaporation at *ca.* 60° under vacuum in such a way as to deposit the salt as a *thin film* on the walls of the flask. *Proper filming is important.* The flask was then placed 4 cm from a GE 275-W sun lamp and rotated under vacuum (5–10 mm) with the condensing flask of the rotary evaporator cooled in Dry Ice and acetone and aligned in a horizontal fashion. As the reaction proceeded, the lamp was moved right up to the flask. The *syn*-**7** bromide **7** collected as a colorless mass of crystals at the condenser joint (0.143–0.187 g, 6.5–8.5%, mp 50–58°). It was

(26) We thank the Dow Chemical Co., Midland, Mich., for samples of this material early in the work. We later made it by reaction of tetrachloroethylene with bromine (275-W sun lamp, white solid, dec pt *ca.* 100°).

(27) The 2,4-dinitrophenylhydrazone of benzonorbornen-2-one has λ^{max} (EtOH) 361 mμ (ε 43,600).[3] While all the bromo ketones studied here had essentially this same λ^{max} for their 2,4-dinitrophenylhydrazone derivatives, none possessed the molar absorptivity reported for the parent ketone.

readily recrystallized from petroleum ether (bp 30–60°) as white clusters, mp 61.1–61.7°, with the properties given in the tables and ir λ^{KBr} *3.33*, 7.78, 8.20, *11.78*, *12.81*, 13.28, and *14.50* μ.

The bromide gave an immediate test with alcoholic silver nitrate. It decomposed on an SE-30 column at 180°. Use of tetrahydrofuran instead of only hexane in the formation of the tosylhydrazone salt gave material that produced only some naphthalene in the decomposition described.

2-Bromobenzonorbornadiene (8).—The dibromides **15** and **16** (38 g, 0.13 mol) were added to potassium *t*-butoxide (0.15 mol, freshly made) in *t*-butyl alcohol (250 ml). The solution was stirred under reflux for 22 hr. Most of the solvent was evaporated and water was added, followed by ether. The ether extracts were washed, dried, and freed of ether. Distillation then gave vinyl bromide **8** [14.5 g, 52%, bp 80–100°, redistilled at 80.5–81° (0.9 mm)] as a yellow oil. Although the oil was homogeneous on Reoplex 400 at 190°, nmr analysis showed that 2.3% 2-*t*-butoxybenzonorbornadiene was present (δ^{CCl_4} 1.13, s, *t*-Bu). Therefore the crude oil (5 g) in hexane (15 ml) was shaken with sulfuric acid (15 %, 50 ml) in a pressure bottle at ambient temperature for 2 hr. Processed material now showed 1.4% ether present. Repetition of the above finally produced analytically pure bromide: see the tables; ir λ^{neat} 3.31, *6.39*, 6.90, 7.87, 10.05, 11.9, and 13.2–13.4 μ.

The oil darkens on standing. It readily developed a precipitate of silver bromide with alcoholic silver nitrate. We ascribe this uncommon reactivity for a vinyl halide to its highly strained double bond. Presumably addition of solvent along with electrophilic assistance in bromide ion loss by silver ion occurs.[28] When bromide **8** was hydrolyzed in concentrated sulfuric acid (0°, 15 min), the processed material yielded an oil with an ir spectrum very similar to that of benzonorbornene-2-one. Since the melting point of the 2,4-dinitrophenylhydrazone derivative (mp 164–168°) could not be improved by further recrystallization (lit.[3] mp 175.4–177°), some contaminant is probably also present.

1-Bromobenzonorbornadiene (9).—In a pressure bottle, vinyl bromide **8** (1.02 g, 4.6 mmol) was treated with hydrobromic acid (48%, 50 ml) at 60–70° for 3 hr in a shaker. Further shaking at 25° was continued for 3 hr, water was added, followed by petroleum ether (bp 30–60°). The organic extracts were made neutral, washed, dried, and then freed of solvent to leave an oil (1.00 g, 72%) consisting of 1,*exo*-2-dibromobenzonorbornene (**27**, 60%) and 2,2-dibromobenzonorbornene (**26**, 40%): δ^{CCl_4} 1.9–2.9, 3.1–3.6, 3.7–4.1, and 7.0–7.6 (all cm); λ^{neat} 5.78 (weak, trace of benzonorbornen-2-one), 6.88, 10.32, 10.70, and 13.25 μ. The composition was decided on the basis of dibromide **27** *via* the integration of the aromatic proton downfield (δ 7.25–7.6) from the others (sharp AA'BB', centered at δ 7.1). Such a deshielded proton indicates a bridgehead-substituted benzonorbornene and is frequently a useful diagnosis for them.[5] Treatment of bromide **8** with hydrobromic acid under reflux gave a complex product mixture with an increased amount of ketonic material.

The mixture of **26** and **27** (1 g, 3.3 mmol) was then added to potassium *t*-butoxide (16.6 mmol, freshly made) in *t*-butyl alcohol (25 ml) and refluxed with stirring for 70 hr. Isolation of product as described for **8** gave a red oil (0.66 g) which was distilled in a micro Hickman still at 0.08 mm, bath to 140°, to give 0.4 g (63%) of a mixture of starting **8** (38%) and the bridgehead bromide **9** (54%), along with olefin **10** (8%). Separation was effected on a Reoplex 400 column at 154° affording **9** as a colorless oil: see the tables; ir λ^{neat} 3.31, 7.72, 8.56, 10.29, 11.11, 13.20, 13.76, and *14.40* μ.

***syn*-7-Bromo-*exo*-2-chlorobenzonorbornene (18).**—In a flask irradiated by a GE 275-W sun lamp, *syn*-7 bromide **4** (4.4 g, 0.02 mol) in carbon tetrachloride (20 ml) was treated dropwise under reflux with sulfuryl chloride (3.24 g, 0.024 mol) in additional carbon tetrachloride (20 ml). After 3 hr of irradiation, the cooled solution was diluted with more solvent and water added. The organic phase was washed to neutrality, rinsed, and dried. Upon removal of the solvent, a mixture of starting **4** and **18** (4.6 g) was obtained in the ratio of 15:85, respectively. This mixture could be resolved by glpc on Reoplex 400 at 194° to give **18** as a white crystalline solid: mp 100–102.5° subl; nmr in Table II; ir λ^{KBr} 8.23, 12.78–12.90, 13.27, 14.20, and 15.2–15.5 μ.

(28) For a discussion of uncatalyzed polar addition to **10**, *cf.* S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 2741 (1966).

Anal. Calcd for $C_{11}H_{10}BrCl$: C, 51.29; H, 3.92. Found: C, 51.28; H, 4.09.

Dehydrohalogenation Studies on 18 and 17.—Reaction of crude chlorobromide **18** with potassium *t*-butoxide in *t*-butyl alcohol under reflux for 6 days gave a lower boiling fraction of bromide **4** (contaminant in **18**) and ***syn*-7-*t*-butoxybenzonorbornadiene**, bp 97–105° (0.8 mm), δ^{CCl_4} 6.60 (t, CH=CH), 4.08 (t, *anti*-7 H), and 1.05 (s, *t*-Bu), and a higher boiling fraction, mostly **18**. No bromide **7** was detected.[29] Similarly, reaction of the dibromide mixture of **17** plus **15** under these conditions (reflux, 67 hr gave the *t*-butyl ether along with vinyl bromide **8**. Again no **7** was found.

Treatment of **17** plus **15** with freshly sublimed potassium *t*-butoxide in dimethyl sulfoxide at 125° for 3 hr produced a mixture of *naphthalene* and bromide **8**. This dehydrohalogenation did not affect **18** in 1 hr but in 28 hr at 130° naphthalene formed. Processes employing sodium amide in benzene (reflux, 4 hr) and collidine–lutidine (reflux, 5 hr) were without effect on **17** plus **15**. Similarly, potassium triethylcarbinoxide in its alcohol (reflux, 1 hr) or lithium diisopropylamide in ether (reflux, 12 hr) did not react with **18**.

***exo*-3-Bromobenzonorbornen-2-one (28).**—Benzonorbornene-2-one[3,30] (7.92 g, 0.05 mol) in glacial acetic acid (30 ml) was heated short of reflux with a GE 275-W sun lamp while bromine (16 g, 0.1 mol) in additional glacial acetic acid (20 ml) was added dropwise over a 1.5-hr period. After 45 min of further irradiation, water was added and the material was extracted with ether. The extracts were made neutral and dried and the solvent was removed. Distillation then gave bromo ketone **28** [9.6 g, 81%, bp 134–150°, redistilled at 131–132° (2 mm)] as a pale yellow oil: for nmr, see Table II; ir λ^{neat} *5.71*, 6.85, 8.91, 13.16, and 15.50 μ. No evidence was found for the *endo* bromo ketone. The bromo ketone reacted slowly with alcoholic silver nitrate at 25° but much faster on heating.

Anal. Calcd for $C_{11}H_9OBr$: C, 55.72; H, 3.83. Found: C, 55.55; H, 4.08.

The **2,4-dinitrophenylhydrazone** was yellow-orange from ethyl acetate–ethanol, mp 203–206.5° dec, λ^{max} (EtOAc) 359 mμ 29,000).[27]

Anal. Calcd for $C_{17}H_{13}O_4BrN_4$: N, 13.43. Found: N, 13.34.

Reduction of Bromo Ketone 28.—Reduction was carried out in the usual manner employed with each of the reagents. (1) Excess diborane swept into **28** (7.63 g, 0.032 mol) in tetrahydrofuran afforded upon processing[31] a mixture of ***exo*-3-bromo-*endo*-2-benzonorbornenol (29)** and ***exo*-3-bromo-*exo*-2-benzonorbornenol (30)** as a viscous oil [7.46 g, 97%, bp 105–117° (0.2 mm) in a Hickman still]: see Table II for nmr; ir λ^{neat} 2.97, 9.3–9.6, 13.1–13.2, and 13.84 μ. The ratio of **29** to **30** was 80:20 from nmr analysis and was unchanged upon column chromatography. (2) Addition of 4 equiv of sodium borohydride in water to **28** in methanol at 25° for 3 hr gave a ratio of 45:55. (3) Addition of excess lithium aluminum hydride in ether to **28** at 25° for 4 hr gave a ratio of 37:63. Numerous attempts to rearrange the mixture of **29** and **30** into other products containing some *syn*-7 derivative were unsuccessful: 48% hydrobromic acid, lithium bromide in dimethylformamide, silver tosylate in acetonitrile, and potassium hydroxide in various solvents.

***anti*-7-Bromobenzonorbornen-2-one (33).**—In the manner used to prepare indene bromohydrin,[32] olefin **10** (20.5 g, 0.144 mol) was converted into a mixture of dibromide **13** and ***anti*-7-bromo-*exo*-2-benzonorbornenol (31)**. The bromohydrin was separated by recrystallization from petroleum ether (bp 30–60°) and ether as a white solid (13.8 g, 40%): mp 97–99.5°; nmr in Table II; ir λ^{CCl_4} 2.85, λ^{KBr} 6.87, *7.39*, 8.09, *8.61*, *9.42*, *10.46*, 12.12, 13.22, and 13.90 μ (lit.[19] mp 95–96°). The bromohydrin also resulted

(29) Dehydrochlorination of *anti*-7-bromo-*exo*-2-chlorononorbornane proceeds similarly: H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, **78**, 5678 (1956).

(30) This ketone was additionally characterized as its **oxime**, mp 115.5–117° from methanol–water (unpublished work with R. Gajewski). *Anal.* Calcd for $C_{11}H_{11}ON$: C, 76.27; H, 6.40. Found: C, 76.60; H, 6.42. In the course of other transformations attempted on this ketone not herein described, its **azine** was also prepared, mp 174–186° (mixture of stereoisomers) from ether–benzene. *Anal.* Calcd for $C_{22}H_{20}N_2$: N, 8.97. Found: N, 8.92.

(31) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

(32) D. Porter and C. M. Suter, *ibid.*, **57**, 2022 (1935). See also, W. J. Pope and J. Reed, *J. Chem. Soc.*, **99**, 2071 (1911); **101**, 760 (1912).

from reaction of dibromide **13** with excess calcium carbonate in wet dimethylformamide (reflux 3 days).

Anal. Calcd for $C_{11}H_{11}OBr$: C, 55.25; H, 4.64. Found: C, 55.01; H, 4.93.

The **tosylate 32** was made in the usual fashion (white needles from ether–benzene, mp 117–119.5°) and also from dibromide **13** upon treatment with silver tosylate in acetonitrile containing a few drops of pyridine; nmr appears in Table II.

Anal. Calcd for $C_{18}H_{17}O_3BrS$: C, 54.97; H, 4.36. Found: C, 55.18; H, 4.52.

Oxidation of bromohydrin **31** (7.13 g, 0.03 mol) at 25° for 40 hr with chromium trioxide in pyridine as described earlier for bromo ketone **24** gave bromo ketone **33** as a pale yellow solid (6.65 g, 94%, mp 52–55°). Recrystallization from petroleum ether (bp 30–60°) and ether mixtures gave the analytical sample: mp 54.7–55.4°; nmr in Table II; ir λ^{KBr} *5.74*, *8.07*, 9.26, *12.19*, and *13.80* μ (lit.[19] mp 54.5–55.5°).

Anal. Calcd for $C_{11}H_9OBr$: C, 55.72; H, 3.83. Found: C, 55.89; H, 4.15.

Its **2,4-dinitrophenylhydrazone** was a yellow solid, mp 251.5–252° from ethyl acetate, λ^{max} (EtOAc) 357 mμ (ϵ 25,000).[27]

Anal. Calcd for $C_{17}H_{13}O_4BrN_4$: M, 13.43. Found: N, 13.55.

The bromo ketone was inert to boiling alcoholic silver nitrate for 2 min. It also resulted from dibromide **13** when it was heated in dimethyl sulfoxide containing an equinolar amount of sodium bicarbonate[13] at 130–170° for 1 hr.

Its **tosylhydrazone** (white solid, mp 217–224° dec, crude yield 72%) was prepared in standard fashion. In two reactions with methyllithium at 25°,[20] one gave no bromide **5** with 53% recovery of the tosylhydrazone, while the other gave traces of **6** with 80% recovery. No better results were found with *n*-butyllithium.

Bromo ketone **33** was recovered (88%) unchanged after a 2-hr reflux in dimethylformamide containing 1.1 equiv of lithium chloride. Likewise, a 20-min reflux of **33** in glacial acetic acid containing excess silver acetate afforded unchanged **33** (95%) contaminated slightly by an acetate that appeared by nmr to be still an *anti*-7 derivative.

Homogeneity and *exo* Stereochemistry of Benzonorbornene-2-carboxylic Acid (11).—A sample of acid **11** (*unpurified*, 0.5 g, 2.7 mmol) was methylated with diazomethane. Upon work-up the oily residue (0.52 g, 97%) solidified. Other than light material, only one peak was seen upon glpc on Reoplex 400 at 185°. The material so collected appeared to be but *one* ester [white crystalline solid; mp 52.5–53.5°; δ^{CCl_4} 7.05 (m, Ar-H), 3.67 (s, $-COOCH_3$), 3.5 (m, 1 H), 3.3 (m, 4 H), and 1.2–2.5 (cm, ring H's); λ^{melt} 5.82, 8.1–8.7, and 13.32], presumably **methyl benzonorbornene-*exo*-2-carboxylate**.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.18; H, 7.09.

Methyllithium (0.15 mol) in ether was added to the **crude acid 11** (1.03 g, 5.5 mmol) in ether and the solution was stirred for 30 min. The material was cautiously hydrolyzed and processed in the usual manner. No recovered **11** was obtained but rather glpc on Reoplex 400 at 186° afforded colorless **methyl *exo*-benzonorbornenyl ketone** (**12**, 0.276 g, 27%, oil): nmr in Table II; ir λ^{neat} 5.92, 6.91, 7.43, 8.5–8.7, and 13.0–13.5 μ.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.89; H, 7.52.

The **2,4-dinitrophenylhydrazone** formed light orange platelets from ethyl acetate–alcohol, mp 193.5–195°.

Anal. Calcd for $C_{19}H_{18}O_4N_4$: N, 15.29. Found: N, 15.52.

No other peak near **12** (retention time, 20 min) was observed in glpc. However, ***exo*-2-isopropenylbenzonorbornene** (55%, retention time, 7.2 min) was observed: δ^{CCl_4} 4.8 (m, $=CH_2$), and 1.8 (s, CH_3); λ^{neat} 6.09 and 11.31. As no such resonances were in the nmr spectrum of the reaction material itself, clearly this olefin was formed during glpc by dehydration of the corresponding alcohol. This latter arose from reaction of excess methyllithium on **12**.

Ketone **12** (0.1 g, 0.5 mmol) and *m*-chloroperbenzoic acid (Aldrich, 0.13 g of 85% material, 0.64 mmol of reagent) were dissolved in ethylene chloride (7 ml) and refluxed for 1.25 hr. Further solvent was added and the solution was then washed to neutrality, rinsed, and dried. After removal of the solvent, the crude oil remaining was shown by nmr analysis to be unchanged **12** (64%) and ***exo*-2-benzonorbornenyl acetate** (34%), the latter being identical with authentic material prepared[3] from olefin **10**. No evidence was found for any *endo*-2 product during the entire sequence from acid **11**, establishing the stereochemistry of this acid therefore to be *exo*, and totally *exo*.

Abortive attempts to synthesize acid **11** included reaction of *exo*-2 bromide **1** with sodium cyanide in dimethyl sulfoxide at 70° for 6 hr (no conversion, **1** recovered) and hydrolysis of *exo*-2-trichloromethylbenzonorbornene[6] with concentrated sulfuric acid on a steam bath for 5.5 hr (apparent sulfonation of the aromatic ring).

Registry No.—**1**, 23526-72-9; **2**, 23526-73-0; **3**, 7605-11-0; **4**, 23526-75-2; **5**, 23537-58-8; **6**, 7605-10-9; **7**, 22436-26-6; **8**, 23537-79-3; **9**, 23537-80-6; **11**, 23537-81-7; **12**, 23537-82-8; 2,4-dinitrophenylhydrazone of **12**, 23537-83-9; **13**, 14362-55-1; **15**, 23537-85-1; **16**, 23537-86-2; **17**, 23612-80-8; **18**, 23537-87-3; **22**, 23526-80-9; **23**, 23526-81-0; **24**, 23526-82-1; 2,4-dinitrophenylhydrazone of **24**, 23526-83-2; tosylhydrazone of **24**, 23526-84-3; **28**, 23526-85-4; 2,4-dinitrophenylhydrazone of **28**, 23526-86-5; **29**, 23526-87-6; **30**, 23526-88-7; **31**, 17497-61-9; **32**, 23526-90-1; **33**, 23526-91-2; 2,4-dinitrophenylhydrazone of **33**, 23526-92-3; benzonorbornen-2-one oxime, 23537-88-4; benzonorbornen-2-one azine, 23537-89-5.

Acknowledgment.—We thank Drs. H. F. Dabek, Jr., and J. L. Huston for the mass spectra and Mr. C. Nawrot for the uv spectra. We also appreciate receipt of preprints of related work from Professors S. J. Cristol and A. J. Fry and their coworkers.

Studies of Benzonorbornene and Derivatives. III. The Solvolysis of *syn*- and *anti*-7-Bromobenzonorbornadiene and Related Bromides[1,2]

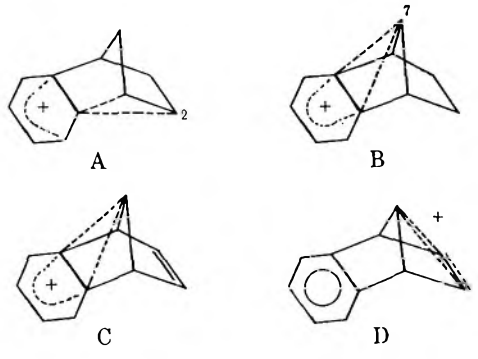
JAMES W. WILT AND PHILIP J. CHENIER[3]

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

Received July 14, 1969

The rates and activation parameters of the solvolysis of the *ac*-bromobenzonorbornenes and -dienes in 80% ethanol have been reported. The bromides show a spread in reactivity of 10^{10} between the slowest bromide amenable to study, *syn*-7-bromobenzonorbornene (**4**), and the fastest, *syn*-7-bromobenzonorbornadiene (**7**). All the solvolyses were cleanly first order and nearly theoretical infinity titers were observed. Normal *exo/endo* and *syn/anti* epimeric rate ratios were found. The bromides show a close similarity in these rate ratios to the corresponding brosylates (where known), although entropic factors seem more important for the rates of the bromides. In all but one case, from the solvolyses in aqueous dioxane containing 2,6-lutidine, one member of an epimeric pair gave structurally and stereochemically retained alcohol product while the other did not. The exception was the case of the 7-bromobenzonorbornadienes (**6** and **7**). *Each gave retained alcohol product,* even though the *syn* epimer **7** is 44,000 times faster in rate than the *anti* epimer **6**. The matter is briefly discussed. The bridgehead bromides were essentially inert. 1-Bromobenzonorbornadiene (**9**) does undergo reaction with hot alcoholic silver nitrate, but the forcing conditions suggest a pathway unrelated to normal solvolysis.

Since Bartlett and Giddings first reported[4] the acetolysis of benzonorbornenyl and -dienyl brosylates in 1960, these systems have ranked among the favorites for studies in solvolytic participation. The results have shown that the aromatic ring participates either as a phenonium ion (A)[5,6] or as a symmetrical ion



(B),[7] depending upon the site of solvolysis, C-2 or C-7. The rate data imply that assistance *via* A is more effective than *via* B,[4,8] though steric factors aside from participation may play a sizable role in the rate differences observed.[9] The incorporation of a double bond, however, increases participation as in C and an estimate of 10^4 in driving force was given for this increase.[4]

It therefore became of interest to see if the stereoelectronic "holding power" of C could match that of the related *syn*-7-benzonorbornadienyl-derived cation D (shown so as to emphasize its relationship to the firmly holding *anti*-7-norbornenyl cation[10]).[11] Having developed syntheses for the bromide precursors to C and D,[1a] we were able to investigate this point. Our results indicate that C and D are indeed nonequilibrating in 80% ethanol because the bromides *solvolyze with retention in each case.*

Results and Discussion

Rates.—Table I gives the kinetic and activation parameter data for the bromides while Table II shows some comparisons of the rates within these systems. The solvolyses were smoothly first order in all cases where actual rates are given. It may be seen that the expected *exo/endo* and *anti/syn* epimeric rate ratios are observed in these bromides *vis-à-vis* the corresponding brosylates. Indeed, when compared with *exo*-2-norbornyl, the bromides and brosylates show a close similarity (Table III). Extensive discussion of these rate differences in brosylates has appeared[4,5,7-9] and the matter for the bromides will not be dwelled upon here, but certain aspects are worth mentioning in passing.

First entropic differences appear more significant in the determination of the rates of the bromides than the tosylates. For example, $\Delta(\Delta H^*)$ for **3** and **4** is 0.7 kcal mol^{-1} while $\Delta(\Delta S^*)$ is 10.7 eu. The corresponding values for the brosylates are 3.9 kcal mol^{-1} and 2.7 eu.[13]

Second, the effect of an aromatic ring compared with a double bond in participatory ability can be seen in

(1) (a) For paper II, see J. W. Wilt and P. J. Chenier, *J. Org. Chem.*, **35**, 1562 (1970). (b) Some of this work has appeared in preliminary form: J. W. Wilt and P. J. Chenier, *J. Amer. Chem. Soc.*, **90**, 7366 (1968); the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968, Abstracts of Papers, p 36.

(2) Taken from the Dissertation of P. J. C., Loyola University of Chicago, 1969.

(3) National Science Foundation Trainee, 1965–1968; University Fellow, 1968–1969.

(4) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960).

(5) (a) W. P. Giddings and J. Dirlam *ibid.*, **85**, 3900 (1963). (b) D. V. Braddon, G. A. Wiley, J. Dirlam, and S. Winstein, *ibid.*, **90**, 1901 (1968).

(6) This intermediate has also been demonstrated in certain additions to benzonorbornadiene by S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 2741 (1966).

(7) The evidence for this symmetrical ion has been summarized by H. Tanida, *Accounts Chem. Res.*, **1**, 239 (1968).

(8) (a) H. Tanida, T. Tsuji, and S. Teratake, *J. Org. Chem.*, **32**, 4121 (1967). See, however, (b) H. Tanida, H. Ishibobi, and T. Irie, *J. Amer. Chem. Soc.*, **90**, 2688 (1968). For a recent study of A, *cf.* H. Tanida, H. Ishitobi, T. Irie, and T. Tsushima, *ibid.*, **91**, 4512 (1969).

(9) H. C. Brown and G. L. Tritle, *ibid.*, **88**, 1320 (1966); **90**, 2689 (1968).

(10) (a) S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955); (b) S. Winstein, M. Shatavsky, *ibid.*, **78**, 592 (1956); (c) W. G. Woods, R. A. Carboni and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

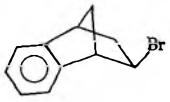
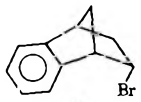
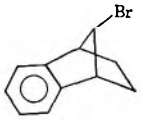
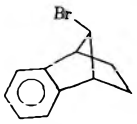
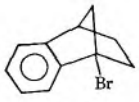
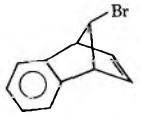
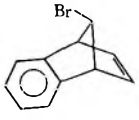
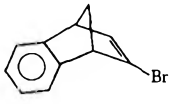
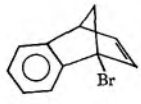
(11) During the course of this work, the acetolysis of the epimeric 7-chlorobenzonorbornadienes and 5,12-diphenyl-6,11-dihydro-6,11-(chloromethano)naphthacenes was reported.[12] As do the corresponding bromides,[1b] these chlorides also give retained product. The *syn*-7 chloride analogous to bromide **7** showed peculiar kinetics in acetolysis, unlike the clean behavior of **7** in the present work. We thank Professor Cristol for preprints of this related work.

(12) S. J. Cristol and G. W. Nachtigall, *ibid.*, **90**, 7132, 7133 (1968).

(13) (a) Data for *anti*-7 brosylate from H. Tanida, T. Tsuji, and H. Ishitobi, *ibid.*, **86**, 4904 (1964). (b) Data for the *syn*-7 brosylate from H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *ibid.*, **89**, 2928 (1967).

TABLE I

RATE DATA FOR BROMIDES IN 80% (V/V) ETHANOL CONTAINING 1.2 EQUIV OF SODIUM ACETATE[a]

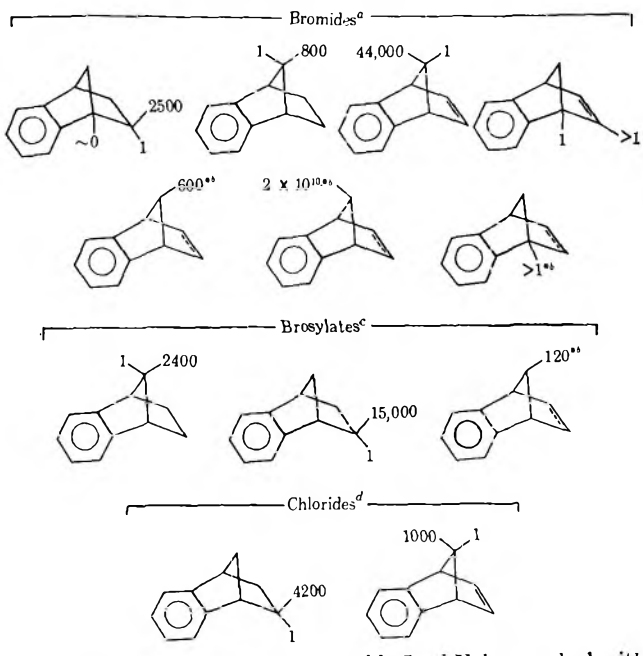
Bromobenzonorbornene or -diene	Temp, °C[b]	10^5 k_1, sec^{-1} [c]	ΔH^*, kcal mol^{-1}	ΔS^*, eu
 1	79.5	5.19 ± 0.49		
	89.2	13.5 ± 1.1		
	100.1	35.6 ± 7.9		
	(25.0)	(1×10^{-7})[d]	23.3 ± 0.7	−12.5 ± 1.8
 2	121.0	0.151 ± 0.012		
	131.7	0.392 ± 0.024		
	139.3	0.676 ± 0.121		
	(25.0)	(4×10^{-11})[d]	25.0 ± 2.2	−22.3 ± 5.4
 3	120.2	0.605 ± 0.161		
	130.4	1.54 ± 0.16		
	137.5	2.90 ± 0.34		
	(25.0)	(4×10^{-11})[d,e]	28.7 ± 0.2	−10.3 ± 0.5
 4	179.3	0.173 ± 0.026		
	187.0	0.317 ± 0.042		
	195.7	0.573 ± 0.049		
	(25.0)	(5×10^{-14})[d]	29.4 ± 1.7	−21.0 ± 3.7
 5	196	*ca.* 0[f]		
 6	79.2	1.18 ± 0.07		
	89.8	3.27 ± 0.38		
	98.6	7.92 ± 2.12		
	(25.0)	(2.4 ± 10^{-8})[d]	23.6 ± 1.3	−14.6 ± 3.5
 7	19.4	50.1 ± 7.9[g]		
	25.4	109 ± 16		
	32.9	238 ± 39		
	(25.0)	(1.05 ± 10^{-3})[d]	20.6 ± 1.4	−3.3 ± 4.6
 8	25	0[h]		
 9	100	0[i]		

[a] Except as noted (also, see Experimental Section). [b] Control was within 0.5° except for 4 (±1°) and 7 (±0.2°). [c] Normal increases in rate (1–6%) were observed for bromides 1–3 and 6 when the sodium acetate concentration was doubled. [d] Calculated from data at other temperatures. [e] The temperature coefficients of 2 and 3 cross between 25 and 120°; so the two bromides show comparable reactivity upon extrapolation to 25°, whereas 3 is somewhat faster at the higher temperatures. [f] *Ca.* 7% reaction observed after 24 hr with no further change after 97 hr (see Experimental Section). [g] Rate by conductometry in 80% (v/v) ethanol without sodium acetate present. The Volhard method was used for the others. [h] Immediate reaction with silver nitrate in 95% alcohol. [i] Reaction after 88 hr with alcoholic silver nitrate.

Table IV. Unfortunately, several desirable norbornenyl bromides have not apparently been studied and the data in places involves some extrapolation from the analogous chlorides, as indicated. In any event, the values confirm the belief[4] that aromatic π participation is less favorable than olefinic π participation in all instances. However, at C-2 the difference between the two is much less, indicating that less participation is involved and that steric factors are important in the *exo/endo* ratio at this position.[8,9]

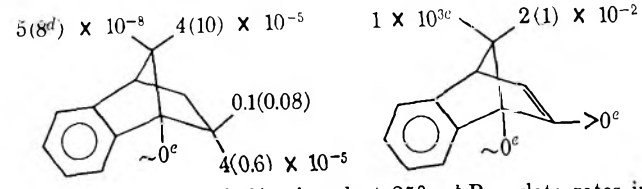
Products.—In Table V are collected the products of solvolysis for most of the bromides. The procedure involved and the characterization of the products is reserved for the Experimental Section. Bromide 1 solvolyzed with *retention* (albeit undoubtedly *via* the phenonium ion A which would allow racemization in an

TABLE II
RELATIVE SOLVOLYTIC REACTIVITIES OF BENZONORBORNENYL AND -DIENYL SUBSTRATES



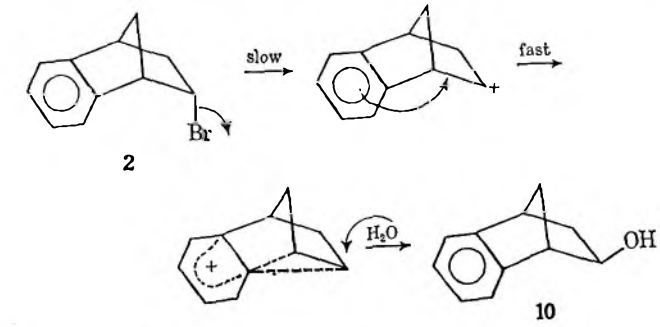
[a] In 80% ethanol, 25°. From Table I. [b] Value marked with an asterisk is the benzonorbornadienyl/benzonorbornenyl rate ratio. [c] In acetic acid, 25°; for the *anti/syn* ratio at 50°, see ref 13b; for the *exo/endo* ratio, see ref 4 and 8a; for the asterisk value, see ref 4. [d] For the *exo/endo* ratio at 77.6° in 70% acetone, see ref 8b; for the *syn/anti* ratio at 81.9° in acetic acid, see ref 12.

TABLE III
BROMIDES[a] *vs.* BROSYLATES[b] RELATIVE TO *exo*-2-NORBORNYL[c]



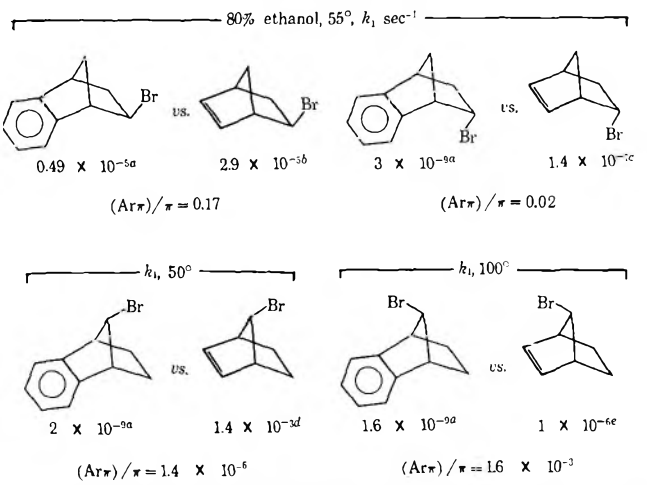
[a] Present work in 80% ethanol at 25°. [b] Brosylate rates in HOAc at 25° were taken from ref 4, 8a, and 13b. The brosylate ratios are in parentheses. [c] The values used for *exo*-2-norbornyl: bromide, 1.1×10^{-6} sec^{-1} [J. W. Wilt and W. J. Wagner, *J. Amer. Chem. Soc.*, **90**, 6135 (1968)]; brosylate, 8.82×10^{-5} sec^{-1} [S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *ibid.*, **74**, 1127 (1952)]. The ratios are rounded off to one significant figure. [d] Extrapolated from data in ref 13b. [e] As yet unknown.

active substrate[5a]), whereas its epimer **2** solvolyzed with *inversion*. Presumably, the process took the following course, analogous to that followed by *endo*-2-norbornyl bromide[14] and by *endo*-2-benzonorbornenyl



(14) (a) J. D. Roberts, W. Bennett, and R. Armstrong, *J. Amer. Chem. Soc.*, **72**, 3329 (1950). (b) J. D. Roberts and W. Bennett, *ibid.*, **76**, 4623 (1954).

TABLE IV
PARTICIPATION OF AROMATIC (Ar π) *vs.* OLEFINIC (π) π-ELECTRON SYSTEMS



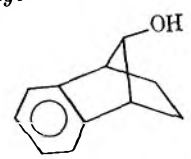
[a] Calculated from data in Table I. [b] Extrapolated from data in ref 10b. [c] The value 0.017 hr^{-1} is given in ref 14a. As this is in error,[14b] but has not been corrected, we have assumed that the bromide is as fast at 55° as is the chloride at 85°. The latter has the value 1.4×10^{-7} sec^{-1} at 85°. [d] Calculated from data for the chloride[10c] increased by 16-fold. This factor was employed because it is the ratio of rates of *exo*-2-norbornyl and *exo*-2-benzonorbornenyl bromides *vs.* chlorides (for the former, *cf.* ref 10b and c; for the latter, *cf.* this work and ref 6). [e] Calculated from data for the chloride[10c] again using the factor 16.[d] As the chloride was studied in 50% ethanol, an additional factor of $^1/_{36}$ was used to correct its rate to 80% ethanol. This factor was found by comparing the rates of other chlorides studied in both solvents.[10c]

TABLE V
PRODUCTS OF THE SOLVOLYSIS OF THE BROMIDES IN 70% DIOXANE CONTAINING 2,6-LUTIDINE[a,b]

Bromide	Product	% yield[c]
1	10	~100
2	10	98
3	11	92
4[d]	12	*anti*,[e] 90.5
		syn, 9.5
5	*f*	
6	13	74[g]
7	14	85[g]
8	*h*	
9	*i*	

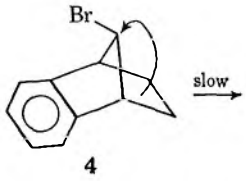
[a] Except as noted. [b] This system was chosen to simplify product analysis. Use of sodium acetate in aqueous dioxane gave some acetate ester products. [c] Isolated yields. The crude reaction materials showed no contamination by other alcohols. [d] Products obtained from kinetic study (Table I). [e] By nmr analysis; see Experimental Section. [f] No product study made as **5** is inert. [g] These alcohols are somewhat sensitive substances and the lower yields reflect this. No other products were observed in the crude product, however. [h] Benzonorbornen-2-one is the probable, but not proved, product. [i] Not determined.

brosylate.[4] Similarly, bromides **3** and **4** behaved as expected. Bromide **3** *via* ion B[7] afforded *retained* product (*anti*-7 alcohol **11**) just as does the corresponding brosylate[4] and *anti*-7-norbornenyl brosylate.[10] The *rearrangement* to **12** attending **4** in sol-

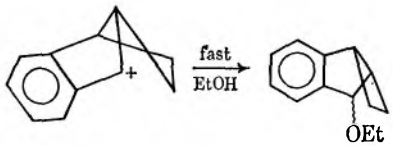


11

volysis, shown below, is the same as that found by Tanida and coworkers for the brosylate,[13b,15] and by Winstein's group for *syn*-7-norbornenyl brosylate.[16]



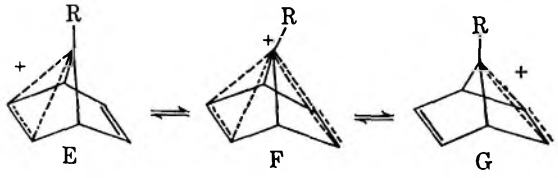
4



12

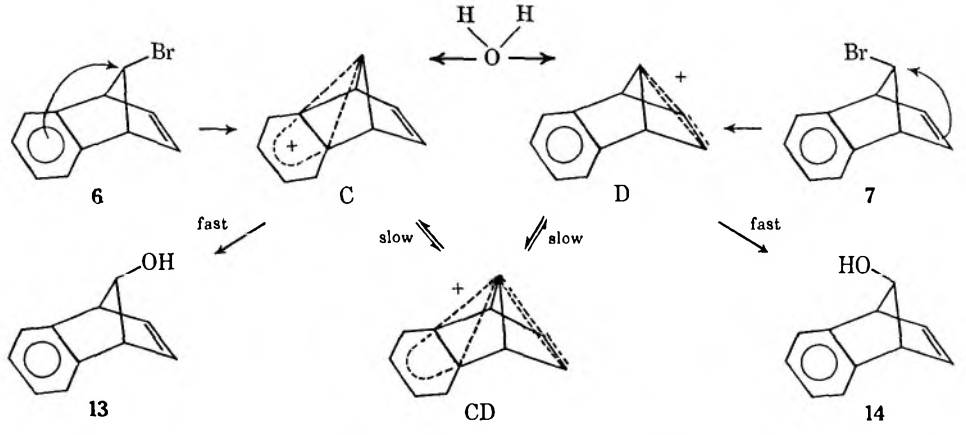
The most noteworthy aspect of the study is, of course, the behavior of bromides **6** and **7** which is unprecedented. Even though much different in rate (k_7/k_6 = 44,000), and even though the driving force due to the *anti* π system in each bromide is much different (600-fold in **6**, 2×10^{10} fold in **7**), *each epimer gave retained alcohol.* The *anti*-7 alcohol **13** (mp 104°, CHOH, δ 3.89) is readily differentiable from the *syn*-7 alcohol **14** (mp 94°, CHOH, δ 4.25).

The integrity of 7-norbornadienyl cations is well established by low temperature nmr studies.[17] There is an energy barrier to bridge flipping, dependent



E F G

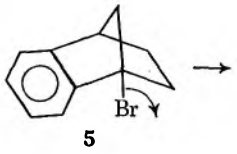
upon the nature of R, ranging from under 7.6 to over 19 kcal mol^{-1}. The behavior of bromides **6** and **7** illustrates this barrier to bridge flipping in another way, *viz.*, the formation of retained alcohol product faster



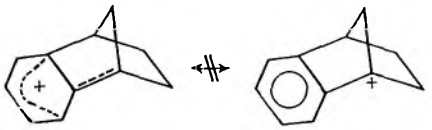
from C and D than their equilibration under the conditions employed, as shown.

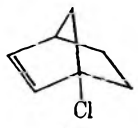
It should also be mentioned as a disclaimer that the representations C, CD, and D are used for simplicity. The "real" nature of 7-norbornenyl and -dienyl cations is clouded in controversy, some of which has been touched upon in the present systems by Cristol and Nachtigall.[18]

The Bridgehead and Vinyl Bromides.—Lastly, the lack of reactivity (Table I) in the bridgehead bromide **5** is not unexpected because such halides are characteristically inert. The possibility for benzylic stabilization of the cation from **5** is absent, undoubtedly for stereoelectronic reasons. Interestingly, both 2- and



5





14

1-bromobenzonorbornadiene (**8** and **9**) appeared to undergo to slight solvolysis (Table I). Similar slight reactivity has been reported for 1-chloronorbornene (**14**)[19] and its origin is intriguing,[20] but, because our studies on these halides are continuing, discussion of this point will be deferred.

Experimental Section

Melting points and boiling points are uncorrected for stem exposure. The former were taken on a Fisher-Johns block. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Nuclear magnetic resonance (nmr) spectra are given in δ values and were determined on a Varian A-60A spectrometer, using 15% solutions in the solvent listed with 1% TMS (δ 0.0) added. The usual abbreviations for splittings are used. Proton integrations were within 10% of the proper value. Infrared (ir) spectra were taken on a Beckman IR-5A instrument

(15) H. Tanida, Y. Hata, and H. Ishitobi, *Tetrahedron Lett.*, 361 (1967).

(16) S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.*, **79**, 505 (1957); S. Winstein, F. Gadient, E. T. Stafford, and P. E. Klinedinst, Jr., *ibid.*, **80**, 5895 (1958).

(17) R. K. Lustgarten, M. Brookhart and S. Winstein, *ibid.*, **89**, 6350, 6352, 6354 (1967). E, F, and G may be even more complex than shown.

(18) See ref 12 for citations on the controversy and brief discussion.

(19) J. W. Wilt, C. F. Parsons, C. A. Scheider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968).

(20) The addition of hydrogen chloride (CCl_4, −78°) proceeds much faster to 2-chloronorbornene than to **14** [A. J. Fry and W. B. Farnham, *Tetrahedron Lett.*, 3345 (1968)]. This may be relevant to the reactivities of **8** and **9** found in the present work if in some way a proton addition is indeed involved in their solvolyses.

and are given in microns (μ). Only significant absorptions are recorded. Gas–liquid partition chromatography (glpc) was performed on a Wilkens (Varian) Aerograph Model A-90P with helium gas carrier. Reoplex 400 is polypropylene glycol adipate.

Materials.—The bromides were available as described:[1a] **1**, thrice distilled, bp 88–89° (1 mm) $n^{15}D$ 1.5950, d^{27}_4 1.405, no *endo* by nmr, glpc inapplicable as **1** decomposes; **2**, twice distilled, bp 105–106° (2 mm), 96% pure by glpc, contained some **8** and some *endo*-2-*t*-butoxybenzonorbornene; **3**, twice distilled, bp 91–103° (0.9–1.1 mm), low-melting solid, 99% pure by glpc (contained 1% benzonorbornene); **4**, thrice recrystallized, mp 122–123°, pure by glpc; **5**,[21] once distilled, bp 68–70° (0.1 mm), 96% pure by glpc, contaminant(s) unknown; **6**, twice distilled, bp 100–107° (1.2 mm), mp 52°, pure by glpc; **7**, once recrystallized, mp 60°, glpc inapplicable as **7** decomposes; **8**, once distilled, bp 80.5–81° (0.9 mm), 98% pure by glpc, contained some 2-*t*-butoxybenzonorbornadiene; **9**, collected twice by glpc, negative to alcoholic silver nitrate at room temperature.

Kinetic Procedure. Volhard.[22]—Solutions of the bromide and sodium acetate trihydrate, 0.03 *M* and 0.036 *M*, respectively, were made in 80% absolute ethanol–20% water (v/v). Aliquots were sealed in ampoules and thermostated at the given temperature (see Table I). For determinations, the contents of the ampoules were vigorously shaken with petroleum ether (bp 30–60°) followed by water. The aqueous phase was then titrated for bromide ion by the Volhard method. The first point (0 time) was taken after 10 min at the temperature used. The rates are believed accurate to within 5%. Identical runs were made using 0.072 *M* sodium acetate trihydrate to check salt effects and SN2 components. The increased rates were 1–6% higher (normal salt effects).

Kinetic Procedure. Conductance.[22]—Bromide **7** was much too fast for the Volhard procedure above (its half-time is 11 min at 25° whereas that of **4** is 4 million years). A typical conductance run is described. Bromide **7** (46.4 mg) was quickly dissolved in absolute ethanol (4 ml) in a Freas cell at the appropriate temperature, followed by 80% ethanol (2 ml) and distilled water (1 ml), giving 0.03 *M* bromide. The conductance was measured immediately using an Industrial Instruments, Model RC-16B2, 1000-cps, ac, bridge. The infinity conductance was taken after 10 half-lives. The technique was checked with pure *t*-butyl bromide, $k_1 = 4.2 \times 10^{-4}$ sec^{-1} at 25.9°, lit.[23] $k_1 = 3.85 \times 10^{-4}$ at 25°. Bromide **7** is nearly three times faster.

Calculations.[22]—For the Volhard method, a plot of $-\ln$ [milliliters of $KSCN_t$ − milliliters of $KSCN_\infty$] *vs.* time gave the first-order rate constant, while, for the conductance method, a plot of $-\ln (C_\infty - C_t)$ *vs.* time was used. First-order kinetics were very good throughout the runs. The infinity titers follow (average of four determinations): **1**, 96%; **2**, 93%; **3**, 93%; **4**, 98%; **6**, 92%; **7**, 92% (one value by Volhard method after 21 hr at 25°). The activation parameters were calculated in the usual way from the Eyring equation. The errors listed in Table I for these parameters are average deviations for ΔH^* and ΔS^* computed graphically *via* the best (visual) straight-line fit of the data.

Product Studies.—Bromide **1** (0.5 g) in 70% purified dioxane–20% water (v/v, 25 ml) containing redistilled 2,6-lutidine (0.29 g, 1.2 equiv) was refluxed for 22 hr. Water (200 ml) was added and the solution then was thoroughly extracted with ether. The ether extracts were made neutral, rinsed, dried, and evaporated to afford crude *exo*-**2-benzonorbornenol** (**10**, 0.38 g, quantitative yield, homogeneous on Reoplex 400 at 193°) which was recrystallized from petroleum ether (bp 30–60°)–ether: mp 71–74°, lit.[4] mp 74.1–75.4°; δ^{CCl_4} 7.26–6.9 (m, ArH, AA′BB′), 4.05–3.83 (m, CHOH), 3.63 (s, OH, variable), 3.4–3.15 (m, bridgehead H's), 2.25–1.6 (m, other ring H's). The ir,[4] nmr, and glpc comparisons of **10** with authentic material confirmed its structure. No *endo* alcohol [ir;[4] δ^{CCl_4} 7.3–6.8 (m, ArH, AA′BB′), 4.5–4.1 (m, CHOH), 3.3–3.0 (m, bridgehead H's), 2.4–1.9 (seven-line m, *exo*-3 H, 1.9–1.4 (m, bridge H's), 1.0 (s, OH, variable), 0.8–0.5 (dt, *endo*-3 H)[24]] was observed in the ir or nmr spectra of the crude solvolysis product. Use of sodium acetate (1.2 equiv) instead of lutidine produced 12% *exo*-**2-benzonorbornenyl acetate** (δ^{CCl_4} 2.04 (s, $-OCOCH_2$, confirmed with that known) along with **10**.

Bromide **2** (1.22 g) similarly treated in 70% dioxane (100 ml) and lutidine at 150° for 310 hr gave crude **10** (0.86 g, 98%, purified mp 71.5–74.0°), again confirmed *via* ir, nmr, and glpc analysis. No other product was found.

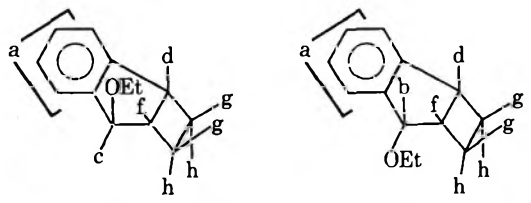
Bromide **3** (2.01 g) so treated at 150° for 144 hr gave *anti*-**7-benzonorbornenol** (**11**, 1.33 g, 92%, mp 92–100°, recrystallized as above to mp 100–104°, lit.[4] mp 104.1–105.7, 105.6–107.1, and 103–104.6°). Identification was made *via* ir,[4] nmr,[25] and glpc comparison with authentic material. No other product was seen.

Since sealed vessels containing bromide **4** in 70% dioxane at 200° exploded, the petroleum ether washes of the kinetic study ampoules were combined, washed, dried, and evaporated. The oily solid residue was studied by glpc on Reoplex 400 at 185°. The first fraction was a mixture of ethyl ethers **12** (see following text) while bromide **4** was the second. Alcohol products were not observed, presumably being retained on this column. The bulk residue was therefore taken up in acetone and chilled to precipitate unchanged **4**. The mother liquor was then chromatographed on Reoplex 400 at 185° to afford *anti*- and *syn*-**2-ethoxybenzo[3,4]bicyclo[3.2.0]hept-3-ene** (**12**) as an oil: ir λ^{neat} 3.4–3.6, 7.54, 9.15–9.30, and 13.32 μ.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.89; H, 8.45.

The nmr spectrum was quite complex and is given in Table VI. From the integrations of protons b and c there appeared to be 87–94% *anti*-**12** and 6–13% *syn*-**12**. Tanida and coworkers reported the corresponding alcohols: proton b, δ^{CCl_4} 5.26 (d, J = 7.1 cps); proton c, δ^{CCl_4} 4.66 (s). The ratio of alcohols (*anti*/*syn* = 98.6:1.4) found by the Tanida group was sensitive to conditions (*syn* epimerized to *anti*).

TABLE VI



anti-**12** *syn*-**12**

Proton	δ^{CCl_4}	J, cps
a	7.0–7.6 (m)	
b	4.98 (d)	bf, 7
c	4.55 (broad s)	cf, 0
d	3.5–4.0 (m)	
$-OCH_2CH_3$ (e)	3.42 (q)	ei, 7
f	2.9–3.2 (m)	
g	1.9–2.6 (m)	
h	1.4–1.9 (m)	
$-OCH_2CH_3$ (i)	1.1 (t)	

No product was isolated from bromide **5** because of its inertness (Table I). The slight reaction (*ca.* 7%) is believed to be due to contamination of **5** by a 1,2-dibromide by-product of the Hunsdiecker reaction used to prepare **5**.

Treatment of bromide **6** (1.33 g) in aqueous dioxane–lutidine as above (reflux, 71 hr) afforded crude *anti*-**7-benzonorbornadienol** (**13**, 0.7 g, 74%, mp 90–104°, lit.[4] mp 106.3–108.2°). The nmr[26] and ir[4] spectra of the crude product were identical with those of authentic material. Alcohol **13** decomposed on Reoplex 400 at 200°. The two major fractions were apparently aldehydes (yellow oil): ir λ^{neat} 3.58, 3.70, and 5.96 μ; nmr δ^{CDCl_3} 9.77 (s) and 20.5 (s), naphthalene pattern in aromatic region. Similar behavior has been noted for **13** by others.[4] The crude **13** was acetylated in pyridine to only *anti*-**7-benzonorbornadienyl acetate** (oil, 183° from Reoplex 400): ir λ^{neat} 3.3, 5.76, 8.15, 9.6, and 14.3; δ^{CCl_4} 7.07 (m, ArH, A_2B_2), 6.55 (m, HC=CH), 4.65 (m,

(21) We thank Dr. Henry F. Dabek, Jr., for this bromide, prepared as given in his dissertation, Loyola University of Chicago, 1969.

(22) For complete details, the dissertation of P. J. C.[2] should be consulted.

(23) O. T. Benfey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2494 (1952).

(24) G. Gutman, M.S. Thesis, Loyola University of Chicago, 1966.

(25) K. Tori, K. Aono, Y. Hata, R. Muneyuki, T. Tsuji, and H. Tanida, *Tetrahedron Lett.*, 9 (1966).

(26) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3738 (1967).

-CHOAc), 3.97 (q, bridgehead H's), 1.92 (s, -OCOCH$_3$); lit.[27] mp 56–57°.

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.79; H, 6.18.

The *crude* solvolysis product (0.13 g) was also hydrogenated in absolute ethanol (2.5 hr, 5% Pd–C) to afford *only anti*-7-**benzonorbornenol** (**11**, 0.12 g), the spectra and glpc behavior of which matched that of authentic **11**. No nmr resonance at δ 3.97 due to the saturated *syn* epimer[25] could be detected, even at high amplitude.

The small quantity of bromide **7** available necessitated a smaller scale product study. Bromide **7** (0.1 g) was allowed to stand in 70% dioxane (5 ml) containing lutidine (0.058 g, 1.2 equiv) at room temperature for 22 hr. Processing as before gave *syn*-7-**benzonorbornadienol** (**14**, 0.061 g, 85%): mp 94–94.8° after three recrystallizations from petroleum ether (bp 30–60°); ir λ^{KBr} 3.01, 3.34, 9.22, 9.41, 13.71, and 14.40; δ^{CDCl_3} 7.0–7.6 (m, ArH, A_2B_2), 6.7 (t, HC=CH), 4.1–4.4 (broad m, CHOH), 3.73 (q, bridgehead H's, $J_{\text{bridgehead vinyl}}$ = 2.5, $J_{\text{bridgehead CHOH}}$ = 1.5 cps), 2.1–2.6 (broad s, OH).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.43; H, 6.37.

The crude solvolysate showed no trace of the *anti* epimer **13**, whose -CHOH resonance at δ 3.89 (m)[26] is readily discernible from that of **14** [δ 4.1–4.4 (m)]. Also, the two epimers have several differences in the ir that make contamination obvious, and the crude solvolysate showed only **14**. Alcohol **14**, like **13**, decomposed over Reoplex at 200°, apparently again yielding aldehydes of as yet unknown structure.

Some early attempts to study the rate of solvolysis of **7** in 80% ethanol containing 1.2 equiv of sodium acetate as described for the ether bromides afforded petroleum ether washes of the reaction material. Work-up of these as detailed for **1** led to an oily product that decomposed upon attempted glpc (see **14**). Its spectra indicated it to be principally *syn*-7-**ethoxybenzonorbornadiene** [δ^{CCl_4} 6.8–7.4 (m, Ar, H, A_2B_2), 6.67 (t, HC=CH), 3.97 (t, -CHOEt), 3.77 (q, bridgehead H's, $J_{\text{bridgehead vinyl}}$ = 2, $J_{\text{bridgehead CHOET}}$ = 1.5 cps), 3.39 (q, -OCH$_2$CH$_3$, J = 7 cps), 1.00 (t, -OCH$_2$CH$_3$)], although some acetate ester (λ^{neat} 5.79 μ) was also present. The triplet nature of the -CHOEt resonance indicated the *syn* stereochemistry of the ether.[28] Unfortunately, analytical material *via* glpc could not be obtained because of the lability of the compound.

Registry No.—**1**, 23526-72-9; **2**, 23526-73-0; **3**, 7605-11-0; **4**, 23526-75-2; **5**, 23537-58-8; **6**, 7605-10-9; **7**, 22436-26-6; *anti*-**12**, 23526-77-4; *syn*-**12**, 23552-88-7; **14**, 23526-79-6; *anti*-7-benzonorbornadienyl acetate, 16031-3-9.

Acknowledgment.—We thank Dr. Henry F. Dabek, Jr., for the sample of bromide **5**. We also appreciate the preprints of related work from Professor S. J. Cristol.

(27) Cristol and Nachtigall[12] in their preliminary report give this melting point. Our sample has not yet solidified, but the multiplet shown by the -CHOAc proton in the nmr spectrum and the other work described above support the structure.

(28) The stereochemistry of the proton at the bridge in 7-substituted benzonorbornenes and -dienes is better established by the nmr splittings than by chemical shifts. The matter has been discussed.[1a]

Reactions of Alkenes with Di-*t*-butyl Peroxide and *t*-Butyl Peroxypivalate

J. REID SHELTON AND CHRISTOPHER W. UZELMEIER[1]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received October 16, 1968

A variety of alkenes structurally related to 4-vinylcyclohexene have been allowed to react with *t*-butoxy radicals from both di-*t*-butyl peroxide (DTBP) and *t*-butyl peroxypivalate (TBPP) to relate variations in reactivity and products to the structure of the alkenes. The major products were *t*-butyl alcohol and dehydro dimers when allylic hydrogen was present and vinyl unsaturation absent, as in the cycloalkenes (C_5–C_7). Addition dimers and polymer were also obtained when nonallylic radicals were formed in the presence of double bonds, as in cyclooctene and vinylcyclohexane. Minor amounts of acetone and *t*-butyl ethers were produced from β scisson and addition of *t*-butoxy radicals, respectively. More addition occurred with cyclooctene, alkenes with no allylic hydrogens, and conjugated alkenes. A decrease in relative reactivity toward hydrogen abstraction by *t*-butoxy radical was observed with increasing ring size from cyclopentene to cyclooctene. Other products from TBPP decomposition include carbon dioxide and products derived from *t*-butyl radical by addition, hydrogen transfer, and coupling reactions. Interactions of *t*-butyl and *t*-butoxy radicals, in or near the perester solvent cage, account for the formation of di-*t*-butyl ether and a portion of the *t*-butyl alcohol and isobutylene.

Three modes of reaction are available to *t*-butoxy radicals generated in the presence of alkenes.

$$(CH_3)_3CO\cdot \longrightarrow CH_3COCH_3 + CH_3\cdot \quad (1)$$

$$(CH_3)_3CO\cdot + RH \longrightarrow (CH_3)_3COH + R\cdot \quad (2)$$

$$(CH_3)_3CO\cdot + >C{=}C< \longrightarrow (CH_3)_3CO\overset{|}{C}\overset{|}{-}\overset{|}{C}\cdot \quad (3)$$

Acetone indicates those *t*-butoxy radicals that are wasted by β scission (eq 1), *t*-butyl alcohol measures hydrogen abstraction (eq 2), and *t*-butyl ethers provide a measure of the addition reaction (eq 3).

Previous studies have shown[2–4] that *t*-butoxy radicals preferentially abstract the secondary allylic hydrogens of 4-vinylcyclohexene to form *t*-butyl alcohol and biallyls rather than add to either double bond. On the other hand, an investigation[5] of the liquid-phase oxidation of cyclic alkenes disclosed that some 70% of the cyclooctene reacted by addition of oxy and peroxy radicals, although other cycloolefins gave mostly products derived from allylic hydrogen abstraction. Moreover, the overall rate of oxidation decreased in progressing from cyclopentene to cyclooctene.

These results led us to examine the reaction of a variety of alkenes structurally related to 4-vinylcyclohexene with *t*-butoxy radicals obtained by photolysis of di-*t*-butyl peroxide (DTBP) and by thermal decomposition of *t*-butyl peroxypivalate (TBPP). The objective of this work was to relate the observed reaction products and the relative reactivities toward *t*-butoxy radical attack to the structure of the alkenes. Ques-

(1) Taken from the Ph.D. Thesis of C. W. Uzelmeier, Case Institute of Technology, 1967.

(2) J. R. Shelton and J. N. Henderson, *J. Org. Chem.*, **26**, 2185 (1961); J. R. Shelton and A. E. Champ, *ibid.*, **28**, 1393 (1963).

(3) W. J. Farrissey, *ibid.*, **29**, 391 (1964).

(4) J. R. Shelton and J. F. Siuda, *ibid.*, **31**, 2028 (1966).

(5) D. E. Van Sickle, F. R. Mayo, and R. M. Arluck, *J. Amer. Chem. Soc.*, **87**, 4824 (1965).

TABLE I

PRODUCTS FROM PHOTOLYSIS OF DI-t-BUTYL PEROXIDE IN VARIOUS ALKENES

Alkene[a]	Yield, % Acetone[b]	t-BuOH[b]	t-Butyl ether[b]	Dimer[c]	t-BuOH formed/ alkene consumed
Vinylcyclohexane	4.3	94	1.0	33	0.73
4-Vinylcyclohexene	2.3	92	2.0[d]	43	0.86
4-Ethylcyclohexene	2.0	94	2.2	63	0.90
1-Ethylcyclohexene	1.5	99	0.7	54	1.08
None	49	37	0	10[e,f]	...

[a] 2.24 *M* alkene and 0.37 *M* DTBP in benzene. [b] Based on amount of DTBP decomposed after 24-hr photolysis at 86 ± 3°. [b] Based on amount of *t*-BuOH formed. [d] Contained a fourfold excess of adduct of internal double bond. [e] Biphenyl. [f] 15% toluene also formed.

TABLE II

PRODUCTS FROM PHOTOLYSIS OF DI-t-BUTYL PEROXIDE IN CYCLIC ALKENES AND RELATED COMPOUNDS

Hydrocarbon[a]	Yield, % Acetone[b]	t-BuOH[b]	t-Butyl ether[b]	Dimer[c]	t-BuOH formed/ alkene consumed
Cyclopentene	1.6	98	4.4	61	0.90
Cyclohexene	*d*	98	3.4	54	1.03
Cycloheptene	3.2	97	3.1	54	0.88
Cyclooctene	4.0	82	3.4	55	0.68
1,5-Cyclooctadiene	1.6	89	3.7	48	0.98
Cyclododecene	2.2	95	*d*	*d*	1.24
Cyclohexane	5.1	88	...	4[e]	1.44[f]
Toluene	25	76	...	43	0.89[f]

[a] 2.28 *M* hydrocarbon and 0.38 *M* DTBP in benzene. [b] Based on amount of DTBP decomposed after 24-hr photolysis at 86 ± 3°. [c] Based on amount of *t*-BuOH formed. [d] Not determined. [e] 41% yield of solvent-derived product (cyclohexylbenzene). [f] Relative to hydrocarbon consumed.

tions of particular interest were (1) the factors affecting the relative importance of the abstraction and addition reactions of the *t*-butoxy radical, (2) the effect of ring size in cycloalkenes on the reactivity of the double bond and associated allylic hydrogens, and (3) the relative reactivity of the tertiary allylic hydrogen of vinyl-substituted cycloalkenes and alkanes toward *t*-butoxy radical. In addition, it was desired to observe the reactions of alkenes with *t*-butyl radical from TBPP decomposition and to correlate variations in products and reactivities of this radical with alkene structure.

Results and Discussion

Fate of the *t*-Butoxy Radical in the Presence of Alkenes.—Tables I and II show amounts of reactants consumed and products formed in the photolysis of DTBP in benzene solutions of alkenes. Results for cyclohexane and toluene are also included in Table II for comparison. The data show that in most cases the volatile products (alcohol, acetone, and ether) account for 95–100% of the *t*-butoxy radicals generated. An important exception is the case of cyclooctene, where *t*-butyl alcohol, acetone, and cyclooctyl *t*-butyl ether account for only 89.4% of the *t*-butoxy radicals, the remainder being present in the higher molecular weight residue formed by initiation as in eq 3 with one or more additions before termination by hydrogen abstraction. Nevertheless, with all substrates, hydrogen abstraction is the predominant reaction pathway of the *t*-butoxy radical when sufficiently reactive allylic hydrogens are present.

Table III shows the yields of products from the thermal decomposition of TBPP in benzene solutions of various alkenes and related compounds. The major *t*-butoxy radical product was again *t*-butyl alcohol, which is formed along with small but significant amounts of acetone and di-*t*-butyl ether. Their sums quantitatively accounted for the *t*-butoxy radicals generated in all cases except cyclooctene (5.7% missing *t*-BuO·). Traces (<1%) of volatile *t*-butoxy radical addition products also were present. As expected, these products are formed in somewhat smaller amounts, since the perester only generates one oxy radical per mole and the same 6:1 molar ratio of substrate to radical source was used as in the DTBP reactions.

Considerable variation in the extent of *t*-butoxy radical addition to alkenes has been reported in the literature. Generally, addition to conjugated alkenes occurs readily.[6-8] In contrast, the addition of *t*-butoxy radicals to isolated double bonds occurs only to a minor extent in most cases. Walling and Thaler[8] observed 3–6% *t*-butoxy radical addition to a variety of butenes and methylbutenes. A notable fact of this work was the lack of high reactivity in terminal vinyl compounds (1-butene and *trans*-2-butene each gave *ca.* 3% adduct). Farmer and Moore[9] also noticed very little addition in studying the reactions of DTBP with cyclohexene and 1-heptene. Exceptions include intramolecular alkoxy radical addition in the photolysis of a steroidal nitrite[10] and the formation of 65% adduct when norbornene was allowed to react with *t*-butyl hypochlorite.[11]

The small amount of addition to most alkenes observed in our work (1–4%) closely parallels Walling and Thaler's data, even though their source of *t*-butoxy radicals was different (*t*-BuOCl). The *t*-butyl ethers obtained with 4-vinylcyclohexene and related systems

(6) M. S. Kharasch, F. S. Arimoto, and W. Nudenberg, *J. Org. Chem.*, **16**, 1556 (1951).
(7) J. K. Allen and R. G. Bevington, *Proc. Roy. Soc.*, **262**, 271 (1961).
(8) C. Walling and W. Thaler, *J. Amer. Chem. Soc.*, **83**, 3877 (1961).
(9) E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 131 (1951).
(10) A. L. Nussobaum, R. Wayne, E. Yuan, O. Z. Zarre, and E. P. Oliveto, *J. Amer. Chem. Soc.*, **87**, 2451 (1965).
(11) E. Tobler, D. E. Baltin, and D. F. Foster, *J. Org. Chem.*, **29**, 2834 (1964).

TABLE III
THERMAL DECOMPOSITION OF *t*-BUTYL PEROXYPIVALATE IN VARIOUS ALKENES AND RELATED COMPOUNDS

	Yield,[a] %										
Product	Benzene	Toluene	4-VCH[b]	VCHA[c]	4-ECH[d]	1-ECH[e]	Cyclopentene	Cycloheptene	Cyclooctene	1,5-COD[f]	Cyclohexane
t-Butyl alcohol	67	82	97	92	95	100	100	95	88	100	93
Acetone	30	16	1.4	3.5	1.8	0.8	1.3	1.7	2.7	1.3	7.3
Di-*t*-butyl ether	3.0	3.7	3.0	4.0	3.0	3.2	2.1	3.0	3.6	3.6	...[g]
Carbon dioxide	109	104	98	96	94	94	85	95	99	95	87
Isobutylene	18	7.0	19	11	13	10	13	9.7	11	9.0	11
Isobutane	14	10	11	3.6	15	15	15	8.3	6.0	14	8.8
Hexamethylethane	3.0	5.0	...	...	...	...	...	...	2.2	...	...
Dehydro dimer	2.0[h]	5.5	9	6.5[i]	19	19	14	14	12[i]	13	<1
t-Bu addition product	...[j]	...	21[k]	17	12[l]	...	9.6	3.9[l]	11	3.2	...[m]
t-Bu coupling product	...	11[n]	...	...		7.2	9.1		...	1.2	...
t-Butylated dimer	...	...	6.0	10	...	...	...	...	...	...	...

[a] From 0.06 mol of hydrocarbon and 0.01 mol of TBPP in 42 ml of benzene after 7 hr at 70°. [b] 4-Vinylcyclohexene. [c] Vinylcyclohexane. [d] 4-Ethylcyclohexene. [e] 1-Ethylcyclohexene. [f] 1,5-Cyclooctadiene. [g] Not determined. [h] Biphenyl. [i] Also includes addition dimer. [j] 12% toluene. [k] At terminal vinyl bond. [l] Inseparable by glpc. [m] 11% cyclohexylbenzene also formed. [n] Neopentylbenzene.

TABLE IV
CHARACTERIZATION OF DIMERIC PRODUCTS

	Bromine no.		Mol wt		Nmr paraffinic/olefinic proton ratio	
Dimer of	Obsd	Calcd[a]	Obsd	Calcd[b]	Obsd	Calcd[b]
4-Vinylcyclohexene	269	299	216	214	1.6	1.2
Vinylcyclohexane	99	145	227	218	11.0	3.7[c]
4-Ethylcyclohexene	139	145	220	218	6.6	5.5
1-Ethylcyclohexene	144	145	218	218	13.3	12.0
Cyclopentene	240	238	169	134	2.5	2.5
Cyclohexene	191	198	177	162	3.9	3.5
Cycloheptene	168	163	205	190	4.5	4.5
Cyclooctene	110	147	220	218	9.6	5.5
1,5-Cyclooctadiene	188	299	218	214	2.1	1.75

[a] Grams of bromine per 100 g of dehydro dimer structure. [b] For dehydro dimer structure. [c] If coupled through tertiary position, 12.0 if coupled through primary position.

indicate that the terminal vinyl bond is less susceptible to addition of *t*-butoxy radicals than *cis* internal unsaturation. Similar results were obtained for the addition of acetoxy to alkenes.[12]

Cyclooctene was the exception in that 14% addition occurred in the DTBP reaction compared with 82% hydrogen abstraction; yet even in this case abstraction was the predominant reaction. This is in contrast to the observation[5] that in autoxidation, cyclooctene reacted 70% by addition with only 30% abstraction by alkoxy radicals. Possibly the difference lies in the nature of the alkoxy radical, which in autoxidation is the 3-cyclooctenyloxy type.

Fate of the Substrate Radical.—Substrate radicals formed by hydrogen abstraction may either couple to form dehydro dimers, or add to a double bond to give a dimer radical which may propagate by addition to monomer, or terminate either by coupling or hydrogen abstraction. Equation 2 predicts that the ratio of alcohol formed to alkene consumed should be unity, but every addition of a radical to a double bond increases by one the number of alkene molecules consumed and reduces correspondingly the unsaturation of the total product. On the other hand, biallyls resulting from preferential coupling of radicals formed by abstraction of allylic hydrogen can compete effectively with the monomer as hydrogen donors in the later stages of the reaction and thus increase the formation of alcohol. Coupling of monomeric and dimeric radicals leads to the formation of dehydro trimers and tetramers which retain the unsaturation level characteristic of the monomer.

Data showing consumption of alkene relative to appearance of *t*-butyl alcohol in the DTBP reactions are included in Tables I and II. The cyclic alkenes (cyclopentene, cyclohexene, cycloheptene, and 1- and 4-ethylcyclohexene) most closely conform to eq 2 owing to the high reactivity of their allylic hydrogens toward *t*-butoxy radicals. The resulting radicals are resonance stabilized and relatively unreactive toward addition to a cyclic double bond. Opposing effects of small amounts of *t*-butoxy radical addition to the monomer and hydrogen abstraction from the dimer maintain the ratio of alcohol formed to alkene consumed near unity. Ratios greater than unity reported for cyclododecene and cyclohexane indicate that hydrogen is abstracted from species other than starting material. Since it is known[13] that secondary alkyl radicals of the cyclohexyl type add to aromatic solvents in preference to dimerization, it would be expected that the cyclohexadienyl radical intermediates formed in this process would act as hydrogen donors.

Distillation of the reaction mixtures at reduced pressure afforded a dimer fraction and a residue composed of trimer and higher molecular weight products. These were characterized as shown in Tables IV and V by infrared, nmr, and glpc analysis, and by determination

(12) J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Amer. Chem. Soc.*, **89**, 129 (1967).

(13) J. R. Shelton and C. W. Uzelmeier, *ibid.*, **88**, 5222 (1966).

TABLE V
CHARACTERIZATION OF DISTILLATION RESIDUES

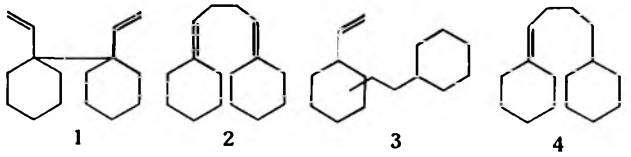
Residue from	Wt formed[a]	Mol wt[b]	Bromine no.[c]	Residual unsaturation,[d] %
Norbornene	56	437 (4.6)	27	16
Vinylcyclohexane	25	517 (4.7)	45	31
Cyclooctene	14	458 (4.2)	42	29
4-Vinylcyclohexene	12	529 (4.9)	146	50
1,5-Cyclooctadiene	8.8	407 (3.8)	144	45
Cycloheptene	8.8	314 (3.3)	146	89
1-Ethylcyclohexene	8.2	366 (3.3)	177	110
Cyclohexene	7.4	315 (3.8)	170	89
4-Ethylcyclohexene	6.8	382 (3.5)	122	82
Cyclopentene	6.7	235 (3.5)	189	80

[a] Grams of residue normalized to 100% DTBP decomposition (0.10 mol). [b] *Via* vapor pressure osmometry; average number of monomer units shown in parentheses. [c] Grams of bromine per 100 g of sample. [d] Calculated from the observed bromine number of the residue and the theoretical value of the dehydro dimer.

of yields, molecular weight, and residual unsaturation. True dehydro dimers of the cyclic alkenes are formed in relatively high yield. Small amounts of residue are also formed, which are characterized by 80% retention of unsaturation and appear to be mixtures of dehydro trimers and tetramers. Toluene reacts similarly with *t*-butoxy radicals to give *t*-butyl alcohol and bibenzyl, although more β scission (eq 1) occurs in this case.

Cyclooctene and the alkenes containing terminal vinyl unsaturation showed greater tendencies to add carbon radicals. Olefin consumption was somewhat greater than alcohol production for 4-vinylcyclohexene, and was considerably greater for cyclooctene and vinylcyclohexane. Dimers possessed less unsaturation, and consisted of mixtures of addition and dehydro dimers. Moreover, larger amounts of residue were obtained (especially with vinylcyclohexane and cyclooctene), which were typified by very low unsaturation and higher molecular weight. This is consistent with the previously demonstrated reactivity of alkyl radicals toward addition to the terminal vinyl bond.[14-17]

Consideration of the vinylcyclohexane dimer fraction is helpful in understanding both the addition and coupling reactions. Analysis by glpc, ir, and nmr is consistent with a mixture of 0% **1**, 33% **2**, 60% **3**, and 7% **4**.



Abstraction of the tertiary allylic hydrogen produces a radical which adds in part to produce **4**, but which mainly couples through the primary allylic position to give **2** (rather than the more highly hindered dehydro dimer **1**). The essential feature of the vinylcyclohexane (and cyclooctene) system is the ability of *t*-butoxy radicals to abstract nonallylic hydrogens, thereby generating a higher energy radical which preferentially adds to olefinic unsaturation to give **3**. Cadogan and co-workers[18] similarly generated cyclohexyl radicals from the reaction of benzoyl peroxide with a large excess of cyclohexane in the presence of 1-octene and obtained 1-cyclohexyloctane in 42% yield.

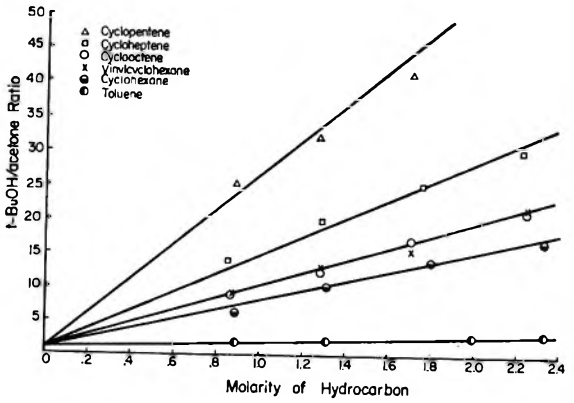


Figure 1.—Plot of *t*-BuOH to acetone ratios *vs.* [RH] in benzene (from DTBP photolysis).

Relative Reactivities of Alkenes toward the *t*-Butoxy Radical.—Relative reactivities of the cyclic alkenes, vinylcyclohexane, cyclohexane, and toluene toward *t*-butoxy radicals were measured by two methods. The first involved measurement of *t*-butyl alcohol to acetone ratios at varying hydrocarbon concentrations using DTBP and TBPP as radical sources.[8] The relative magnitudes of slopes obtained from graphical treatment of the data (Figure 1) were a measure of the relative rates of hydrogen abstraction. The second method utilized competition between two substrates in reaction with *t*-butyl hypochlorite.[19] The results of these experiments are shown in Table VI and compared with existing literature data.

TABLE VI
RELATIVE REACTIVITIES (k) OF HYDROCARBONS TOWARD THE *t*-BUTOXY RADICAL

Hydrocarbon	k(*t*-BuOH/acetone) DTBP (84 ± 4°)	TBPP (70°)	k(*t*-BuOCl) 65–70°	40° (lit. values)[a]
Toluene	1.0	1.0	1.0	1.0
Cyclohexane	8.2	2.7	4.1	6.0
Cyclooctene	11	7.5	6.2	...
Vinylcyclohexane	11	5.6	7.4[b]	11 (calcd)
Cycloheptene	14	13	16	...
Cyclohexene	...	...	27	51
Cyclopentene	27[c]	21	34	53

[a] Data of Walling and Thaler (see ref 8). [b] Chloride products: 55% β-chloroethylidenecyclohexane, 45% nonallylic vinylcyclohexyl chlorides. [c] 70–75°.

The relative reactivities of the cycloolefins in Table VI decrease as ring size increases from five to eight carbons, as also observed by Van Sickle, Mayo, and Arluck[5] in autoxidation. They pointed out that cyclopentene, being the most nearly planar of the ring systems, has a lower activation energy for abstraction because the developing allkyl radical is best able to achieve maximum overlap, while cyclooctene suffers from steric repulsions and two of the four allylic hydrogens are severely hindered from attack. As a result, attack at

(14) J. R. Shelton and H. G. Gilde, *J. Org. Chem.*, **29**, 482 (1964).
(15) J. R. Shelton and A. E. Champ, *ibid.*, **30**, 4183 (1965).
(16) J. R. Shelton and E. E. Borchert, *Can. J. Chem.*, **46**, 3833 (1968).
(17) M. S. Karasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).
(18) J. I. G. Cadogan, D. H. Hey, and S. H. Ong, *J. Chem. Soc.*, 1939 (1965).
(19) C. Walling and B. B. Jacknow, *J. Amer. Chem. Soc.*, **82**, 6108 (1960).

nonallylic positions becomes important, manifesting itself in the observed cyclooctene addition dimer.

Walling and Thaler's values[8] for the relative reactivities of various C–H bonds predict a reactivity for vinylcyclohexane of 1.8 relative to cyclohexane at 40° and 54% attack at the tertiary allylic hydrogen. Our results thus indicate that the tertiary allylic hydrogen of vinylcyclohexane is comparable in reactivity with an acyclic hydrogen of the same type.

Fate of the *t*-Butyl Radical from TBPP.—Various products were observed which reflected the alternatives open to the *t*-butyl radical—addition, gain or loss of hydrogen, dimerization, and mixed coupling.

In the presence of terminal vinyl unsaturation, preferential addition of *t*-butyl radicals occurred. When reactive allylic hydrogens were also present, as in 4-vinylcyclohexene, the adduct radical terminated by hydrogen abstraction or coupling with other allylic radicals. On the other hand, the *t*-butyl radical adduct of vinylcyclohexane tended to undergo further propagation.

The *t*-butyl radical showed a much lower inclination for addition when confronted with only *cis* internal unsaturation, as in the cycloalkenes, which gave a combination of addition and allylic coupling products. The more highly hindered trisubstituted double bond of 1-ethylcyclohexene did not add *t*-butyl radicals.

A bicyclo[3.3.0]octane derivative was formed in low yield by addition of *t*-butyl radicals to 1,5-cyclooctadiene. A similar *t*-butoxy radical addition product was observed in the reaction with DTBP. Other transannular radical additions to this diene have been observed.[20,21]

The relative amounts of isobutylene and isobutane varied with the substrate. In those cases where *t*-butyl radical addition predominated, the amount of isobutane formed was diminished. In contrast, those alkenes containing accessible allylic hydrogens but no terminal vinyl unsaturation gave more isobutane than isobutylene, indicative of allylic hydrogen abstraction by *t*-butyl radicals.

Small amounts of hexamethylethane (2–5%) produced by coupling of *t*-butyl radicals were observed in a few systems containing hydrogens of low reactivity. Disproportionation must have also occurred in these cases, but much of the isobutane and isobutylene formed in the more reactive systems must result from other hydrogen-transfer reactions.[16]

In no instance did the total of observed products account for all of the *t*-butyl radicals produced. This is in contrast to the quantitative recovery of carbon dioxide and *t*-butoxy radical products. Alkyl radical addition processes and polymerization reactions involving isobutylene evidently divert *t*-butyl reaction products to the residue.[22]

Cage Reactions with TBPP.—The constancy in yield of di-*t*-butyl ether (3–4%) over a wide range of substrates and reactant concentrations is suggestive of a cage combination of *t*-butyl and *t*-butoxy radicals following loss of carbon dioxide by the perester. Since yields of products of cage combinations depend on solvent viscosity,[23,24] TBPP was decomposed in mineral oil at 70° for 24 hr. An 8.4% yield of di-*t*-butyl ether was observed, which represented approximately a 2.5-fold increase consistent with a cage effect. The higher ratio of isobutylene (13%) to isobutane (2.7%) formed in the more viscous solvent indicates that hydrogen transfer between *t*-butyl and *t*-butoxy radicals also occurs.

$$(CH_3)_3CO\cdot + (CH_3)_3C\cdot \longrightarrow (CH_3)_3COH + (CH_3)_2C{=}CH_2 \quad (4)$$

When 0.01 mol of TBPP was heated for 7 hr in benzene solution at 70° with 0.06 mol of 2-methyl-2-propanethiol, no di-*t*-butyl ether was obtained. However, this result cannot be attributed to scavenging of free radicals, since an induced decomposition of the peroxide through prior association with thiol could account for this observation. An 82% yield of di-*t*-butyl disulfide and 17% of *t*-butyl isobutyl sulfide (based on perester) was obtained. If the sulfide is formed by eq 5 and 6, 17% isobutylene must have been consumed. Formation of this much product resulting from loss of hydrogen by *t*-butyl radical in a system primed for proton donation by the thiol would have been unusual were it not for the occurrence of the reaction of eq 4 near or within the solvent cage.

$$(CH_3)_3CS\cdot + (CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2SC(CH_3)_3 \quad (5)$$

$$(CH_3)_2\dot{C}CH_2SC(CH_3)_3 + (CH_3)_3CSH \longrightarrow (CH_3)_2CHCH_2SC(CH_3)_3 + (CH_3)_3CS\cdot \quad (6)$$

Experimental Section

Reagents.—4-Vinylcyclohexene, cyclooctene, and 1,5-cyclooctadiene were obtained from the Columbian Carbon Division of Cities Service Co. Cyclohexane and cyclohexene were products of Matheson Coleman and Bell. 3,3-Dimethyl-1-butene was obtained from Sinclair Petrochemicals. All hydrocarbons were distilled prior to use.

DTBP and TBPP (Lupersol 11) were obtained from the Lucidol Division, Wallace and Tiernan Inc. *t*-Butyl hypochlorite was prepared by the procedure of Gilliom and Ward.[25]

4-Ethylcyclohexene.—4-Vinylcyclohexene was allowed to react with 1 mol of hydrogen over Raney nickel in a Parr hydrogenator.[26] The crude product was brominated in CCl_4, and 4-ethylcyclohexene dibromide as removed by distillation, bp 140° (30 mm). Subsequent debromination with zinc–ethanol afforded 4-ethylcyclohexene, bp 130–131°, in 60% overall yield.

1-Ethylcyclohexene.—Reaction of ethereal ethylmagnesium bromide with cyclohexanone and dehydration of the resulting 1-ethylcyclohexanol with boiling 15% aqueous oxalic acid gave a 50% yield of 1-ethylcyclohexene, bp 133–134°.

Cyclopentene.—Dehydration of cyclopentanol with concentrated H_2SO_4 gave a 64% yield of cyclopentene, bp 44°.

Photolysis of DTBP.—The photolysis apparatus consisted of a Pyrex reaction vessel equipped with thermometer, condenser, nitrogen inlet, and Pyrex insert containing a GE H100-A4/T mercury lamp. The outer glass jacket of the lamp was removed to allow its insertion into the apparatus. Since DTBP shows a broad, regularly increasing absorption from 2200 to 3400 Å,[27] the wavelengths emitted by the lamp which were effective for DTBP decomposition were 3022, 3131, and 3341 Å.

The photolysis apparatus was charged with 0.60 mol of alkene, 0.10 mol of DTBP, and 190 ml of benzene, and flushed with nitrogen for 1 hr. The contents were then photolyzed for 24 hr at the reflux temperature, utilizing heat from the lamp regulated by a cooling stream of air. Under these conditions, 70–80% of the peroxide decomposed in most cases.

(20) R. Dowbenko, *Tetrahedron*, **20**, 1843 (1964).
(21) L. Friedman, *J. Amer. Chem. Soc.*, **86**, 1885 (1964).
(22) P. D. Bartlett and D. M. Simons, *ibid.*, **82**, 1753 (1960).
(23) R. Hiatt and T. G. Traylor, *ibid.*, **87**, 3766 (1965).
(24) T. Koenig and M. Deinzer, *ibid.*, **88**, 4518 (1966).
(25) R. Gilliom and B. Ward, *ibid.*, **87**, 3944 (1965).
(26) O. C. W. Allenby, U. S. Patent 2,576,743 (1951).
(27) D. Volman and W. Graven, *J. Amer. Chem. Soc.*, **75**, 3111 (1953).

TABLE VII
QUANTITATIVE GLPC ANALYSIS OF REACTION MIXTURES

Column[a]	Temp, °C	Internal standard	Reactants and products separated
A	100	2-Butanone	Acetone, *t*-butyl alcohol, cyclohexene, cyclooctene, 1,5-COD, cyclopentene, di-*t*-butyl ether, DTBP, 4-ethylcyclohexene, hexamethylethane, toluene, 4-vinylcyclohexene
B	110	Ethylbenzene	Cycloheptene, vinylcyclohexane,
	180	Bicyclohexyl Cyclohexylbenzene	*t*-butyl ethers of 4-vinylcyclohexene, *t*-butyl radical addition products
C	125	Bicyclohexyl	*t*-Butyl radical coupling products,
	130	*o*-Dichlorobenzene (ODCB)	*t*-butyl ethers of 1,5-COD, cycloheptene, cyclooctene, 1-ethylcyclohexene, 4-ethylcyclohexene, vinylcyclohexane
	180	ODCB or bicyclohexyl	Dimers
D	25	Isopentane	Isobutane, isobutylene

[a] Column A: 12 ft × 0.25 in. 20% Carbowax 6000 on 60/80 mesh Chromosorb W. Column B: 12 ft × 0.25 20% Hi-vac silicone grease on 40/60 mesh Chromosorb P. Column C: 6 ft × 0.25 30% Carbowax 6000 on 60/80 mesh Chromosorb W. Column D: 16 ft × 0.25 in. 30% Dowtherm A on 60/80 mesh Chromosorb W.

Thermal Decomposition of TBPP.—A 100-ml, two-necked flask was equipped with a condenser and rubber septum for admitting nitrogen. The top of the condenser was connected in series with two Miller absorption tubes containing drying agent and ascarite, respectively, and also with a trap kept at Dry Ice temperature. The stirred reaction mixture of 0.06 mol of alkene, 0.01 mol of TBPP, and 42 ml of benzene was flushed with nitrogen for 15 min, then allowed to react at 70° for 7 hr, after which nitrogen was again bubbled through the solution to remove dissolved volatile products to the absorption tubes and Dry Ice trap.

Characterization of Products.—*t*-Butyl alcohol and acetone were identified by their retention times on a 12 ft × 0.25 in. 20% Carbowax 6000 glpc column at 100°. Di-*t*-butyl ether was identified by comparison of glpc retention time and ir spectrum with those of an authentic sample.[23]

Carbon dioxide, isobutylene, and isobutane were identified by comparison of their retention times with those of authentic samples on both a 30 ft × 0.25 in. benzyl cyanide–$AgNO_3$ column and a 16 ft × 0.25 in. Dowtherm A column at room temperature.

Following their distillation from the reaction mixture, the dimers were characterized by their ir and nmr spectra, molecular weight, bromine number,[29] and where possible, by comparison with authentic material. Individual components of the dimers were collected upon emergence from the gas chromatograph and identified by ir and nmr spectra. The nonvolatile residues were characterized according to molecular weight and residual unsaturation.

Coupling products of alkenes were independently synthesized by allylic bromination with N-bromosuccinimide, followed by either self-coupling with magnesium to give dehydro dimers or cross-coupling with *t*-butyl Grignard reagent to give *t*-butyl-substituted alkenes.

t-Butyl radical addition products were identified by their ir spectra. Except for the addition product of 4-vinylcyclohexene, where bands owing to *cis* internal unsaturation were present (3030 and 660 cm^{-1}), the addition products of vinylcyclohexane, the cycloolefins, and 1,5-cyclooctadiene had no absorptions owing to residual unsaturation but did show the characteristic absorption of the *t*-butyl group (2960, 1390, and 1360 cm^{-1}).[30]

t-Butoxy radical addition products were readily identified by strong ir absorptions owing to the *t*-butyl group, the ether linkage, and any residual unsaturation. In the cyclohexene reaction, cyclohexyl *t*-butyl ether was independently synthesized by the method of Lawesson and Yang.[31] Elemental analyses were obtained for the *t*-butyl ethers of 4-vinylcyclohexene and 4-ethylcyclohexene.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.12; H, 12.09; O, 8.79. Found: C, 79.21; H, 11.94; O, 8.85 (by difference). Calcd for $C_{12}H_{24}O$: C, 79.26; H, 13.04; O, 8.70. Found: C, 78.86; H, 13.12; O, 8.02 (by difference).

Photochemical Decompositions of *t*-Butyl Hypochlorite.—For competitive studies, 0.05 mol of each hydrocarbon, 0.01 mol of *t*-butyl hypochlorite, and 0.05 mol of chlorobenzene (added as an internal standard) were dissolved in 20 ml of benzene in a 50-ml, three-necked flask equipped with a thermometer, a rubber septum for admitting nitrogen, and a condenser connected to a bubbler. The system was flushed with nitrogen for 30 min and then irradiated with a 275-W Kenmore sun lamp situated to provide a reaction temperature of 65–70°. It was usually necessary to pass the alkenes through an alumina column immediately before use to remove hydroperoxides, which inhibited the chain chlorination. Under these conditions the yellow color of the hypochlorite was completely discharged in 30–60 min.

Quantitative Analysis of Volatile Products.—Carbon dioxide from the TBPP reactions was determined gravimetrically in a Miller absorption tube filled with ascarite and anhydrous $CaSO_4$.

The volatile products were analyzed quantitatively by glpc. An internal standard, which had previously been calibrated with the products for detector response, was added to the reaction mixture at its completion. Table VII lists the type of column, its temperature, and the internal standard used for separation and determination of reactants and products.

Registry No.—DTBP, 110-05-4; TBPP, 927-07-1; 4-ethylcyclohexene, 3742-42-5; 1-ethylcyclohexene, 1453-24-3; cyclopentene, 142-29-0.

Acknowledgment.—This work is part of a continuing study of free-radical reactions supported by the Goodyear Tire and Rubber Co., Akron, Ohio.

(28) J. L. Erickson and W. H. Aston, *J. Amer. Chem. Soc.*, **63**, 1769 (1941).
(29) H. L. Johnson and R. A. Clark, *Ind. Eng. Chem., Anal. Sect.*, **19**, 869 (1947).
(30) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons Inc., New York, N. Y., 1962.
(31) S. O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, **81**, 4230 (1959).

Photochemistry of Benzo[b]thiophenes

DOUGLAS C. NECKERS[1]

Department of Chemistry, Hope College, Holland, Michigan 49423

J. H. DOPPER AND HANS WYNBERG

Department of Organic Chemistry, The University, Groningen, The Netherlands

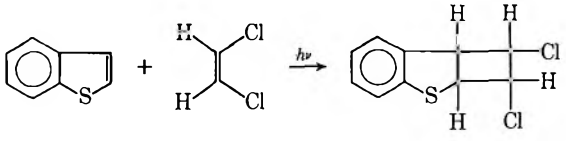
Received May 14, 1969

Addition reactions of haloolefins to benzo[b]thiophene and several of its alkylated derivatives are reported.

The naphthalene-related coal tar derivative, benzo[b]thiophene, has received little attention from photochemists.[2] Interest in the preparation of unusual fused benzo[b]thiophenes led us to examine sensitized photoaddition reactions to this and related fused heteroaromatic systems. Our results indicate that photoadditions to benzo[b]thiophene and its derivatives provide high yields of cyclobutane adducts.

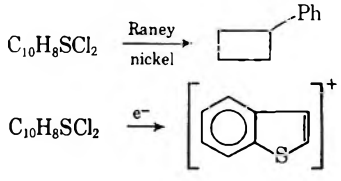
Results

Photosensitized addition reactions of haloolefins to linear and cyclic dienes,[3,4] as well as olefins[5,6] produce high yields of 1:1 adducts. Among the major products in these reactions are the cyclobutanes.[7] Using these methods as models, we have found that 1:1 adducts form from the photosensitized addition of *cis*- or *trans*-1,2-dichloroethylene to benzo[b]thiophene. Two major products are separable by vpc (eq 1) and can be isolated in yields as high as 90%.



(1)

That the adducts are fused benzo[b]thiophenocyclobutanes is proven by the fact that each is desulfurized and dehalogenated to phenylcyclobutane. Further, the mass spectrum of the adducts includes a parent peak at the *m/e* of the original benzo[b]thiophene (eq 2 and 3),



(2)

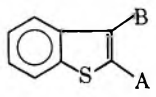
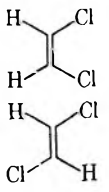
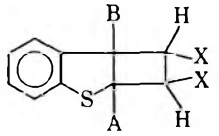
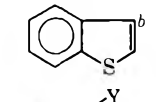
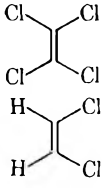
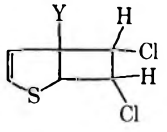
(3)

proving that the benzo[b]thiophene nucleus is undisturbed in the adducts. (The intensity of the benzo[b]thiophene peak in the mass spectrum of the adducts is at least five times larger than the next largest peak.)

We conclude that the products are stereoisomers of 1,2-dichloro-3,4-(2,3-benzo[b]thiopheno)cyclobutane.

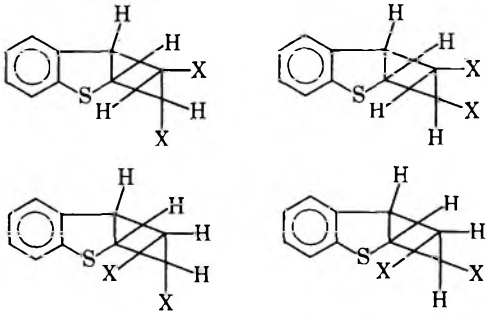
Additions of haloolefins to benzo[b]thiophenes appear general. High-yield reactions also occur when alkylated benzo[b]thiophenes are used in place of the unsubstituted derivative. Some examples of additional reactions of haloolefins and heteroaromatic compounds are reported in Table I.

TABLE I

Aromatic compound[a]	Olefin	Products
 A = H; B = H A = D; B = H A = Me; B = H A = Me; B = Me A = H; B = Me A = Cl; B = Cl		
 Y = H, Ph[c]		

[a] The sensitizer in all cases was benzophenone or acetophenone. [b] Three 1:1 adducts formed. Because the products were not stable, the reaction was stopped after 1% conversion. [c] In the addition of *cis*-dichloroethylene to 3-phenylthiophene, the major products were a mixture of *m*- and *p*-chlorobiphenyl. These products arise through an apparent 1,4 addition to the phenylthiophene nucleus. More will be reported about this reaction later.

Ruling out the existence of *trans* ring-fused products,[8] four stereoisomers can be formed from the addition of symmetrical olefins to benzo[b]thiophene and its derivatives.



(1) To whom inquiries should be addressed.

(2) For earlier studies on the photochemistry of benzo[b]thiophene, see W. E. Haines, R. V. Helm, G. L. Cook, and J. S. Ball, *J. Phys. Chem.*, **60**, 549 (1956); W. E. Haines, G. L. Cook, and J. S. Ball, *J. Amer. Chem. Soc.*, **78**, 5213 (1956).

(3) N. J. Turro and P. D. Bartlett, *J. Org. Chem.*, **30**, 1849 (1965).

(4) P. D. Bartlett, R. Helgeson, and O. A. Wersel, *Rev. Pure Appl. Chem.*, **16**, 187 (1968).

(5) W. Metzner and W. Hartmann, *Chem. Ber.*, **101**, 4099 (1968).

(6) D. Wendisch and W. Metzner, *ibid.*, **101**, 4106 (1968).

(7) For recent reviews see (a) R. Steinmetz, *Fortschr. Chem. Forsch.*, **7**, 445 (1967); (b) D. R. Arnold in "Advances in Photochemistry," Vol. 6, John Wiley & Sons, Inc., New York, N. Y., 1968, p 301; (c) D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corp., New York, N. Y., 1967.

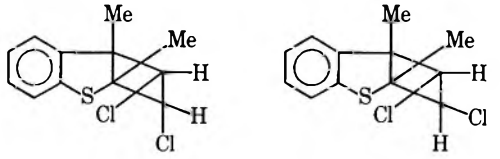
(8) H. Weitkamp and F. Korte, *Chem. Ber., Suppl.*, **7**, 75 (1966).

Since the addition products from 2,3-dimethylbenzo[b]thiophene and dichloroethylenes gave the simplest nmr spectra, we chose to investigate this system in detail. All four stereoisomers are observed in the additions of dichloroethylene to 2,3-dimethylbenzo[b]thiophene. Three of the products can be separated in pure form, while the fourth product constitutes less than 2% of the total adduct yield. We obtained the distribution of products from the addition of *cis*- or *trans*-1,2-dichloroethylene to 2,3-dimethylbenzo[b]thiophene shown in Table II.

TABLE II

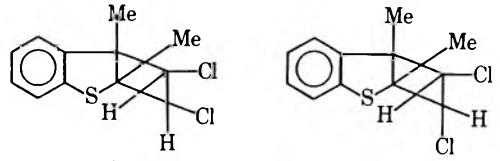
ADDITION OF DICHLOROOLEFINS TO 2,3-DIMETHYLBENZO[b]THIOPHENE

Isomer	*cis*, %	*trans*, %
1	1	1
2	40	60
3	47	27
4	11	12



1 *cis,endo*

2 *trans*



3 *cis,exo*

4 *trans*

Structures are assigned on the basis of the following evidence. (A) Sensitized additions of *cis*- and *trans*-dichloroethylenes to indene take place with *cis* products being predominant in the case of the *cis*-dichloroethylene addition and *trans* product being predominant in *trans*-dichloroethylene addition.[4] Therefore, compound **3** is probably an adduct with the two chlorines *cis*, compound **2** an adduct with two chlorines *trans*. Minor product **4** cannot be assigned on this basis. (B) The coupling constants of cyclobutane hydrogens have been shown generally to be larger for compounds where the hydrogens are *cis* to one another than where the hydrogens are *trans*; *i.e.*, $J_{cis}/J_{trans} > 1.0$. Thus the AB coupling constant for compound **3** should be larger than for compound **2**, as is observed (Table III).

The complete structures **2** and **3** are proposed. Further evidence that these structures are correctly assigned derives from the observation that the chemical shifts of the methyl groups differ the most in **2**. The *cis* chlorine–methyl relationship of the methyl attached to the thioether carbon results in a maximum downfield shift of the methyl hydrogens. The minimum effect should result from the relationship of the other chlorine and methyl.

When the relationship of the 3-methyl group to chlorine is made *cis* (**3**), this chemical-shift difference decreases. Compound **4** is the other *trans* isomer, and compound **1** the other *cis,endo* isomer based on arguments like those above.

TABLE III

NMR SPECTRA OF ADDUCTS FROM *cis*-1,2-DICHLOROETHYLENE AND 2,3-DIMETHYLBENZO[b]THIOPHENE

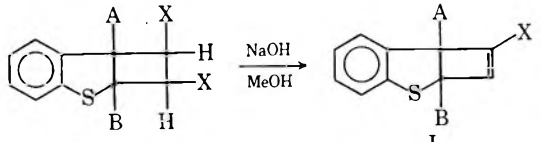
Compd	System	Nmr data[a]		
2	AB	J_{AB} = 7.0 cps		Me-2 1.64
		H_A 4.70		Me-3 1.43
		H_B 4.90		Aryl 7.13
3	AB	J_{AB} = 8.5 cps		Me-2 1.58
		H_A 4.25		Me-3 1.52
		H_B 4.38		Aryl 7.13
4	AB	J_{AB} = 9 cps		Me-2 1.56
		H_A 4.17		Me-3 1.38
		H_B 4.40		Aryl 7.16

[a] Chemical shifts given in parts per million.

The results of a comparison of the product distributions to the case of indene additions are given in Table IV.

Structure assignment in the additions of haloolefins to less highly substituted benzo[b]thiophenes are based on the nmr spectra reported in Table V as well as by dehydrohalogenation experiments. ABC systems are observed in all the stereoisomers separated from 2- and 3-methylbenzo[b]thiophene, while four-proton systems are observed with the addition products from benzo[b]thiophene itself. The distribution of products is reported in Table VI.[9]

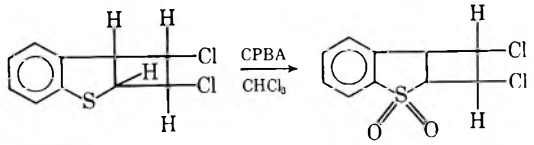
Chemical Reactions of the Addition Products—The adducts of *cis* and *trans* dihaloolefins and benzo[b]thiophenes easily lose 1 mol of HCl in refluxing methanolic NaOH. The products isolated (yields averaged *ca.* 60%) were the corresponding cyclobutenes. The nmr spectra of the isomeric mixtures confirmed that the elimination went in the direction shown in eq 4, and I was the major isomer in all cases examined. As might be expected, rapid dehydrohalogenation occurs for those isomers with *trans* HCl stereochemistry, while the *trans*-dihalocyclobutanes were recovered even after 24-hr reaction with methanolic NaOH. There was no tendency for any of the adducts to lose a second mole of HCl under the conditions of the experiment, and in all cases the products were thermally stable at 60°.[10]



(4)

A = Me; B = H
A = H; B = Me
A = H; B = D
A = H; B = H

m-Chloroperbenzoic acid smoothly oxidized the saturated adducts to the sulfone (eq 5).

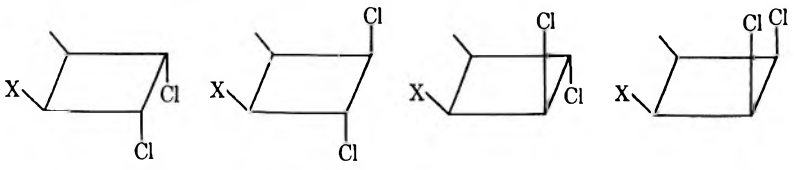


(5)

(9) For leading references concerning the nmr spectra of halogenated cyclobutanes, see ref 4 and (a) R. Steinmetz, W. Hartmann, and G. O. Schenk, *Chem. Ber.*, **98**, 3854 (1965); (b) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Amer. Chem. Soc.*, **84**, 2210 (1962); (c) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *ibid.*, **86**, 604 (1964).

(10) Thermal rearrangements of these molecules do occur at higher temperatures: J. H. Dopper and D. C. Neckers, *Tetrahedron Lett.*, 2913 (1969).

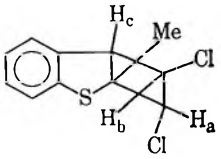
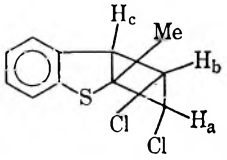
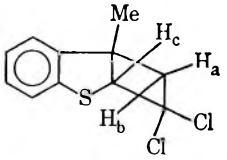
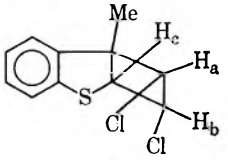
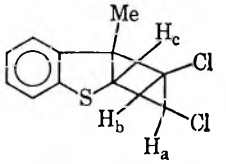
TABLE IV



	cis-Dichloroethylene			
Indene	53	13	30	4
2,3-Dimethylbenzo[*b*]thiophene	47	40	11	1
	trans-Dichloroethylene			
Indene	16	20	59	5
2,3-Dimethylbenzo[*b*]thiophene	27	60	12	1

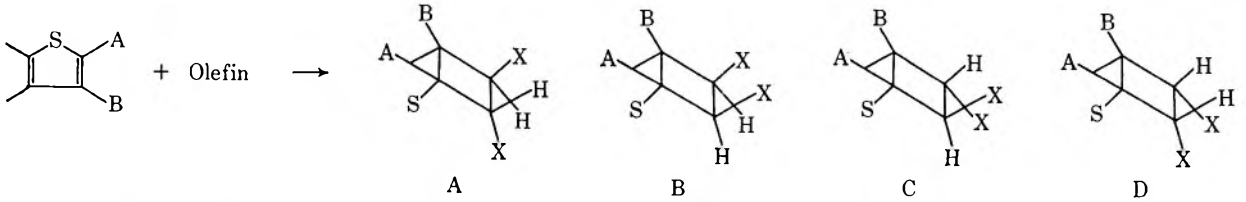
TABLE V

NMR SPECTRA OF HALOOLEFIN ADDUCTS TO BENZO[*b*]THIOPHENES

Compd	Registry no.	Nmr data[a]	
	23735-57-1	H_a, H_b, and H_c form a complex ABC pattern. H_a is a four-peak multiplet centered at 3.60 ppm. H_b and H_c fall together at 4.35 ppm.	Me 1.76 Aryl 7.13
	23735-58-2	H_a, H_b, and H_c form an ABC pattern at 4.20–4.60 ppm.	Me 1.74 Aryl 7.18
	23735-59-3	H_a, H_b, and H_c form a complex ABX system. H_c is a broad doublet centered at 3.60 ppm. H_a and H_b fall together as three doublets (AX and AB) at 4.00, 4.21, and 4.33 ppm, respectively.	Me 1.62 Aryl 7.11
	23735-60-6	H_a, H_b, and H_c form an ABX system. H_a 3.96 ppm H_c 4.40 ppm H_b multiplet at 4.60–4.80 ppm	Me 1.56 Aryl 7.11
	23735-61-7	ABC system, complex coupling 4.52–4.70 ppm	Me 1.67 Aryl 7.15 br

[a] See Table III, footnote *a*.

TABLE VI



	Olefin	A, %	B, %	C, %	D, %
A = Me, B = H	*cis*-1,2-Dichloroethylene	12	46	12	48
A = Me, B = H	*trans*-1,2-Dichloroethylene	54	21	54	23
A = H, B = Me	*cis*-1,2-Dichloroethylene	...	47	30	23
A = H, B = Me	*trans*-1,2-Dichloroethylene	...	16	41	42

Loss of molecular chlorine occurs with Zn and amyl alcohol (bp 130°). At lower temperatures (*e.g.*, MeOH or EtOH at reflux), loss of chlorine was exceedingly slow. One hydrocarbon product was isolated from the loss of molecular chlorine by the adducts benzo[*b*]thiophene, but it was not monomeric and appeared to be a combination of the adduct minus Cl_2. Experiments with more active dehalogenating agents designed for use at room temperature are currently in progress.

Discussion

Addition reactions of the type reported represent facile entries into substituted dihydrobenzo[*b*]thiophene systems.[11] Several observations bear on the mechanism of the reaction. First, although benzophenone (E_t = 69.2 kcal/mol) and acetophenone (E_t = 73.3 kcal/mol) sensitize the addition of *cis*- and *trans*-1,2-dichloroethylene to 2,3-dimethylbenzo[*b*]thiophene, anthraquinone (E_t = 62 kcal/mol) and 2-acetonaphthone (E_t = 58.9 kcal/mol) do not. Second, the uv spectrum of benzo[*b*]thiophene is essentially the same in *cis*-1,2-dichloroethylene, *trans*-1,2-dichloroethylene, and cyclohexane. Third, although the extent of *cis–trans* isomerization of the haloolefin is limited in all reactions (less than 10%), extensive dimerization of the halocarbon takes place in competition with the addition to the heteroaromatic compound.[12] Finally, the reactions are, at least in part, stereospecific.

As in similar systems[3,4] it appears that sensitized formation of the benzo[*b*]thiophene triplet state is the initial photochemical act involved in the addition. Acetophenone and benzophenone both have triplet energies which make transfer to benzo[*b*]thiophene (E_t = 68.9 kcal/mol)[13] allowed. Anthraquinone and phenanthrene, with triplet energies below 68.9 kcal/mol but above that of the haloolefins (62 kcal/mol), do not sensitize the reaction. The same can be said for 2-acetonaphthone (E_t = 58.9 kcal/mol), although the actual role of this molecule as a sensitizer is still not clear.

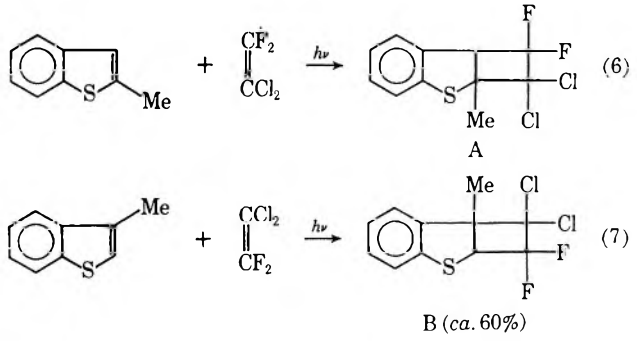
The reaction of benzo[*b*]thiophene and *cis*-dichloroethylene occurs also in the absence of sensitizer. Although this reaction is *ca.* 90% less efficient than the sensitized process, the adduct distribution is virtually identical with the benzophenone sensitized case.

Two facts remain to explain at this point. (A) Why are dimers of the haloolefins observed? (B) Why is the reaction stereoselective?

Dimers of the haloolefin probably derive from the transfer of energy to the haloolefin in competition with the other energy-transfer process, involving the heteroaromatic compound. Although we cannot preclude the photolytic dissociation of the cyclobutane products to an excited haloolefin, followed then by dimerization, this process is deemed unlikely in view of the high yields of adducts actually isolated.

Stereoselectivity in the addition reactions may result from the fact that the additions are conducted in two different solvents. On the other hand, it may be that the adducts, even though they "recognize" the fact that they come from different dihaloolefins, still form from rotationally equilibrated diradical intermediates.[14] The high reactivity of benzo[*b*]thiophene in electrophilic substitution reactions[15–17] suggests that the excited state might react with electropositive olefins rapidly also.

An interesting correlative observation concerning the mechanism of the sensitized cycloaddition reactions derives from the addition of 1,1-dichloro-2,2 difluoroethylene to benzo[*b*]thiophenes. These additions suggest that product control depends, at least in part, on the stability of the intermediate biradical. Thus 2-methylbenzo[*b*]thiophene gives adduct A exclusively (eq 6), while 3-methylbenzo[*b*]thiophene gives adduct B



in major proportions (eq 7). Thus, as in the case of additions of haloolefins to indene, the adducts formed recognize at least partially which haloolefins they come from. Yet additions of unsymmetrical olefins point to a stepwise addition process. Experiments designed to resolve the mechanistic aspects of the problem are currently in progress.

Dehydrohalogenation of the adducts leads to the 2 isomers predicted in every case. The structures of the stereoisomeric cyclobutenes follow from their nmr spectra. One may predict that the major isomer probably forms *via* the transition state shown below, because the abstracted hydrogen at position a is less hindered than its counterpart b next to sulfur. Presumably the olefin II would also be less hindered than

(11) Sensitized additions of maleic anhydride and its derivatives to thiophene were reported some years ago: G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963). Recently, R. M. Kellogg and H. Wynberg [*Tetrahedron Lett.*, 5895 (1968)] reported intercepting the excited singlet state of 2-phenylthiophene by its addition to piperylene. The dimerization of benzo[*b*]thiophene 1,1-dioxide also represents examples of the sort of reaction reported above in heteroaromatic sulfur systems.

(12) Two major dimers are isolated by vpc. These dimers both have the same molecular weight and analyze for $C_4H_4Cl_4$. Nevertheless, the nmr, infrared, and mass spectra of the molecules indicate that they are linear alkenes rather than cyclobutanes. More will be reported on this observation later.

(13) R. C. Heckman, *J. Mol. Spectrosc.*, **2**, 27 (1958).

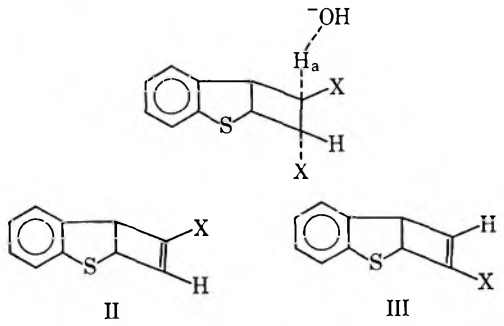
(14) W. L. Dilling, T. E. Tabor, and F. P. Boer, *J. Amer. Chem. Soc.*, **92**, 1399 (1970).

(15) See, *e.g.*, C. A. VanderWerf, "Acids, Bases and the Chemistry of the Covalent Bond," Reinhold Publishing Corp., New York, N. Y., 1963.

(16) That dicyanoethylene is sufficiently reactive to capture the excited singlet state of acetone, for example, was recently demonstrated: N. J. Turro, P. Wriede, J. C. Dalton, D. Arnold, and A. Glick, *J. Amer. Chem. Soc.*, **89**, 3950 (1967).

(17) (a) Significant in this regard is the observation that most olefins which add to photoexcited aromatics are electron poor at the olefinic carbon. Thus dicyanoethylene, maleic anhydride, malemide, etc., add most easily. See *e.g.*, E. Ciganek, *ibid.*, **89**, 1458 (1967); (b) E. A. Hill and J. D. Roberts, *ibid.*, **89**, 2047 (1967). (c) For systems related to those we report, see ref 4 and 5 and J. S. Swenton and A. J. Krubsack, *ibid.*, **91**, 786 (1969).

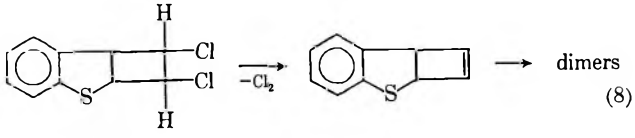
its counterpart III, because chlorine–sulfur interactions are minimized.



That dehydrohalogenation leads to the cyclobutenes shown rather than ring-opened or rearranged products derives from several observations.

First, the methyl-group absorbances in the nmr spectrum in all cases approximate those in the initially formed adducts, thus suggesting that they are attached to a nonolefinic carbon. Second, mass spectra of the adducts contain predominant peaks at the parent benzo[*b*]thiophene. Finally, cycloadducts formed from 2-deuteriobenzo[*b*]thiophene and *cis*-dichloroethylene gave the expected two singlets in the cyclobutene region (vinyl and allyl) of the nmr spectrum after treatment with methanolic sodium hydroxide (see Experimental Section).

Dehalogenation of the cyclic adducts is more difficult than the corresponding reactions in related systems. When two halogens finally are extricated from the molecule, the temperature of the reaction medium is too high for the olefin to survive and dimeric materials form, probably by ring-opening rearrangement and Diels–Alder coupling. Although a peak at *m/e* 128 was predominant in the mass spectrum, peaks above 160



(8)

were also present, thus indicating higher molecular weight materials (eq 8) which easily decompose to form naphthalene. Ring opening and dimerization of benzo[*b*]thiophene are indicated.

Experimental Section

All melting points are uncorrected. Infrared spectra were taken in carbon tetrachloride using a Perkin-Elmer Infracord 137, and nmr spectra were taken (10% in CCl_4) using a Varian A-60 spectrometer. Reference is to tetramethylsilane. Mass spectra were recorded on an A.E.I.-MS 9 equipped with an A-700 Model F & M vpc with thermal conductivity detectors. Analyses were performed by Mr. W. Hazenberg and his associates of one of these laboratories.

Starting Materials.—Benzo[*b*]thiophene, *cis*-dichloroethylene, *trans*-dichloroethylene, benzophenone, acetophenone, and 2-acetonaphthone were commercial materials purified when necessary by conventional methods. 2-Methylbenzo[*b*]thiophene, mp 48.5–51° (lit.[18] mp 51–52°), was prepared by the reaction of 2-benzo[*b*]thienyllithium with dimethyl sulfate. 3-Methylbenzo[*b*]thiophene was prepared by conventional methods[19] and was the gift of Mr. H. Luth.

Preparation of 2-Deuteriobenzo[*b*]thiophene.—2-Benzo[*b*]thienyllithium was prepared from 6.5 g (0.05 mol) of benzo[*b*]thiophene and 0.075 mol of *n*-butyllithium by adding the lithium reagent in ether to a solution of the benzo[*b*]thiophene in 50 ml of ether. After the color changed to orange-red (20 min), an excess of D_2O (15 ml) was carefully added. The ether layer was removed and the product was dried and distilled. The product was shown to be almost completely deuterated by nmr.

Preparation of 2,3-Dimethylbenzo[*b*]thiophene.—3-Methylbenzo[*b*]thiophene (6.5 g, 0.05 mol) was lithiated by the addition of 70 ml of an 0.8 *N* solution of *n*-butyllithium to a solution of the benzo[*b*]thiophene in 125 ml of anhydrous ether. After the color of the solution changed, 12.0 g (0.1 mol) of dimethyl sulfate was added carefully. The reaction mixture spurted vigorously during the addition and a white solid (Li_2SO_4) gradually formed.

After all the lithium adduct was discharged, 100 ml of ethanol and 0.2 g of sodium metal were added to the mixture. The solution was brought to reflux and the excess ether was removed. Then the mixture was refluxed for 40 min more and the solution was allowed to stand at room temperature overnight.

A 400-ml portion of warm water was subsequently added to dissolve the lithium salts and the mixture was extracted with ether. A 5.85-g sample of crude 2,3-dimethylbenzo[*b*]thiophene (purity >95%, yield 85%) was obtained after removal of the ether: nmr δ 2.18 (s, 3 H), 2.36 (s, 3 H), and 6.95–7.60 ppm (m, 4 H).

Anal. Calcd for $C_{10}H_{10}S$: C, 74.14; H, 6.22; S, 19.79; mol wt, 162. Found: C, 73.72; H, 6.22; S, 19.82; mol wt, 162 (mass spectrum).

General Irradiation Procedures.—Irradiations were carried out using a Hanau S-81 or a Hanovia 450-W medium-pressure mercury arc lamp and an immersion well. Yields were somewhat higher when a Pyrex immersion well was used, but use of a quartz well had little or no effect on product compositions. For synthetic purposes, most reactions were run on a 150-ml scale using the haloolefin as the solvent. A 3–4-g sample of the benzo[*b*]thiophene, 1.0 g of the sensitizer, and 100–150 g of the haloolefin were irradiated for periods ranging from 12 to 48 hr. Longer periods of irradiation did not improve the yields much because, by this time, the reaction mixtures were usually brown and contained several outstanding internal filters which prevented further reaction.

After irradiation, the solvent was removed on a rotary evaporator and the products were separated from the sensitizer and residual tars using thick layer chromatography. A 2-mm layer of silica gel (Merck PF 254) was prepared and activated at 110° for 1 hr. *Ca.* 1 g of the crude products was added to the plate (20 × 100 cm) and the elution was carried out using a 50:50 mixture of pentane–CH_2Cl_2. This procedure separated the sensitizer but did not separate the isomeric products from each other or from excess starting materials.

The products were removed from the silica gel by stirring for 2 hr with a large excess of methanol and then evaporating the methanol. Dissolved silica gel had to be removed by taking the oil up in methylene chloride or chloroform, drying over sodium or magnesium sulfate, filtering, and evaporating the solvent.

Separating of the isomeric products could be effected using gas chromatography. Generally better separation occurred using a Carbowax 20 M column, at temperatures of 150–200°. GE-SE30 columns were used for some preparative purposes.

Slightly higher yields of adducts could be obtained when the irradiations were carried out in benzene. In a typical experiment, 3.0 g of 2-methylbenzo[*b*]thiophene, 0.4 g of benzophenone, and 100 ml of 1,2-dichloroethylene in 250 ml of benzene gave >90% yield after purification by column chromatography on silica gel with CCl_4 as the eluting solvent.

Addition of Benzo[*b*]thiophene to *cis*-Dichloroethylene.—From 2.0 g of benzo[*b*]thiophene, 200 g of *cis*-dichloroethylene, and 500 mg of acetophenone was obtained 2.0 g (60%) of crude adduct.

Anal. Calcd for $C_{10}H_8Cl_2S$: C, 51.96; H, 3.49; Cl, 30.67; S, 13.88; mol wt, 230. Found: C, 52.06; H, 3.44; Cl, 30.82; S, 13.74; mol wt, 230 (mass spectrum).

Addition of 2-Methylbenzo[*b*]thiophene to *cis*-Dichloroethylene.—From 3.0 g of 2-methylbenzo[*b*]thiophene, 1.0 g of benzophenone, and 200 g of *cis*-dichloroethylene was obtained *ca.* 1.5 g (*ca.* 50%) of crude adducts.

Anal. Calcd for $C_{11}H_{10}Cl_2S$: C, 53.88; H, 4.11; Cl, 28.92; S, 13.08; mol wt, 244. Found: C, 53.84; H, 4.18; Cl, 28.36; S, 12.92; mol wt, 244 (mass spectrum).

Addition of 3-Methylbenzo[*b*]thiophene to *cis*-Dichloroethylene.—From 2.5 g of 3-methylbenzo[*b*]thiophene, 1.25 g of

(18) C. Hansch and W. A. Blondon, *J. Amer. Chem. Soc.*, **70**, 1561 (1948).
(19) E. G. G. Werner, *Rec. Trav. Chim. Pays-Bas*, **68**, 509 (1949).

benzophenone, and 200 g of *cis*-dichloroethylene was obtained *ca.* 1.5 g (50%) of crude adducts.

Anal. Calcd for $C_{11}H_{10}Cl_2S$: C, 53.88; H, 4.11; Cl, 28.92; S, 13.08; mol wt, 244. Found for isomer 1: C, 54.33; H, 4.18; S, 13.18; mol wt, 244 (mass spectrum). Found for isomer 2: C, 54.19; H, 4.19; Cl, 28.55; S, 13.29; mol wt, 244 (mass spectrum).

Addition of 2,3-Dimethylbenzo[b]thiophene to *cis*-Dichloroethylene.—A 5.0-g sample of 2,3-dimethylbenzo[b]thiophene, 2.0 g of benzophenone, and 150 g of *cis*-dichloroethylene gave *ca.* 3.0 g (50%) of crude product.

Anal. Calcd for $C_{12}H_{12}Cl_2S$: C, 55.61; H, 4.67; Cl, 27.36; S, 12.37; mol wt, 258. Found: C, 55.70; H, 4.56; Cl, 27.00; S, 12.44; mol wt, 258 (mass spectrum).

Addition of 1,1-Dichloro-2,2-difluoroethylene.—An 800-mg sample of the benzo[b]thiophene, 200 mg of acetophenone, and 5 g of 1,1,2,2-dichlorodifluoroethylene were sealed, under vacuum, in a Pyrex tube. After 16-hr irradiation, the tube was opened and the low-boiling materials were removed. The products were separated as before *via* thick layer chromatography and finally collected from a 5% Carbowax 20 M column thermostated at 150°.

The mass spectra of the adducts indicated them to be 1:1 addition products, and they were similar, in every respect, to those formed from benzo[b]thiophene and 1,2-dichloroethylene. The nmr spectra of the adducts, reported below, were used to assign structure.

Raney Nickel Desulfurization. Crude Adducts from Benzo[b]thiophene and *cis*-Dichloroethylene.—Raney nickel (10 g) was prepared in the usual fashion[20] and washed several times with water. When the pH became approximately neutral, the material was considered suitable for use and transferred to a 500-ml, round-bottom flask which was equipped with a stirrer, a condenser, and a dropping funnel. A 400-mg sample of the combined adducts in 200 ml of absolute ethanol was added and the mixture was refluxed for 12 hr. At the end of this period the Raney nickel was removed by filtration and the solvent was dried and evaporated.

The major component of the fraction remaining was a material with a cumene-like odor. Collection of this product from a GE-SE 30 column at 190° produced phenylcyclobutane: mass spectrum *m/e* (rel intensity) 132 (100), 116 (20), 115 (27), 105 (96), 104 (100), 103 (95), 91 (55), 78 (75), and 77 (60); nmr[21] δ 1.65–2.62 (m, 6 H), 3.15–3.70 (m, 1 H), and 7.12 ppm (s, 5 H); mol wt, 132 (mass spectrum).

Oxidation to the Sulfone. General Procedure.—A 2-g sample of the adduct from 2-methylbenzo[b]thiophene and 1,2-dichloroethylene and 3.5 g of *m*-chloroperbenzoic acid were dissolved in 60 ml of $CHCl_3$. An instant warming of the solution took place, after which the mixture was refluxed for 12 hr.

After reaction, the chloroform solution was extracted three times with 50 ml of 1 *N* sodium hydroxide, washed twice with 100 ml of water, and dried over sodium sulfate.

After the chloroform had been removed, the crude sulfone was recrystallized from cyclohexane, and carbon tetrachloride yielded 48% of the isomeric sulfones, mp 125–128°, 132–136°.

Base-Catalyzed Elimination Reactions. General Procedure.—A 1.00-g sample of the mixture of adducts from benzo[b]thiophene and *cis*-dichloroethylene was treated with 1.0 g of NaOH in 4.0 g of MeOH. The material was stirred at reflux for 30 min and then 5 ml of excess methanol was added and the material was refluxed for an additional 12 hr. An extensive precipitate (sodium chloride) formed on the bottom of the flask. The product, a sweet-smelling, slightly yellow liquid, was separated by evaporating all the excess methanol. The crude product was dissolved in chloroform and filtered to remove the excess sodium chloride. The dehydrohalogenated isomer was separated from residual starting material by preparative vpc on a 5% 4-ft Carbowax 20 M column thermostated at 180°.

The nmr spectrum of the major isolated adduct (>90%) showed a vinyl singlet, as well as a pair of doublets (AB), and was consistent with the assigned structure: δ 7.04 (s, 4 H, aryl), 4.81 and 4.59 (two d, 2 H, AB), and 6.00 ppm (s, 1 H, cyclobutene); mass spectrum ratio 3.2:1 [M/(M + 2)].

Anal. Calcd for $C_{10}H_7ClS$: mol wt, 194. Found: mol wt, 194 (mass spectrum).

Deuteration of the benzo[b]thiophene at the 2 position produced adducts which, following base-catalyzed elimination as above, had a change in the nmr spectrum:[8,22,23] the AB doublet collapsed to a singlet at 5.58 ppm. Thus the lower field portion of the AB doublet comes from the proton at the 3 position in the original benzo[b]thiophene, as would be expected from electronegativity arguments.

Dehydrohalogenation of the 2-Methylbenzo[b]thiophene Adducts.—A procedure similar to that outlined above was employed. After preparative vpc two isomers (85:15) were separated as a mixture and the nmr spectra of the materials were obtained: major isomer δ 7.07 (s, 4 H), 5.89 (s, 1 H), 4.09 (s, 1 H), and 1.78 ppm (s, 3 H); minor isomer δ 7.06 (s), 6.01 (d), 4.22 (d, J = 1.5 cps), and 1.78 ppm (s). The singlets for the major isomer were really a very weakly coupled doublet (J < 1 cps).

Anal. Calcd for $C_{11}H_9ClS$: mol wt, 208. Found: mol wt, 208 (mass spectrum).

3-Methylbenzo[b]thiophene Adducts.—A procedure similar to that described above was used. Two adducts were separated as a mixture by preparative vpc and their nmr spectra follow: major isomer δ 7.03 (s, 4 H), 6.00 (s, 1 H), 4.36 (s, 1 H), and 1.68 ppm (s, 3 H); minor isomer δ 7.02, 5.76, 4.12, and 1.67 ppm.

Dehalogenation of the Adducts from Benzo[b]thiophene and *cis*-Dichloroethylene.—A 160-mg sample (0.7 mmol) of the combined adducts from benzo[b]thiophene and *cis*-dichloroethylene was refluxed over 2.0 g of zinc powder which had been washed three times with a 5% ammonium chloride solution and three times with water in *n*-amyl alcohol (bp 137°) to which a crystal of anhydrous zinc chloride had been added. After 24 hr, the zinc products were filtered and the solvent was partially removed by distillation at reduced pressure.

Direct injection from the vpc (GE SE-30, 10% 150°) into the mass spectrometer revealed a single component of molecular weight 220 which showed no molecular ion but whose most intense peak was *m/e* 128 (naphthalene).

Acknowledgments.—One of the authors (D. C. N.) acknowledges the graciousness of the personnel at the University of Groningen during his stay there. He also thanks the administration of Hope College and the University of Groningen for making his year as a Netherlands exchange professor possible. The mass spectra reported were obtained with the assistance of Dr. W. D. Weringa. Finally, D. C. N. thanks Dr. Wolfgang Metzner for helpful discussions and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(20) See, *e.g.*, A. I. Vogel, "Practical Organic Chemistry" Longmans Green, and Co., Ltd., London, 1962, p 821.

(21) J. W. Wilt, L. L. Mavavetz, and J. F. Zawadyki, *J. Org. Chem.*, **31**, 3018 (1966).

(22) It is significant that another isomer appeared when this dehydrohalogenated product was injected into the mass spectrometer using vpc injection techniques. This isomer, although very minor, had the same molecular weight as the dehydrohalogenation product but a much greater peak at M − 32. We attribute this peak to the corresponding naphthalene.

(23) During the elimination reaction, *ca.* 35% exchange of H for D occurred at the 2 position of the dehydrohalogenated product. This suggests that even in the bridgehead system shown, some significant basicity of the position α to the sulfur atom exists.

The Reaction of Thiophthalic Anhydride with Trivalent Phosphorus

J. HODGE MARKGRAF, CHARLES I. HELLER,[1] AND NOYES L. AVERY, III[1]

Department of Chemistry, Williams College, Williamstown, Massachusetts 01267

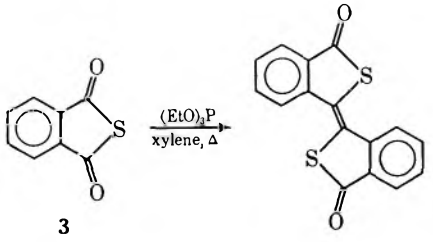
Received September 23, 1969

Thiophthalic anhydride (**3**) undergoes reductive dimerization with triethyl phosphite to yield *trans*-bithiophthalide (**4**), the structure of which was inferred from spectroscopic correlations and confirmed by X-ray analysis. A similar reaction of **3** with tris(dimethylamino)phosphine gives a novel mixture of products (**12** and **13**), the structures of which are assigned from extensive spectral data. The different products are rationalized in terms of the pathways available to a common phosphorane intermediate (**16**).

Among the extensive literature on the reactions of trivalent phosphorus species with carbonyl compounds,[2] cyclic anhydrides have received limited attention.[3] Although it was reported a decade ago that phthalic anhydride (**1**) was converted by triethyl phosphite into 3,3′-biphthalide (**2**),[4] no subsequent studies of this novel reductive dimerization appeared until very recently. The extension of this reaction to disubstituted maleic anhydrides and thiophthalic anhydride (**3**) was reported in a recent communication.[5] We present here the results of a similar study of the reactions of **3** with several P(III) compounds. Our choice of the sulfur analog was based on the greater electrophilicity of sulfur than oxygen toward phosphorus. It was felt that a change in mechanism between **1** and **3**, as was observed with epoxides and episulfides,[6,7] might afford a new process for constructing benzocyclobutenedione systems.[8]

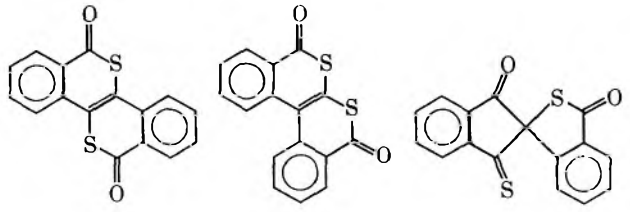
Results

Treatment of **3** with triethyl phosphite (molar ratio 1:2) in refluxing xylene smoothly afforded *trans*-3,3′-bithiophthalide (**4**) in good yield. Despite the mention of **4** in the literature, the structure of the present



3 **4**

product was assigned with some care. 3,3′-Bithiophthalide was characterized in the previous reports[9–11] as green-yellow needles, mp 335°, which sublimed to orange-yellow needles; no data on the sublimate were provided. The question of geometric isomerism received no comment. The earlier workers[9,10] depicted only the *cis* isomer, while the contemporary groups[5,11] have considered only the *trans* isomer. Unfortunately, no spectroscopic data were available from the recent reports. Finally, the limited degradative studies provided no clues to configuration.[9,11] The literature was thus insufficient to assist in a definitive structural assignment. Our compound **4** was an orange-yellow substance, mp 351°, which elemental and mass spectrometric analyses confirmed to be $C_{16}H_8O_2S_2$. In addition to *trans*- (**4**) and *cis*-3,3′-bithiophthalide (**5**), it was necessary to consider the δ-thiolactones **6** and **7** and the spirothiolactone **8**. The infrared spectrum



6 **7** **8**

contained a single carbonyl peak at 1700 cm^{-1} and no double-bond absorption in the 1650–1670-cm^{-1} region.[12] These data are inconsistent with **5**, **7**, and **8**.[15] A decision between the remaining structures (**4** and **6**) was possible on the basis of the carbonyl absorption. The *trans*-3,3′-bithiophthalide formulation was consistent with the known variation of $\nu_{C=O}$ (cm^{-1}) with heteroatom and ring size: phthalide,[16] 1761; thiophthalide,[16] 1686; 3-phenylisocoumarin,[17] 1721; and 3-phenylisothiocoumarin,[18] 1635. An uncertainty, however, was introduced into this correlation. At the time that these deductions about **4** were in progress, there appeared a series of articles in which

(1) Based in part on the Honors Theses, Williams College, of C. I. H. 1964, and N. L. A., 1966.

(2) For general reviews see (a) J. I. G. Cadogan, *Quart. Rev.* (London), **16**, 208 (1962); (b) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemisty," Academic Press, New York, N. Y., 1965, Chapter 6; (c) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., Amsterdam, 1967, Chapter 3.

(3) We refer here to reactivity at the oxygen functions; maleic anhydride reacts at the vinyl carbon. *Cf.* R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **46**, 2178 (1963).

(4) (a) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Org. Chem.*, **24**, 1838 (1959); (b) *J. Amer. Chem. Soc.*, **83**, 173 (1961).

(5) C. W. Bird and D. Y. Wong, *Chem. Commun.*, 932 (1969).

(6) N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, **81**, 578 (1959).

(7) D. B. Denney and M. J. Boskin, *ibid.*, **82**, 4736 (1960).

(8) The same objective, based on the photolysis of a phthaloyl dixanthate, was reported recently: *cf.* A. Shaw, S. N. Singh, and M. V. George, *Tetrahedron Lett.*, 3983 (1968).

(9) S. Gabriel and E. Leupold, *Ber.*, **31**, 2646 (1898).

(10) A. Reissert and H. Holle, *ibid.*, **44**, 3027 (1911).

(11) W. G. Toland and R. W. Campbell, *J. Org. Chem.*, **28**, 3124 (1963).

(12) The exocyclic double bonds of *cis*-bifurandione[13] and *cis*-oxindigo[14] absorb at 1668 and 1647 cm^{-1}, respectively.

(13) J. C. Sauer, R. D. Cramer, V. A. Engelhardt, T. A. Ford, H. E. Holmquist, and B. W. Howk, *J. Amer. Chem. Soc.*, **81**, 3677 (1959).

(14) H. Güsten, *Chem. Commun.*, 133 (1969).

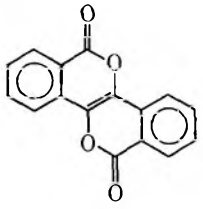
(15) The extremely low solubility of the compound precluded nmr and Raman spectra, which could have corroborated the absence of **5** and **7**.

(16) V. Prey, B. Kerres, and H. Berbalk, *Monatsh. Chem.*, **91**, 774 (1960).

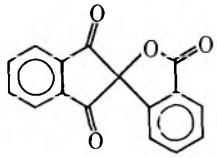
(17) R. L. Letsinger, E. N. Oftedahl, and J. R. Nazy, *J. Amer. Chem. Soc.*, **87**, 742 (1965).

(18) L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1787 (1964).

trans- (2) and *cis*-3,3′-biphthalide (**9**) as well as **10** and **11** were reported.[19-21] There was confusion



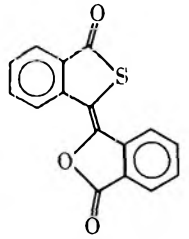
10



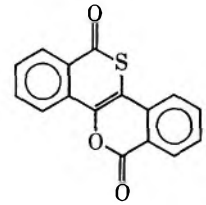
11

among the structural assignments, which cast doubt on the $\nu_{C=O}$ values for the γ- and δ-lactones.[22] At this juncture we obtained independent confirmation of structure **4** by crystallographic methods.[24]

Not only are there differences in the electrophilicity of bivalent oxygen and sulfur toward P(III), but also the reactivities of trivalent phosphorus compounds differ. The relative nucleophilicity of various phosphines has been correlated with their oxidation by sulfur dioxide[25] and dimethyl sulfoxide.[26] From the latter study, in which the data were best correlated by two series of P(III) compounds, it was inferred that two pathways were involved. Our attention was therefore directed to the reaction of **3** with other phosphines. Although triphenylphosphine showed no reactivity toward **3**, the reaction with tris(dimethylamino)phosphine was of more interest. The yellow product, mp 340–341°, obtained in good yield, had the molecular formula $C_{16}H_8O_3S$; mass spectral data confirmed the elemental composition and further established the absence of $C_{16}H_8O_2S_2$ and $C_{16}H_8O_4$ molecular ions. The ir spectrum contained four carbonyl peaks at 1792, 1748, 1701, and 1656 cm^{-1}; the Raman spectrum showed two strong carbon–carbon double bond stretching fundamentals at 1607 and 1552 cm^{-1}; and the uv spectrum was indicative of extended conjugation. These data were consistent with a mixture of the γ- and δ-lactones and thiolactones **12** and **13**.[27] The *trans* isomers were assumed on the basis of the preferred configurations in the biphthalide series.



12

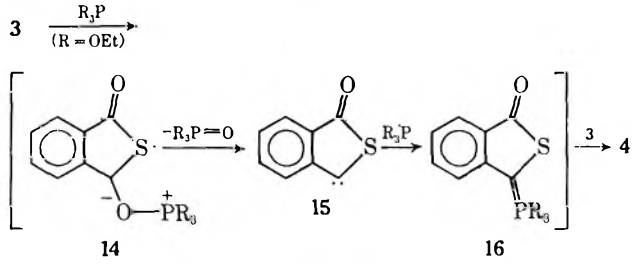


13

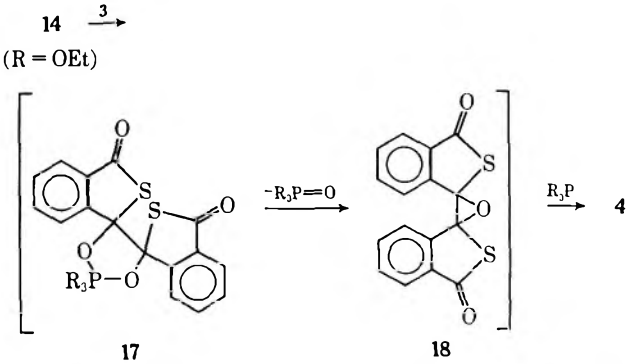
Both compounds are considered primary products, since control experiments established that no isomerization occurred under thermal or acidic conditions. In fact, the same mixture (**12** to **13** ratio *ca.* 1:2) was obtained at room temperature. The carbonyl absorptions (in order of decreasing frequency) are consistent with a γ-lactone, δ-lactone, γ-thiolactone, and δ-thiolactone; the relative intensities of the four peaks support this interpretation. Although the force constants are the same for the exocyclic and endocyclic double bonds, the smaller angles (higher compression) of the bonds in a five-membered ring permit the assignment of the higher Raman frequency to **12**. The extremely low solubility of the product precluded any chromatographic demonstration of a two-component mixture, and the above structural assignments remain tentative. Preliminary X-ray data, however, are consistent with the postulated structures.[28]

Discussion

The conversion of **3** into **4** by triethyl phosphite was considered by Bird and Wong[5] to involve carbene **15** and phosphorane **16**, the latter intermediate proceeding to **4** *via* a Wittig reaction.[29] Although such



an interpretation has been suggested previously,[30] the supporting experiments of Bird and Wong[5] do not appear to exclude an alternate pathway involving a five-membered cyclic oxyphosphorane intermediate (**17**)[31] derived from **14**. It is recognized that **17** may



(19) H.-D. Becker, *J. Org. Chem.*, **29**, 3070 (1964).

(20) R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966).

(21) H. A. Staab and J. Ipaktschi, *ibid.*, 583 (1966).

(22) (a) The correct assignments were recently established: H. A. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968). (b) The biphthalide series, however, still contains inconsistencies; Sauer, *et al.*,[23] as a structure proof for *trans*-bifurandione, converted it into **2** (*sic*), mp 331–334°, *vis-à-vis* authentic **2**, mp 352–354°,[3] and **10**, mp 334–336°.[23]

(23) M. P. Cava, D. R. Napier, and R. J. Pohl, *J. Amer. Chem. Soc.*, **85**, 2076 (1963).

(24) The X-ray diffraction analysis was conducted by Professor R. E. Davis, University of Texas; his results will be published separately.

(25) B. C. Smith and G. H. Smith, *J. Chem. Soc.*, 5516 (1965).

(26) E. H. Amonoo-Neizer, S. K. Ray, R. A. Shaw, and B. C. Smith, *ibid.*, 4296 (1965).

(27) Bird and Wong[5] postulated the previously unknown structure **12** for the product from the reaction of **3** with $(EtO)_3P$ in the presence of **1**; the structural assignment was not discussed.

(28) This analysis was conducted by Dr. K. J. Palmer, Western Utilization Research Laboratory, U. S. Department of Agriculture. The data exhibited regularity along the *a* and *c* axes, but irregularity along the *b* axis. The disordered arrangement along the *b* axis (perpendicular to the plane of the molecule) is indicative of irregular stacking; the regularity along the other two axes supports the same configuration for both planar compounds.

(29) These authors did not indicate the mode of generation of **15**, which could result from nucleophilic attack of the phosphorus at either carbon or oxygen of the carbonyl group; species **14** represents the latter pathway.

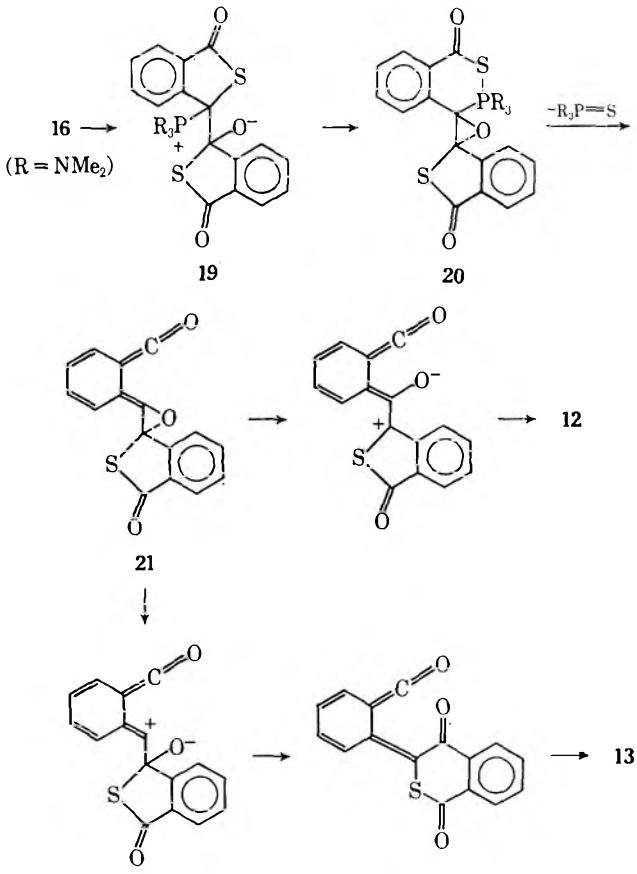
(30) Reference 2b, p 185.

(31) For a recent review of oxyphosphoranes, see F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

also exist as an open zwitterion,[32] but the cyclic form is consistent with products isolated from similar reactions of triethyl phosphite with isatin,[33] indanetrione,[34] and fluorenone.[35]

The reaction of **3** with tris(dimethylamino)phosphine requires a pathway not only different from the above routes to **4** but also one capable of generating the pair of isomeric $C_{16}H_8O_3S$ products. Scheme I accommodates these requirements proceeding from **16** (R = NM_2). The ring expansion represented for **19** → **20** has been proposed for analogous systems.[4a,36]

SCHEME I



It was established that **13** was not derived from **12** and, therefore, species **21** is viewed as the precursor of both products *via* alternate modes of heterolysis of the epoxide ring. The precedent for ascribing different mechanistic involvement to triethyl phosphite and tris(dimethylamino)phosphine stems from earlier work of Ramirez[37] and others.[26]

Experimental Section

Melting points and boiling points are uncorrected. Spectra were recorded on the following instruments: infrared, Perkin-Elmer 237B; ultraviolet, Cary 14; Raman, Perkin-Elmer laser Raman LR-1. Mass spectra were obtained with a CEC 21-110B spectrometer using direct introduction. All distillations and reactions were conducted under a nitrogen atmosphere. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377.

Materials.—Triphenylphosphine[38] was purified by the method of Grisley, *et al.*,[39] mp 80–81° (EtOH) (lit.[40] mp 80°). Triethyl phosphite was treated repeatedly with sodium ribbon and the filtrate was distilled; a middle fraction was collected, bp 42.5–43.0° (6 mm) [lit.[41] bp 46–47° (13 mm)]. Tris(dimethylamino)-phosphine was prepared by the method of Burg and Slota;[42] a middle fraction was collected, bp 40–41° (5 mm) [lit.[43] bp 49–51° (12 mm)]. Thiophthalic anhydride (**3**) was prepared by the method of Reissert and Holle:[10] mp 111.2–112.2° (absolute EtOH) (lit.[10] mp 114°); ir (KBr) 1792 (w), 1742 (w), 1695 (s), and 1658 cm^{-1} (m); uv max (CH_3CN) 221 mμ (ε 2050), 231 (21,800), and 254 (8500). Biphthalide (**2**) was prepared by the method of Ramirez, *et al.*:[4b] mp 350–351.5° (xylene) (lit.[4b] mp 352–354°); ir (KBr) 1786 cm^{-1}; uv max[44] (CH_3CN) 219 mμ (ε 39,500), 225 (39,000), 256 (16,000), 291 (12,500), 303 (14,000), 357 (29,500) and 369 (sh, 24,500); Raman (solid) 1692 cm^{-1}. Xylene (bp 137.0–139.0°, Matheson Coleman and Bell A.C.S. analyzed reagent) was dried over sodium.

Reaction of Thiophthalic Anhydride (3) with P(III) Compounds.—The following general procedure was employed. A solution of **3** (*ca.* 3 mmol) and the phosphite or phosphine (*ca.* 6 mmol) in 10 ml of solvent was stirred at reflux for the periods indicated in Table I; the solid was collected from the cooled reaction mixture, washed with benzene, and dried. Recrystallization from xylene (charcoal treatment) afforded purified product.

TABLE I

REACTIONS OF THIOPHTHALIC ANHYDRIDE AND R_3P

R	Solvent[a]	Time, hr	Yield, %	Product
EtO	Benzene	24	9	**4**
EtO	Toluene	24	64	**4**
EtO	Xylene	24	82	**4**
EtO	Xylene	12	82	**4**
EtO	Xylene	6	68	**4**
EtO	Diglyme	24	64	**4**
Me_2N	Xylene	12	60	**12** + **13**
Me_2N	Xylene[b]	12	72	**12** + **13**
Ph	Xylene	12	0	

[a] All runs conducted at reflux temperature, unless noted. [b] Room temperature.

From the reaction with $(EtO)_3P$ was obtained *trans*-bithiophthalide (**4**): mp 350–351°; ir (KBr) 1700 cm^{-1}; uv max (CH_3CN) 213 mμ (ε 22,900), 243 (32,200), 300 (7800), and 401 (23,000); mass spectrum (70 eV) *m/e* 295.9960 (molecular ion).

Anal. Calcd for $C_{16}H_8O_2S_2$: C, 64.84; H, 2.72; S, 21.64; mol wt, 295.9966. Found: C, 64.98; H, 2.77; S, 21.69.

From the reaction with $(Me_2N)_3P$ was obtained a mixture of **12** and **13**: mp 340–341° (vacuum sublimation); ir (KBr) 1792 (m), 1748 (s), 1701 (m), and 1656 cm^{-1} (s); uv max (CH_3CN) 226 mμ (ε 56,200), 246 (sh, 29,800), 280 (7600), 315 (11,300), 367 (18,400), and 384 (15,600); Raman (solid) 1635 (w), 1607 (s), 1590 (w), 1552 (s), and 1484 cm^{-1} (w); mass spectrum (70 eV) *m/e* 280.0190 (molecular ion).

Anal. Calcd for $C_{16}H_8O_3S$: C, 68.57; H, 2.86; S, 11.43; mol wt, 280.0194. Found: C, 68.14; H, 2.86; S, 11.60.

Attempted Isomerizations.[19]—The product (70 mg of **4** or **12** + **13**) was dissolved in 12 ml of hot, concentrated sulfuric acid, kept at 110° for 1 hr, and poured onto ice. The recovered product in each case exhibited no change in its melting point or ir and uv spectra.

(32) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Amer. Chem. Soc.*, **87**, 4973 (1965).

(33) A. Mustafa, M. M. Sidky, and F. M. Soliman, *Tetrahedron*, **22**, 393 (1966).

(34) A. Mustafa, M. M. Sidky, S. M. A. D. Zayed, and M. R. Mahran, *Justus Liebigs Ann. Chem.*, **712**, 116 (1968).

(35) (a) F. Ramirez and C. P. Smith, *Chem. Commun.*, 662 (1967); (b) I. J. Borowitz and M. Anschel, *Tetrahedron Lett.*, 1517 (1967).

(36) W. Adam, R. J. Ramirez, and S.-C. Tsai, *J. Amer. Chem. Soc.*, **91**, 1254 (1969).

(37) F. Ramirez, A. S. Gulati, and C. P. Smith, *ibid.*, **89**, 6283 (1967).

(38) We thank the Metal & Thermit Corp. for a generous gift of this material.

(39) D. W. Grisley, Jr., J. C. Alm, and C. N. Matthews, *Tetrahedron*, **21**, 5 (1965).

(40) F. Ramirez, C. P. Smith, A. S. Gulati, and A. V. Patwardhan, *Tetrahedron Lett.*, 2151 (1966).

(41) T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1917 (1962).

(42) A. B. Burg and P. J. Slota, Jr., *J. Amer. Chem. Soc.*, **80**, 1107 (1958).

(43) V. Mark, *Org. Syn.*, **46**, 42 (1966).

(44) H.-D. Becker, Report No. 64-RL-3631C, General Electric Co., 1964.

Registry No.—**2**, 19357-64-3; **3**, 5698-59-9; **4**, 23667-32-5; **12**, 23667-33-6; **13**, 23667-34-7.

Acknowledgments.—The authors are grateful to Dr. C. W. Koch, University of California, Berkeley, and Dr. J. R. Scherer, Western Utilization Research Laboratory, USDA, for the mass spectral and Raman data, respectively. We are indebted to Professor R. E. Davis and Dr. K. J. Palmer for the X-ray analyses. We thank Dr. H.-D. Becker, General Electric Co., for helpful correspondence relating to the biphthalide structures.

Electronic Effects of the Substituents Containing the Thiocarbonyl Group

TAKESHI NISHIGUCHI AND YOSHIO IWAKURA

Department of Synthetic Chemistry, Faculty of Engineering, University of Tokyo, Tokyo, Japan

Received August 12, 1969

The Hammett substituent constants, σ_m and σ_p, of 3-ethylthioureido, 3-ethylureido, thioacetamido, acetamido, methylaminothiocarbonyl, and methylaminocarbonyl groups were obtained from the dissociation constants of the *meta*- and *para*-substituted benzoic acids for the discussion of the electronic effects of the thiocarbonyl and carbonyl group. Their σ_I and σ_R values were also calculated from the σ_m and σ_p values. The result shows that the thiocarbonyl group attracts electrons from the adjacent nitrogen atom more strongly by resonance and more weakly by induction than the carbonyl group. As a whole, the thiocarbonyl group has stronger electron-withdrawing power than the carbonyl group.

It has been reported by Luttringhaus and Grohmann[1] that the dipole moments of *para,para'*-substituted thiobenzophenones are larger than those of the corresponding benzophenones when the *para,para'* substituents are strongly electron releasing by resonance and smaller when the substituents are not so strongly electron releasing by resonance. The fact may suggest that the thiocarbonyl group is more strongly electron withdrawing by resonance and more weakly so by induction that the carbonyl group. The concept that the thiocarbonyl group of thioamides has stronger resonance interaction with the adjacent nitrogen atom than the carbonyl group of amides is supported by the fact that thioamides have larger dipole moments,[1,2] higher rotational energy barriers[3] about the C–N bond, larger ^{13}C–H coupling constants[3e] in the nmr spectra of NCH_3, and shorter C–N bond distances[2a] than the amides. The above concept about thioamides and amides is also discussed with respect to the infrared[2a,d] and ultraviolet spectroscopy,[2a,d,4] the ability to form hydrogen bonds,[2c,5] and LCAO-MO treatment.[3f,4,6] Further, the presumption that the electron density on the nitrogen of thioamides is lower than that of the corresponding amides may be derived from the pK_a value of thioacetamide,[7] the coupling constants described above,[3e] and Janssen's observation that the dissociation constants of the thiocarbonyl compounds of the acids AC(=X)BCH$_2$COOH (X = O and S, A = Me, B = S; A = Me_2N, B = O; A = Me_2N, B = S) are larger than those of the carbonyl analogs.[8]

In the course of the study of 1-substituted aziridines and azetidines,[9] it was found that there existed a remarkable difference between the reaction mechanism of the isomerization of the 1-acyl and 1-thioacyl compounds and that the thiocarbonyl compounds had the proton signals of the ring methylenes at lower magnetic field in the nmr spectra than the corresponding carbonyl compounds. For example, 1-thiobenzoylazetidine shows peaks of methylene protons at τ 5.70 and 7.73, while 1-benzoylazetidine shows these peaks at τ 5.86 and 7.76. These phenomena may be rationalized by the assumption that the thiocarbonyl group of thioamides and thioureas attracts electrons more strongly from the adjacent nitrogen than the carbonyl group of amides and ureas. Electronic effects of substituents containing the thiocarbonyl group have not been elucidated sufficiently, and no σ parameters of such substituents seem to have been reported except for those of thioureido group obtained from ^{19}F nmr measurement (σ_m = 0.22, σ_p = 0.16, σ_I = 0.29, and σ_R = −0.13).[10] In order to clarify the electronic effects of thioamide and thiourea linkage quantitatively and to compare them with those of amide and urea linkage, the Hammett σ constants were determined from the dissociation constants of *meta*- or *para*-substituted benzoic acids.

Results

The substituted benzoic acids were prepared and purified as described in the Experimental Section and their physical properties and analyses are given in Table I.

The Hammett σ values obtained from the dissocia-

(1) V. A. Luttringhaus and J. Grohmann, *Z. Naturforsch.*, **10b**, 365 (1955).

(2) (a) M. C. Lee and W. D. Kumler, *J. Org. Chem.*, **27**, 2052 (1962); (b) G. K. Kstok and S. P. Sood, *J. Phys. Chem.*, **66**, 1372 (1962); (c) M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Amer. Chem. Soc.*, **87**, 892 (1965); (d) H. G. Mautner and W. D. Kumler, *ibid.*, **78**, 97 (1956).

(3) (a) G. Schwenker and H. Rosswag, *Tetrahedron Lett.*, 4237 (1967); (b) R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, **89**, 3412 (1967); (c) A. Leowenstein, A. Melara, P. Ringnag, and W. Walter, *J. Phys., Chem.*, **68**, 1597 (1964); (d) R. C. Neuman, Jr., and L. B. Young, *ibid.*, **69**, 1777 (1965); (e) *ibid.*, **69**, 2570 (1965); (f) J. Sandström, *ibid.*, **71**, 2318 (1967).

(4) U. Breg and J. Sandström, *Acta Chem. Scand.*, **20**, 689 (1966).

(5) (a) N. Kulevsky, and P. M. Froehlich, *J. Amer. Chem. Soc.*, **89**, 4839 (1967); (b) E. P. Dudek and G. Dudek, *J. Org. Chem.*, **32**, 823 (1967).

(6) (a) M. J. Janssen, *Rec. Trav. Chim. Pays-Bas*, **79**, 1066 (1960); (b) M. J. Janssen and J. Sandström, *Tetrahedron*, **20**, 2339 (1964).

(7) J. T. Edward and T. C. Wang, *Can. J. Chem.*, **40**, 399 (1962).

(8) M. J. Janssen, *Rec. Trav. Chim. Pays-Bas*, **82**, 931 (1963).

(9) (a) T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Amer. Chem. Soc.*, **91**, 5835, 5841 (1969); (b) Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Polym. Sci., Part A-1*, **6**, 2591 (1968); (c) Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Org. Chem.*, **32**, 2362 (1967); (d) Y. Iwakura, A. Nabeya, T. Nishiguchi, and Y. Ichikawa, *ibid.*, **30**, 3410 (1965); (e) Y. Iwakura, A. Nabeya, T. Nishiguchi, and K. Ohkawa, *ibid.*, **31**, 3352 (1966); (f) Y. Iwakura, A. Nabeya, and T. Nishiguchi, *ibid.*, **31**, 1651 (1966).

(10) J. C. Kauer and W. A. Sheppard, *J. Org. Chem.*, **32**, 3580 (1967).

TABLE I

meta- OR *para*-SUBSTITUTED BENZOIC ACIDS

Substituent	Registry no.	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir spectra,[b] cm⁻¹ νNH	Ir spectra,[b] cm⁻¹ νC=O
m-CH_3CSNH	23667-97-2	224 dec	$C_9H_9NO_2S$	55.38	4.65	7.18	55.64	4.80	7.09	3160	1680
m-CH_3CONH	587-48-4	246-247[c]	$C_9H_9NO_3$	60.33	5.06	7.82	60.01	4.93	7.82	3360	1705, 1640
p-CH_3CSNH	23667-98-3	219 dec	$C_9H_9NO_2S$	55.38	4.65	7.18	55.75	4.85	7.12	3150	1690
p-CH_3CONH	556-08-1	256-257[d]	$C_9H_9NO_3$	60.33	5.06	7.82	59.98	5.04	7.82	3330	1675
m-$C_2H_5NHCSNH$	19384-17-9	204-206	$C_{10}H_{12}N_2O_2S$	53.57	5.39	12.50	53.79	5.17	12.52	3270, 3230	1685
m-$C_2H_5NHCONH$	23754-39-4	234 dec	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46	57.44	5.84	13.45	3340, 3290	1690, 1640
p-$C_2H_5NHCSNH$	15863-32-8	208 dec	$C_{10}H_{12}N_2O_2S$	53.57	5.39	12.50	53.59	5.50	12.29	3300, 3250	1650
p-$C_2H_5NHCONH$	23754-41-8	>280	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46	57.74	5.64	13.39	3320	1680, 1643
m-CH_3NHCS	23754-42-9	190-192	$C_9H_9NO_2S$	55.38	4.65	7.18	55.50	4.53	7.15	3340	1675
m-CH_3NHCO	23754-43-0	233-234	$C_9H_9NO_3$	60.33	5.06	7.82	60.21	5.02	7.79	3300	1683, 1640
p-CH_3NHCS	23754-44-1	228-229	$C_9H_9NO_2S$	55.38	4.65	7.18	55.34	4.58	7.19	3340	1680
p-CH_3NHCO	23754-45-2	260-262	$C_9H_9NO_3$	60.33	5.06	7.82	60.13	5.01	7.73	3300	1685[e]

[a] All melting points are uncorrected. [b] The infrared spectra were measured as a Nujol mull. [c] Literature mp 248°, 250°: B. Pawlewski, *Ber.*, **35**, 110 (1902); F. Ullman and J. B. Uzbachian, *ibid.*, **36**, 1797 (1903). [d] Literature mp 250–251°, 256.5°, 255°: F. Ullman and J. B. Uzbachian, *ibid.*, **36**, 1797 (1903); A. Kaaiser, *ibid.*, **18**, 2942 (1885); G. W. K. Cevill and J. M. Vincent, *J. Soc. Chem. Ind.*, **67**, 25 (1948). [e] Broad.

TABLE II

SUBSTITUENT CONSTANTS OBTAINED FROM THE DISSOCIATION CONSTANTS OF *meta*- OR *para*-SUBSTITUTED BENZOIC ACIDS IN 50% AQUEOUS ETHANOL AT 25°

Substituent	σ_m	σ_p	σ_I	σ_R
CH_3CSNH	0.24	0.12	0.30	−0.18
CH_3CONH[a]	0.16[b]	−0.07[c]	0.27[d]	−0.34[e]
$C_2H_5NHCSNH$	0.30	0.07	0.41	−0.34
$C_2H_5NHCONH$	0.04	−0.26	0.19	−0.45
CH_3NHCS	0.30	0.34	0.28	0.06
CH_3NHCO	0.35	0.36	0.35	0.02

[a] The σ values of the acetamido group reported in the literature were obtained from the dissociation constants or the reactivities [D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958); R. W. Taft, Jr., N. C. Deno, and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 287 (1958)] and from ^{19}F nmr chemical shift measured in specific solvents [ref 10; R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963)]. [b] Literature (McDaniel and Brown) 0.15, 0.270; (ref 10) 0.13 (measured in acetonitrile). [c] Literature (McDaniel and Brown) −0.06, −0.015, −0.053; (ref 10) 0.02 (measured in acetonitrile). [d] Literature (Taft, Deno, *et al.*) 0.28; (ref 10) 0.24 (measured in acetonitrile); (Taft, Price, *et al.*) 0.20 (measured in dimethylformamide), 0.24 ± 0.01 (measured in protonic solvents which are no more acidic than formic acid). [e] Literature (Taft, Deno, *et al.*) −0.22; (ref 10) −0.22 (measured in acetonitrile).

tion constants are summarized in Table II. Taft and Lewis[11] have shown that σ values can be divided fairly well into inductive, σ_I, and resonance contribution, σ_R, by the following formulas: $\sigma_I = {}^1/_2(3\sigma_m - \sigma_p)$; $\sigma_R = {}^3/_2(\sigma_p - \sigma_m)$. The values of σ_I and σ_R thus obtained are also shown in Table II.

Discussion

Since such substituents as thioacetamido, acetamido, 3-ethylthioureido, and 3-ethylureido group are attached to other groups at the same element, nitrogen, the values of σ_I of these substituents may be considered as the indices of the electron density of the nitrogen atom. As shown in Table II, the σ_I value of the 3-ethylthioureido group is greater than that of the 3-ethylureido group and that of the thioacetamido group seems to be greater than that of the acetamido group. Therefore, it may be concluded that the thiocarbonyl group of thioamide and thiourea linkage attracts electrons more strongly from the adjacent nitrogen atom than the carbonyl group of the amide and urea linkage does. The electronic effects of substituents may be regarded as the sum of inductive and resonance effects,[11] and in some cases the inductive effect is rationalized by electronegativity of particular atoms of substituents.[12] As the electronegativity of sulfur is smaller than that of oxygen,[13] the thiocarbonyl group should have weaker electron-withdrawing power by induction than the carbonyl group, and this seems to be shown by the fact that the σ_I value of the methylaminothiocarbonyl group is smaller than that of the methylaminocarbonyl group. Accordingly, the stronger electron-withdrawing power of the thiocarbonyl group may be attributable to resonance rather than to induction. It is pointed out by many authors that in the resonance $-C(=X)N< \leftrightarrow -C(X^-)=\overset{+}{N}<$ (X = O, S), the dipolar canonical form contributes more in thioamides and thioureas (X = S) than in amides and ureas (X = O). The phenomenon is considered to be closely related to the fact that heavy elements hardly form $p\pi$–$p\pi$ multiple bonds. The reason why bivalent sulfur has less tendency to form double bonds than oxygen has been speculated in the literature as follows. (A) the contraction of bond distance to form multiple bonds may be more difficult for sulfur, which has ten electrons in the inner shells, than for oxygen, which has only two.[2a,d] The repulsion of inner-shell electrons in general bonding has been discussed from the viewpoint of the repulsion energy of nonbonding electrons.[14] (B) Because the 2p orbital of oxygen is roughly as large as that of carbon, the two orbitals will overlap well.[5a] However, as the 3p orbital of sulfur is considerably larger than the 2p orbital of oxygen, the 3p and the 2p orbital will not overlap so well.[5a] (C) Since the 3p orbital has two nodes where the signs of the four lobes are reversed, the $2p\pi$–$3p\pi$ bonding will have partial antibonding charac-

(11) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).

(12) (a) R. W. Taft, Jr., *J. Chem. Phys.*, **26**, 93 (1957); (b) J. W. Rakshys, R. W. Taft, and W. A. Sheppard, *J. Amer. Chem. Soc.*, **90**, 5236 (1968).

(13) (a) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 63; (b) M. J. Janssen, *Rec. Trav. Chim. Pays-Bas*, **81**, 650 (1962).

(14) C. A. Coulson, "Valence," 2nd ed, Clarendon Press, Oxford, 1961, Chapter 7.

ter and lower overlap integral value than the $2p\pi$–$2p\pi$ bonding, as shown in Figure 1.[15] Speculations B and C treat of the overlap of p orbitals, but the former seems to be unable to rationalize the fact that $p\pi$–$p\pi$ multiple bonds between heavy elements of the same size also are hardly formed, for example, the fact that the double bond between silicons is formed very difficultly.[16] Therefore, C seems to be better than B.

The second-row elements have d orbitals available while the first-row elements have not, and Rakshys, *et al.*, have shown that the $2p\pi$–$3d\pi$ interaction between aromatic rings and tricoordinated phosphorus substituents is considerably important.[12b] The stronger electron-attracting power of the thiocarbonyl group may be partly attributable to the ability of the 3d orbitals of sulfur to accept electrons from the 2p orbitals of carbon by the $2p\pi$–$3d\pi$ interaction.

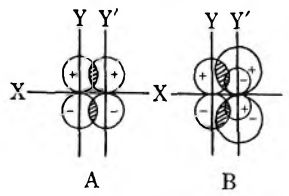


Figure 1.—(A) $2p\pi$–$2p\pi$ bonding; (B) 2 $p\pi$–$3p\pi$ bonding.

Experimental Section[17]

***m*-Thioacetamidobenzoic Acid.**—To a solution of 3.0 g (0.02 mol) of thioacetylthioglycolic acid and 0.8 g of sodium hydroxide in 20 ml of water was added a solution of 2.7 g (0.02 mol) of *m*-aminobenzoic acid in 20 ml of water. The reaction mixture was left standing for 1 hr at room temperature and acidified with dilute hydrochloric acid. The resulted solid was separated by filtration, washed with cold water, and recrystallized from ethanol–water or ethanol only. The yield was *ca.* 80% after a recrystallization. *p*-Thioacetamidobenzoic acid was prepared in the same way from *p*-aminobenzoic acid and thioacetylthioglycolic acid. Thioacetylthioglycolic acid was obtained by the method of Jensen and Pedersen.[18]

***m*-Acetamidobenzoic Acid.**—To an equimolar mixture of *m*-aminobenzoic acid and triethylamine in tetrahydrofuran, an equimolar amount of acetyl chloride in tetrahydrofuran was added dropwise with stirring and cooling. After the solution had been stirred for 1 hr, the solvent was removed from the reaction mixture. The residue was washed with cold water, dried, and recrystallized from ethanol. *p*-Acetamidobenzoic acid was synthesized from acetyl chloride and *p*-amiobenzoic acid in the same manner.

***m*-(3-Ethylthioureido)benzoic Acid.**—Equimolar amounts of ethyl isothiocyanate and the sodium *m*-aminobenzoate were refluxed in methanol for 2 hr. After the methanol was removed from the reaction mixture, the residue was dissolved in water and acidified with cold, dilute hydrochloric acid. The resulting precipitate was collected on a filter and recrystallized from methanol. *p*-(3-Ethylthioureido)benzoic acid was prepared from ethyl isothiocyanate and *p*-aminobenzoic acid in a similar manner.

***m*-(3-Ethylureido)benzoic acid** was prepared from ethyl isocyanate and *m*-aminobenzoic acid in tetrahydrofuran and purified by repeated recrystallizations from ethanol. The *para* isomer was obtained in the same way from ethyl isocyanate and *p*-aminobenzoic acid.

***m*-Methylaminocarbonylbenzoic Acid Methyl Ester.**—Isophthalic acid monomethyl ester was prepared by the method of Wohl[19] from dimethyl isophthalate. The monomethyl ester was heated under reflux with excess thionyl chloride until the gas evolution ceased to give isophthalic acid chloride monomethyl ester, bp 155° (22 mm). To an aqueous solution of 2.1 mol of monomethylamine was added a solution of isophthaloyl chloride monomethyl ester in dry tetrahydrofuran dropwise with stirring below 0°. Immediately after the addition was over, the tetrahydrofuran was removed from the mixture under reduced pressure without heating. The remained aqueous solution was acidified with hydrochloric acid and ice. The resultant solid was collected on a filter, washed with cold water, and dried. The infrared spectrum of the solid had absorptions at 3280 (NH), 1730, and 1645 cm^{-1} (two C=O).

***p*-Methylaminocarbonylbenzoic Acid Methyl Ester.**—Terephthalic acid monomethyl ester was obtained by the method of Cohen.[20] The reaction between the ester and thionyl chloride was carried out in the same manner described above and the excess thionly chloride was removed thoroughly under reduced pressure. The solid residue gave the title compound after the treatment with methylamine solution. The infrared spectrum had bands at 3360 (NH), 1740, and 1640 cm^{-1} (two C=O).

***m*-Methylaminothiocarbonylbenzoic Acid Methyl Ester.**—*m*-Methylaminocarbonylbenzoic acid methyl ester (3.0 g) and powdered phosphorus pentasulfide (1.0 g) were refluxed in 40 ml of xylene for 1 hr with stirring and the additional 60 ml of xylene was added to the reaction mixture. The hot solution was filtered to remove solid impurities and the xylene was removed from the filtrate under reduced pressure. The residue was recrystallized from *n*-hexane–benzene to give 3.0 g (70% yield) of yellow needles, mp 69–70°.

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.49; H, 5.41; N, 6.63.

The *para* isomer was prepared in a similar manner in 73% yield, melted at 141–141.5°, and had bands at 3350 (NH) and 1713 cm^{-1} (C=O) in its infrared spectrum.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.68; H, 5.34; N, 6.57.

Hydrolysis of *meta*- or *para*-Substituted Benzoic Acid Methyl Esters.—Equimolar amounts of methylaminothiocarbonylbenzoic acid methyl esters or methylaminocarbonylbenzoic acid methyl esters and potassium hydroxide were heated in dry methanol under reflux for 1 hr and the methanol was removed. The residue was dissolved in water and filtered to remove solid impurities. The filtrate was acidified with hydrochloric acid and ice. The resultant solid was collected on a filter, dried, and recrystallized from ethanol–water or *n*-hexane–ethanol.

Determination of Dissociation Constants and ρ Value.—Because of the limited solubility of the benzoic acids in water, their dissociation constants were determined in 50% aqueous ethanol at 25° in the same way as reported by Monagle, Mengenhauser, and Jones.[21] The ρ value for the dissociation of benzoic acids in this solvent system was determined. Treatment of the dissociation constants of *m*- and *p*-chlorobenzoic acid, benzoic acid, *p*-toluic acid, and *p*-anisic acid with the method of least squares gave 1.48 as the ρ value, 0.98 as the correlation coefficient γ, and 0.12 as the standard deviation. The ρ value was smaller than the reported values, 1.570,[22] 1.681,[21] and 1.851.[23]

Registry No.—*m*-Methylaminocarbonylbenzoic acid methyl ester, 23668-00-0; *p*-methylaminocarbonylbenzoic acid methyl ester, 23754-46-3; *m*-methylaminothiocarbonylbenzoic acid methyl ester, 23754-47-4; *p*-methylaminothiocarbonylbenzoic acid methyl ester, 23754-48-5.

Acknowledgments.—The authors wish to express hearty thanks to Dr. Aiko Nabeya for very helpful discussion. They are indebted to Dr. Masanori Kise for helpful suggestion.

(15) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962.
(16) G. Urry, *Angew. Chem.*, **70**, 379 (1958).
(17) Melting points and boiling points are uncorrected.
(18) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1807 (1961).
(19) A. Wohl, *Chem. Ber.*, **43**, 3474 (1910).
(20) J. B. Cohen and H. S. de Pennington, *J. Chem. Soc.*, **113**, 57 (1918).
(21) J. J. Monagle, J. V. Mengenhauser, and D. A. Jones, Jr., *J. Org. Chem.*, **32**, 2477 (1967).
(22) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **78**, 815 (1959).
(23) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

Isomeric 3-Carboxy-1,4-thiazane S-Oxides

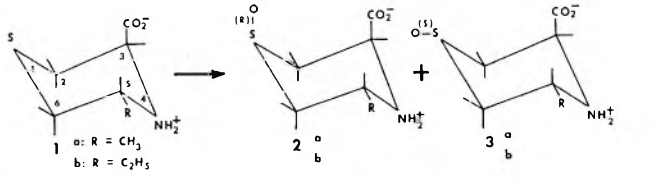
J. F. CARSON, LOIS M. BOGGS, and ROBERT E. LUNDIN

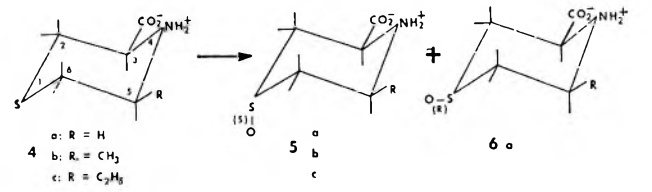
Western Regional Research Laboratory,[1] Albany, California 94710

Received July 11, 1969

3-(*R*)-Carboxy-5-(*R*)-methyl-1,4-thiazane S-(*S*)-oxide (**3a**) and the ethyl homolog **3b**, isomers of the corresponding *R* sulfoxides **2a** and **2b**, have been prepared. An isomer of chondrine (**5a**) with the sulfoxide in the opposite configuration (**6a**) has also been obtained. Nmr and infrared spectra of the new isomers are generally consistent with conformations with sulfoxide equatorial, but abnormally high *gauche* coupling constants for **3a** and **3b** (equatorial sulfoxides) suggest a probable highly puckered chair form for these compounds.

In previous investigations, the 3-carboxy-1,4-thiazane S-oxides (axial) (**2a** and **2b**) have been obtained from the cyclization of the corresponding 1-propenyl-[2] and 1-butenyl-L-cysteine S-oxides.[3] Chondrine[4] (**5a**) was also prepared by oxidation of the corresponding sulfide **4a**. We now report the preparation of the corresponding diastereomers with opposite configuration at sulfoxide **3a**, **3b**, and **6a**. The conformations of the three new sulfoxides were established by nmr.





Reduction of the previously prepared sulfoxide **2a** (R = CH_3) to sulfide **1a** and reoxidation yielded a mixture of the original **2a**, $[\alpha]^{26}D$ −113° (water), as the less soluble isomer and the new sulfoxide **3a**, $[\alpha]^{26}D$ −25.6° (water). Similarly, sulfide **1b** (R = C_2H_5) yielded on oxidation a mixture of **2b**, $[\alpha]^{27}D$ −101° (water), as the less soluble isomer and the new isomer **3b**, $[\alpha]^{27}D$ −28.7° (water). Reduced chondrine **4a** (R = H) on oxidation yielded chondrine (**5a**), $[\alpha]^{25}D$ +20.0° (water), and the new isomer **6a**, $[\alpha]^{25}D$ −55.1° (water).

The conformations of asymmetric centers and the conformation in the solid state of **5b** (cycloalliin)[5] and of **2a**[6] are known from X-ray analysis. The configurations of all asymmetric centers of the corresponding ethyl homologs **5c** and **2b** have been established by optical rotation and chemical correlation with **5b** and **2a**.[3]

The conformation of chondrine (**5a**) has recently been established from X-ray analysis.[6] The new sulfoxides **3a** and **3b** are *S* therefore at sulfoxide and the isomer **6a** of chondrine is *R* at this center. Since many cyclic sulfoxides have been shown to be thermodynamically more stable in the axial than in the equatorial conformation,[7,8] it was necessary to establish the conformations of the new isomers.

Table I gives nmr data for the pairs of isomers **2a** and **3a**, **2b** and **3b**, and **5a** and **6a** and also for cycloalliin (**5b**) (R = CH_3) and its ethyl homolog **5c** (R = ethyl). Figures 1 and 2 show the nmr spectra of **2a** and **3a**. The spectra were measured at 100 MHz in D_2O–*t* BuOH (internal standard) and because of the unusual values for some of the coupling constants, ABX calculations to improve the parameters were applied wherever possible. The accuracy of the values for the coupling constants for the six ring protons in the most critical case **3a** may be judged by calculations of parameter ratios and comparison with previously published data.[9]

The coupling constants of the ring protons of **3a** calculated from two ABX systems are $J_{5,6}$ = 3.1 (*ae*) and 8.6 Hz (*aa*), $J_{6,6'}$ = 13.5 Hz (*gem*), $J_{2,3}$ = 3.4 (*ae*) and 7.4 Hz (*ee*), and $J_{2,2'}$ = 13.9 Hz (*gem*). These values, although anomalous, are more consistent with a conformation with the sulfoxide equatorial, as shown in **3a**, than with the inverted chair conformation: $J_{5,6}$ = 8.6 Hz (*aa*) is rather small and $J_{2,3}$ = 7.4 Hz (*ee*) is abnormally large when compared with the corresponding coupling constants of the isomeric axial sulfoxide **2a**. On the other hand, inversion of the ring of **3a** to the opposite chair conformation with sulfoxide and methyl both axial and carboxyl equatorial would yield far more improbable assignments, $J_{2,3}$ = 3.4 (*aa*) and 7.4 Hz (*ae*), to be compared with cycloalliin (**5b**), differing only in the configuration of C_5 with $J_{2,3}$ = 12.9 (*aa*) and 2.8 Hz (*ae*). The unusually large effect of the equatorial sulfoxide on the coupling constants of the 2 and 3 protons may be rationalized by assuming a highly puckered chair form. The possibility that in solution two opposite interconvertible chair forms exist in equilibrium seems unlikely, since the coupling constants do not change significantly with temperature. Thus $J_{2,3}$ (*ee*) has the values 7.4, 7.6, and 7.6 Hz in D_2O at 31, 70, and 95°, respectively. Compound **3b** similarly

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **31**, 2862 (1966).

(3) J. F. Carson, R. E. Lundin, and L. M. Boggs, *ibid.*, **34**, 1996 (1969).

(4) J. F. Carson and F. F. Wong, *ibid.*, **29**, 2203 (1964).

(5) K. J. Palmer and K. S. Lee, *Acta Crystallogr.*, **20**, 790 (1966).

(6) K. J. Palmer and K. S. Lee, unpublished data.

(7) J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, **86**, 2936 (1964).

(8) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 1109 (1965).

(9) The criteria for the validity of the ABX approximation of an ABC system follow: I $(\nu_C - \nu_A) + {}^1/_2(\mp J_{AB} \pm J_{BC}) \gg J_{AB}/2$; II $(\nu_C - \nu_B) + {}^1/_2(\pm J_{AB} \pm J_{AC}) \gg J_{BC}/2$.

Calculation of the ratios of left side to right side of the inequalities gives for the 2,3 protons of **3a** for I, 70.5 and 74.4, and for II, 21.2 and 24.1. For the 5,6 protons, the ratios are I, 21.0 and 23.4, and II, 37.3 and 40.4.

These are to be compared with nmr analysis of C. A. Reilly and J. D. Swalen [*J. Chem. Phys.*, **32**, 1378 (1960)] of styrene epoxide. An ABX analysis of the spectrum gave J_{AB} = 5.66, J_{AC} = 2.42, and J_{BC} = 4.10 Hz. An iterative computer procedure changed these constants only slightly to J_{AB} = 5.65, J_{AC} = 2.49, and J_{BC} = 4.04 Hz. The corresponding parameter ratios in the latter case, however, were smaller than ours for the 2,3 protons of **3a**, namely I, 34.4 and 36.1, and II, 15.0 and 16.6.

TABLE I

NMR SPECTRAL DATA[a] FOR 3-CARBOXY-1,4-THIAZANE S-OXIDES IN D_2O–*t*-BuOH AT 31°

Compd		H-6 (*a*)	H-6 (*e*)	H-5	H-2 (*a*)	H-2 (*e*)	H-3
2a R = CH_3 Ax S–O	δ'[b]	q, 1.82	d of t, 2.06	m, 3.20	q,[c] 2.00	d[c] of q, 2.50	t,[c] 3.06
	J[d]	$J_{6,6'}$ = 15.0 (*gem*)	$J_{6,6'}$ = 14.0 (*gem*)		$J_{2,2'}$ = 15.3 (*gem*)	$J_{2,2'}$ = 15.3 (*gem*)	$J_{2,3}$ = 3.8 (*ee*)
		$J_{5,6}$ = 10.8 (*aa*)	$J_{5,6}$ = 2.6 (*ae*)		$J_{2,3}$ = 5.3 (*ae*)	$J_{2,3}$ = 3.8 (*ee*)	$J_{2,3}$ = 5.3 (*ae*)
			$J_{2,6}$ = 2.6 (lr)			$J_{2,6}$ = 2.1 (lr)	
3a R = CH_3 Eq S–O	δ'	q,[c] 1.83	q[c] and d,[c] 2.19	m,[c] 2.79	q,[c] 2.08	q[c] of d, 2.46	q,[c] 3.30
	J	$J_{6,6'}$ = 13.5 (*gem*)	$J_{6,6'}$ = 13.5 (*gem*)	$J_{5,6}$ = 8.6 (*aa*)	$J_{2,2'}$ = 13.9 (*gem*)	$J_{2,2'}$ = 13.9 (*gem*)	$J_{2,3}$ = 7.4 (*ee*)
		$J_{5,6}$ = 8.6 (*aa*)	$J_{5,6}$ = 3.1 (*ae*)	$J_{5,6}$ = 3.1 (*ae*)	$J_{2,3}$ = 3.4 (*ae*)	$J_{2,3}$ = 3.4 (*ea*)	
			$J_{6,2}$ = 2.0 (lr)	J_{5,CH_3} = 7.0		$J_{2,6}$ = 2.0 (lr)	
2b R = C_2H_5 Ax S–O	δ'	q, 1.82	d of t, 2.13	m, 3.10	q,[c] 2.03	d[c] of q, 2.56	q,[c] 3.06
	J	$J_{6,6'}$ = 15.5 (*gem*)	$J_{6,6'}$ = 15.0 (*gem*)		$J_{2,2'}$ = 15.3 (*gem*)	$J_{2,2'}$ = 15.3 (*gem*)	$J_{2,3}$ = 4.2 (*ee*)
		$J_{5,6}$ = 11.5 (*aa*)	$J_{5,6}$ = 2.5 (*ae*)		$J_{2,3}$ = 5.8 (*ae*)	$J_{2,3}$ = 4.2 (*ee*)	$J_{2,3}$ = 5.8 (*ae*)
			$J_{2,6}$ = 2.5 (lr)			$J_{2,6}$ = 2.5 (lr)	
3b R = C_2H_5 Eq S–O	δ'	q,[c] 1.81	d[c] of q, 2.30	m,[c] 2.56	q,[c] 2.09	q,[c] 2.48	q,[c] 3.28
	J	$J_{6,6'}$ = 13.8 (*gem*)	$J_{6,6'}$ = 13.8 (*gem*)	$J_{5,6}$ = 9.6 (*aa*)	$J_{2,2'}$ = 13.5 (*gem*)	$J_{2,2'}$ = 13.5 (*gem*)	$J_{2,3}$ = 6.9 (*ee*)
		$J_{5,6}$ = 9.6 (*aa*)	$J_{5,6}$ = 2.9 (*ae*)	$J_{5,6}$ = 2.9 (*ae*)	$J_{2,3}$ = 3.9 (*ae*)	$J_{2,3}$ = 6.9 (*ee*)	$J_{2,3}$ = 3.9 (*ae*)
			$J_{6,2}$ = 2.0 (lr)			$J_{2,6}$ = (ur)	
5b R = CH_3 Ax S–O	δ'	q,[c] 1.63	d[c] of t, 2.10	m,[c] 2.79	q,[c] 1.79	d[c] of t, 2.37	q,[c] 3.08
	J	$J_{6,6'}$ = 15.3 (*gem*)	$J_{6,6'}$ = 15.3 (*gem*)	$J_{5,6}$ = 12.5 (*aa*)	$J_{2,2'}$ = 14.7 (*gem*)	$J_{2,2'}$ = 14.7 (*gem*)	$J_{2,3}$ = 12.9 (*aa*)
		$J_{5,6}$ = 12.5 (*aa*)	$J_{5,6}$ = 2.4 (*ae*)	$J_{5,6}$ = 2.4 (*ae*)	$J_{2,3}$ = 12.9 (*aa*)	$J_{2,3}$ = 2.8 (*ae*)	$J_{2,3}$ = 2.8 (*ae*)
			$J_{6,2}$ = 2.7 (lr)	J_{5,CH_3} = 6.9		$J_{2,6}$ = 2.5 (lr)	
5c R = C_2H_5 Ax S–O	δ'	q, 1.57	d of t, 2.18	m, 2.5–2.7	q,[c] 1.81	d[c] of t, 2.37	q,[c] 3.08
	J	$J_{6,6'}$ = 15.0 (*gem*)	$J_{6,6'}$ = 15.0 (*gem*)		$J_{2,2'}$ = 14.6 (*gem*)	$J_{2,2'}$ = 14.6 (*gem*)	$J_{2,3}$ = 13.3 (*aa*)
		$J_{5,6}$ = 12.5 (*aa*)	$J_{5,6}$ = 2.7 (*ae*)		$J_{2,3}$ = 13.3 (*aa*)	$J_{2,3}$ = 2.6 (*ae*)	$J_{2,3}$ = 2.6 (*ae*)
			$J_{6,2}$ = 2.7 (lr)			$J_{2,6}$ = 2.7 (lr)	
5a R = H Ax S–O							q, 3.07
							$\Sigma J_{2,3}$ = 15.3
6a R = H Eq S–O							q, 2.91
							$\Sigma J_{2,3}$ = 13.0

[a] Obtained at 100 MHz. [b] Chemical shifts are in parts per million downfield from *t*-BuOH: d = doublet; d of t = doublet of triplets; d of q = doublet of quartets; t = triplet; q = quartet; m = multiplet; lr = long range, ur = unresolved. [c] Calculated by the ABX approximation. All other parameters are first order. Coupling constants are presented as absolute values. [d] Coupling constants are in hertz.

has a high coupling constant, $J_{2,3}$ (*ee*) = 6.9 Hz, but the data are again more consistent with a conformation with the sulfoxide equatorial. In the nmr spectra of **5a** and **6a**, only the H-3 resonances could be identified. The outer line spacings of the two quartets, 15.3 and 13.0 Hz, which are equal to $\Sigma J_{2,3}$ in an ABX approximation, require a diaxial relation in each case in agreement with the assigned conformations.

Table II shows the sums $\Sigma J_{2,3}$ and $\Sigma J_{5,6}$ of the ABX

TABLE II

Compd	R	S–O	$\Sigma J_{2,3}$	$\Sigma J_{5,6}$
2a	CH_3	Ax	9.1 (no diax)	16.6 (diax)
3a	CH_3	Eq	10.8 (no diax)	11.7 (diax)
2b	C_2H_5	Ax	10.0 (no diax)	14.0 (diax)
3b	C_2H_5	Eq	10.8 (no diax)	12.5 (diax)
5b	CH_3	Ax	15.7 (diax)	14.9 (diax)
5c	C_2H_5	Ax	15.9 (diax)	15.2 (diax)
5a	H	Ax	15.3 (diax)	
6a	H	Eq	13.0 (diax)	

systems of the eight compounds. In particular, **3a** (R = CH_3, equatorial SO) has $\Sigma J_{2,3}$ = 10.8 (diaxial relation absent) and $\Sigma J_{5,6}$ = 11.7 Hz (diaxial relation) and **3b** (R = C_2H_5, equatorial SO) has $\Sigma J_{2,3}$ = 10.8 (no diaxial relation) and $\Sigma J_{5,6}$ = 12.5 Hz (diaxial relation). The near equality of these values suggests the need of caution in using this sum as a criterion of diaxial or nondiaxial relations in the absence of additional information. The nmr spectra show long-range coupling of the order of 2.0–2.7 Hz between the equatorial 2 and 6 protons. This phenomenon has been observed before, not only with cyclic sulfoxides but with the corresponding sulfides.[10]

Physical methods have been developed for distinguishing axial from equatorial sulfoxides, including relative proton chemical shifts and vicinal geminal coupling constants in nmr and shifts in the ir sulfoxide stretching frequencies. It was of interest to determine whether any of these methods would be applicable to a molecule with two heteroatoms further complicated by the presence of two charged groups. In a number of cases, it has been shown that a proton in a *syn* axial position with respect to an axial sulfoxide is more deshielded than a proton in the same position with an equatorial sulfoxide.[11] Compound **2a** (axial sulfoxide) has H-5 (*syn*-axial) at δ' 3.20 ppm, and **3a** (equatorial sulfoxide) has H-5 (axial) at δ' 2.79 ppm. Similarly, **2b** (axial sulfoxide) has H-5 (*syn*-axial) at δ' 3.10 ppm, and the isomeric **3b** (equatorial sulfoxide) has δ' 2.56 ppm for H-5. The greater downfield shift of H-5 in the axial sulfoxides than in the corresponding equatorial sulfoxides shows that the *syn*-axial effect applies to these two cases.

Lambert and Keske,[12] in studies of the low-temperature nmr spectra of thiane S-oxides, showed that the difference in chemical shifts of the α geminal protons [Δ_{ae} (α)] was greater for the equatorial sulfoxide

(10) (a) Y. Allingham, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **24**, 1989 (1968); (b) A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 1086 (1968).

(11) (a) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *ibid.*, 759 (1966); (b) A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 881 (1967).

(12) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

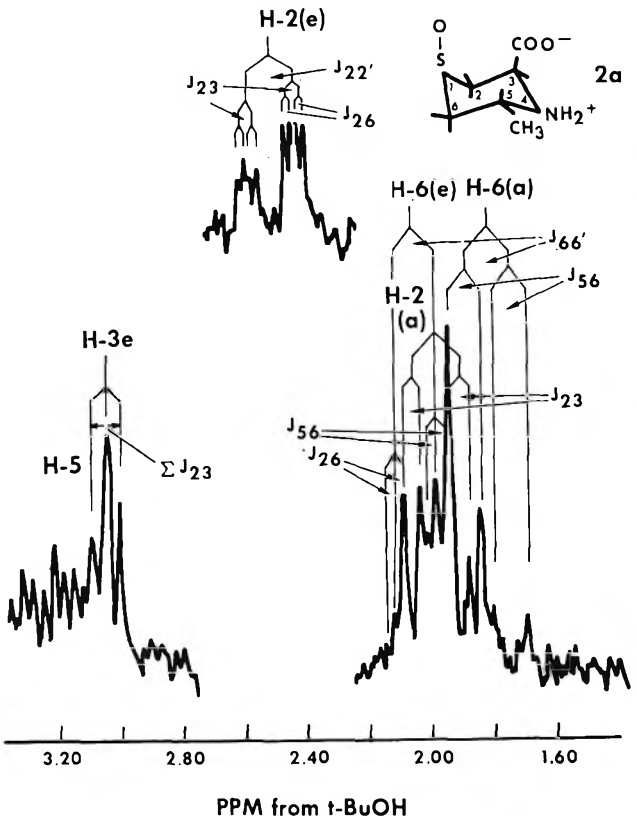


Figure 1.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*R*)-methyl-1,4-thiazane S-(*R*)-oxide in D_2O (*t*-BuON internal standard).

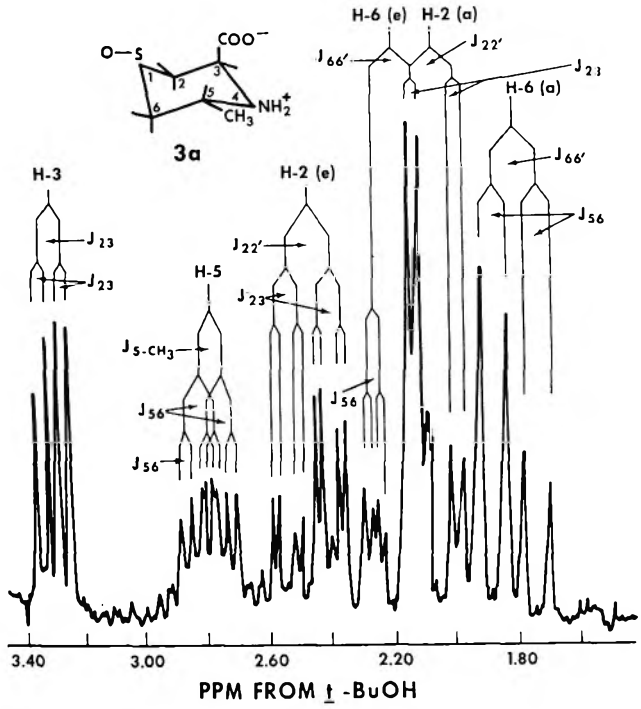


Figure 2.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*R*)-methyl-1,4-thiazane S-(*S*)-oxide in D_2O (*t*-BuOH internal standard).

(axial lone pair) (0.87 ppm) than for an axial sulfoxide (equatorial lone pair) (0.48 ppm). For the H-2 geminal protons of the axial sulfoxides **2a** and **2b**, Δae = 0.50 and 0.53 ppm, respectively, while for the corresponding protons of the equatorial sulfoxides **3a** and **3b**, Δae = 0.38 and 0.39 ppm. The geminal shift differences for the 2 protons on the carboxyl side of the ring are small and opposite to the observations of Lambert and Keske for simple 1,4-thiane oxides. On the other hand, for the H-6 geminal protons of **2a** and **2b**, Δae = 0.24 and 0.31 ppm, while for **3a** and **3b** Δae = 0.36 and 0.49 ppm, respectively. The differences are again small but now agree qualitatively with Lambert and Keske's observations.

Lambert and Keske[12] and Foster, *et al.*,[10b] have observed that vicinal geminal coupling constants for an axial sulfoxide are generally larger in absolute value (larger negative values) than for the corresponding equatorial sulfoxides. Geminal coupling constants shown in Table I are in agreement with this rule. The axial sulfoxides **2a**, **2b**, **5b**, and **5c** have $J_{2,2'}$ and $J_{6,6'}$ in the range 14.5–15.3 Hz. For the equatorial sulfoxides **3a** and **3b**, $J_{2,2'}$ and $J_{6,6'}$ are in the range 13.5–13.9 Hz. The differences are more significant if one compares corresponding J (*gem*) for the isomeric pairs **2a** and **3a** and **2b** and **3b**. For **2a** (axial $J_{2,2'}$ = 15.3 and $J_{6,6'}$ = 14.5 Hz. For **3a** (equatorial) $J_{2,2'}$ = 13.9 and $J_{6,6'}$ = 13.5 Hz. For **2b** (axial) $J_{2,2'}$ = 15.3 and $J_{6,6'}$ = 15.2 Hz. For **3b** (equatorial) the corresponding values are 13.5 and 13.8 Hz, respectively.

In the infrared, the stretching frequencies for equatorial sulfoxides are generally higher than for axial sulfoxides.[13] Our sulfoxides are in general agreement with this rule. In the ir (KBr disk), **2a** (axial) has bands at 1025 (weak) and 1040 cm^{-1} (strong), while the equatorial isomer **3a** has absorption at 1055 cm^{-1}. For the ethyl homologs, **2b** (axial) has absorption at 1025 cm^{-1} and the corresponding equatorial isomer **3b** has bands at 1050 and 1060 cm^{-1}. Chondrine (**5a**) has two bands, 1030 and 1040 cm^{-1}, while its equatorial isomer **6a** has the S–O stretching frequency at 1055 cm^{-1}. The two axial sulfoxides, cycloalliin (**5b**) and its ethyl homolog **5c**, have sulfoxide absorption at 1035 cm^{-1}.

Johnson and McCants[8] have observed that in the oxidation of 4-substituted thianes, a preferential formation of axial or equatorial sulfoxide depends on the oxidizing agent. This relationship has been used as supporting evidence for assigning conformations of cyclic sulfoxides.[11b,13b] In particular, sodium metaperiodate favors the formation of the axial sulfoxide, and hydrogen peroxide in acetic acid tends to yield more equatorial sulfoxide.[8] With three of our compounds no discrimination could be detected with these reagents. Oxidation of **4b** (R = CH_3) and **4c** (R = C_2H_5) with either hydrogen peroxide in acetic acid or with aqueous sodium metaperiodate gave exclusively the axial *S* sulfoxides **5b** and **5c**. Compound **4a** (R = H) with aqueous sodium metaperiodate yielded 83% axial sulfoxide **5a** and 17% of the equatorial isomer **6a**. This ratio was unchanged when hydrogen peroxide–acetic acid was the oxidant. The sulfides **1a** and **1b**, on oxidation with hydrogen peroxide in acetic acid, each gave approximately equal amounts of equatorial and axial isomers. Apparently, for obscure reasons, the sulfoxides with an equatorial carboxyl are formed predominately as axial isomers, and with an equatorial methyl or ethyl at C-5 (*S*), only axial isomers are formed.

(13) (a) P. B. D. de la Mare, D. J. Millen, J. G. Tillett, and D. Watson, *J. Chem. Soc.*, 1619 (1963); (b) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Commun.*, 550 (1967).

However, the sulfoxides with carboxyl axial and with the methyl or ethyl group at C-5 still equatorial but now of *R* configuration are formed, at least with hydrogen peroxide, with no preference for axial or equatorial sulfoxide.

Experimental Section[14]

Oxidation of Deoxycycloalliin (4b to 5b) with Hydrogen Peroxide in Acetic Acid.—To a suspension of 3.787 g (0.0192 mol) of **4b** hydrochloride in 350 ml of acetic acid there was added 2.30 ml of 32.9% hydrogen peroxide (15% excess) over a period of 6 hr at 13–15°. The suspension was then stirred for 20 hr at 25°. Removal of acetic acid *in vacuo* and fractional crystallization from 3 *N* hydrochloric acid gave three fractions (combined yield 86.3%) of **5b**, all with $[\alpha]^{25}D$ in water varying from −12.0 to −12.2. Data for authentic cycloalliin hydrochloride hydrate follow: $[\alpha]^{25}D$ −11.7° (water); ir (identical with authentic compound) 1750 (COOH) and 1035 cm^{-1} (S–O).

Oxidation of **4b** as the free amino acid and fractional crystallization of the sulfoxide as the free base also gave fractions with a constant rotation (combined yield 85%).

Oxidation of 4b with Aqueous Sodium Metaperiodate.—To a solution of 4.29 g (0.0217 mol) of **4b** hydrochloride in 150 ml of water, adjusted to pH 7 with sodium bicarbonate and cooled to 0°, 50 ml of 0.491 *M* sodium metaperiodate was added in 10-ml portions over a period of 4 hr. The suspension was kept in the refrigerator overnight and excess periodate was destroyed by the addition of 5 ml of dimethyl sulfide followed by stirring for 8 hr at 0°. The mixture was poured through a column of Dowex 50 (H^+) (400 cm^3) and precipitated iodine was removed by washing with ethanol and then water. The product was eluted with 1.5 *N* ammonium hydroxide and fractionally crystallized as the free base from aqueous ethanol. Three fractions were obtained (81%), with $[\alpha]^{25}D$ (water) varying from −14.3 to −14.7°. For authentic cycloalliin, the $[\alpha]^{26}D$ value is −14.8° (water).

Attempted epimerization of cycloalliin by the procedure of Barnsley, *et al.*,[15] which was effective for N-acetyl-S-ethyl-L-cysteine sulfoxide, failed. A solution of 1.035 g of cycloalliin in 50 ml of formic acid (88%), after 17 days at 25° and 48 hr at 55°, showed only slight rotational change owing to slight decomposition. The isolated product showed no change in specific rotation. A solution of cycloalliin in 5 *N* hydrochloric acid gradually decomposes at room temperature, but no evidence of racemization at the sulfoxide can be obtained.

Oxidation of 4c to 5c with Hydrogen Peroxide.—A solution of 1.03 g (0.00589 mol) of **4c** in 100 ml of acetic acid was oxidized with 0.85 ml of 30% hydrogen peroxide as in the preparation of cycloalliin to yield 791 mg (70%) of **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane S-(*S*)-oxide (5c)**, $[\alpha]^{26}D$ −22.0° (*c* 3, 2.5 *N* hydrochloric acid), identical with the product previously obtained[3] by cyclization of butenyl cysteine sulfoxide. Fractional crystallization as the free base or as the hydrochloride showed no significant variation in rotation: ir (free base) 1635 cm^{-1} (COO^-) and 1030 cm^{-1} (S–O); ir (hydrochloride) 1740 (COOH) and 1020 and 1035 cm^{-1} (S–O).

(14) Infrared spectra were determined as potassium bromide disks in a Perkin-Elmer Model 237 spectrophotometer. All nmr spectra were taken on a Varian Associates HR-100 spectrometer to which had been added an internal field-frequency lock built at this laboratory. Reference to a company or product name does not imply approval or recommendation by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

(15) E. A. Barnsley, A. E. R. Thomson, and L. Young, *Biochem. J.*, **90**, 588 (1964).

Oxidation of Deoxychondrine (4a) to Chondrine (5a) and Isomer 6a.—A suspension of 3.829 g (0.0260 mol) of **4a** in 175 ml of acetic acid was oxidized with 3.4 ml of 33% hydrogen peroxide by the procedure previously described.[16] The yield of crystalline product was 4.10 g (97%), $[\alpha]^{26}D$ +8.3°. Repeated crystallization from aqueous ethanol yielded 296 mg of chondrine (**5a**) as prisms, $[\alpha]^{27}D$ +20.0° (*c* 2.0, water), identical with chondrine previously prepared[3] by ir and $[\alpha]D$: ir 1635 and 1675 (COO^-) and 1030 and 1040 cm^{-1} (S–O).

From the mother liquor there was obtained, by many recrystallizations from aqueous methanol, 132 mg as needles or blades of **3-(*R*)-carboxy-1,4-thiazane S-(*R*)-oxide**, $[\alpha]^{27}D$ −55.1° (*c* 2, water), ir 1610 (COO^-) and 1055 cm^{-1} (S–O).

Anal. Calcd for $C_5H_9NO_3S$: C, 36.81; H, 5.52. Found: C, 36.5; H, 5.64.

The calculated proportion of isomers was 84.4% axial isomer and 15.6% equatorial isomer.

Oxidation of **4a** with sodium metaperiodate as described in the preparations of cycloalliin yielded 84% sulfoxide calculated to be 83.2% axial and 16.8% equatorial.

Oxidation of 1a to 2a and 3a.—Oxidation of 1.412 g (0.00876 mol) of **1a** with hydrogen peroxide in acetic acid as previously described yielded, on crystallization from water, 583 mg, $[\alpha]^{26}D$ −106.2° (water). Recrystallization from water yielded 450 mg of pure **3-(*R*)-carboxy-5-(*R*)-methyl-1,4-thiazane S-(*R*)-oxide (2a)** as prisms, $[\alpha]^{26}D$ −113° (*c* 0.9, water), identical with the previously prepared compound by $[\alpha]D$ and ir: 1600 and 1630 (COO^-) and 1025 and 1040 cm^{-1} (S–O).

From the mother liquor by recrystallization from aqueous acetone, there was obtained 270 mg (blades) of **3-(*R*)-carboxy-5(*R*)-methyl-1,4-thiazane S-(*S*)-oxide (3a)**, $[\alpha]^{27}D$ −25.6° (*c* 2, water), ir 1620 (COO^-) and 1055 cm^{-1} (S–O).

Anal. Calcd for $C_6H_{11}NSO_3$: C, 40.66; H, 6.26. Found: C, 40.6; H, 6.14.

The yield of mixed isomers was 1.357 g (87.5%), calculated to contain 48% axial (*R*) sulfoxide and 52% equatorial (*S*) sulfoxide.

Oxidation of 1b to 2b and 3b.—A solution of 1.578 g (0.00902 mol) of **1b** in 130 ml of acetic acid and 20 ml of water was oxidized with hydrogen peroxide as already described to yield 1.54 g of mixed sulfoxides (89.3%). Crystallization from water yielded 666 mg of **2b**, and recrystallization of this fraction yielded 590 mg (prisms) of **3-(*R*)-carboxy-5(*R*)-ethyl-1,4-thiazane S-(*R*)-oxide (2b)**, $[\alpha]^{27}D$ −100.9° (*c* 1.1, water), identical by $[\alpha]D$ and ir with the previously prepared sulfoxide, **2b**: ir 1645 (COO^-) and 1025 cm^{-1} (S–O).

The more soluble fractions from the mother liquor were recrystallized from aqueous ethanol to yield 290 mg of **3-(*R*)-carboxy-5(*R*)-ethyl-1,4-thiazane S-(*S*)-oxide (3b)**, $[\alpha]^{25}D$ −24.7° (*c* 2, water), ir 1600 (COO^-) and 1050 and 1060 cm^{-1} (S–O).

Anal. Calcd for $C_7H_{13}NO_3$: C, 43.96; H, 6.85; N, 7.32. Found: C, 44.0; H, 6.74; N, 7.30.

Registry No.—**2a**, 7762-85-8; **2b**, 19206-39-4; **3a**, 23652-72-4; **3b**, 23652-73-5; **5a**, 23652-74-6; **5b**, 23652-75-7; **5c**, 19206-37-2; **6a**, 23652-77-9.

Acknowledgment.—We are grateful to L. M. White and Geraldine Secor for elemental analyses and to Nancy Bennett for assistance with nmr spectra.

(16) Reference 4 contains an error in the Experimental Section, p 2205. Under the heading "(+)-L-1,4-Thiazane-3-carboxylic acid 1-Oxide (Chondrine, IV)," the quantity 1.2 ml of 30% hydrogen peroxide should be 2.1 ml of 30% hydrogen peroxide.

The Aluminum Alkoxide Rearrangement of Epoxides. II.[1] Rearrangement of 3,4-Epoxy-*cis*- and -*trans*-*p*-menthane

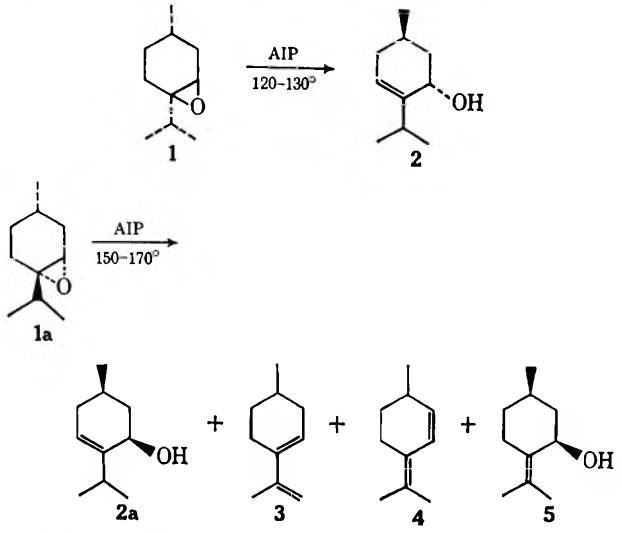
E. H. ESCHINASI

Givaudan Corporation, Clifton, New Jersey 07014

Received June 10, 1969

The aluminum isopropoxide (AIP) catalytic rearrangement of 3,4-epoxy-*cis*-*p*-menthane (1) at *ca.* 120° affords *trans*-3-*p*-menthen-5-ol (2) in almost quantitative yield, whereas the rearrangement of 3,4-epoxy-*trans*-*p*-menthane (1a) requires more drastic conditions and 1a is only partially converted into a mixture of *cis*-3-*p*-menthen-5-ol (2a), traces of *cis*-pulegol (5), and substantial amounts of 3,8- and 2,4(8)-*p*-menthadiene (3 and 4). The last three components were among the typical products reported by us in the AIP reduction of pulegone. A mechanism accounting for the facile AIP rearrangement of 3,4-epoxy-*cis*-*p*-menthane (1) is suggested.

A review of the stereoselectivity of the AIP rearrangement of 3,4-epoxy-*p*-menthanes, reported by us,[1] has disclosed that the *cis* isomer (1) reacts rapidly at *ca.* 120–130° to yield, almost exclusively, the predicted *trans*-3-*p*-menthen-5-ol (2). The cleavage of the epoxide occurs at the site of the most substituted α carbon of the oxirane oxygen accompanied by β-proton elimination from the least substituted carbon at C_5. Under the same conditions, 3,4-epoxy-*trans*-*p*-menthane (**1a**) was recovered almost unchanged. At higher temperature (150–170°), however, **1a** afforded as the major product *cis*-3-*p*-menthen-5-ol (**2a**), traces of *cis*-pulegol (**5**), and substantial amounts of 3,8- and 2,4(8)-*p*-menthadiene (**3** and **4**, respectively).



The presence of **3** and **4** could be rationalized as the dehydration products of *cis*-pulegol (**5**), which was shown to allylomerize to 3-*p*-menthen-8-ol (**6**) in the presence of AIP above 100°.[2]

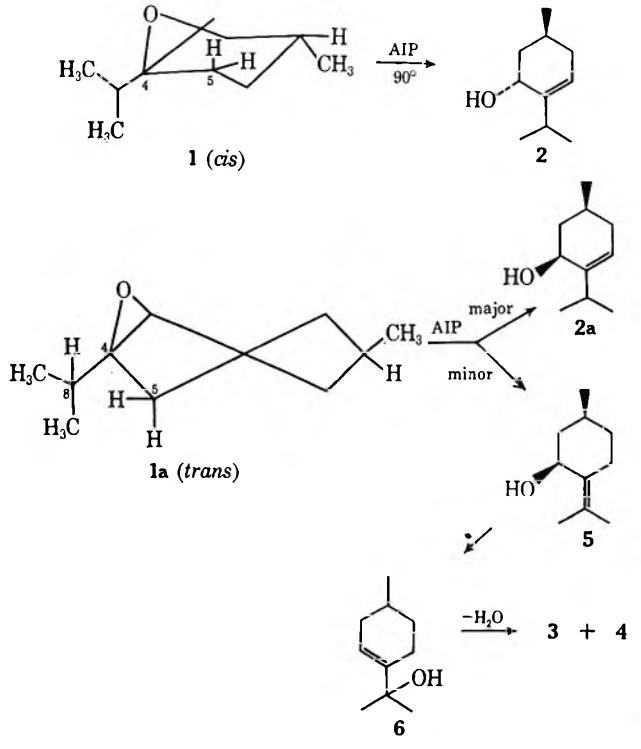
The hydrogenation of *cis*-3-*p*-menthen-5-ol (**2a**) in the presence of Pd–C catalyst afforded almost exclusively menthol, whereas that of *trans*-3-*p*-menthen-5-ol (**2**) afforded isomenthol as the major product. Both **2** and **2a** were identified with the reduction products of 3-*p*-menthen-5-one with lithium aluminum hydride and AIP, respectively.

Results and Discussion

The electrophilic attack of AIP on 3,4-epoxy-*cis*-*p*-menthane (**1**) results, as predicted,[1] in a cleavage of the oxirane oxygen bond at the most substituted α carbon accompanied by β-proton elimination from the least substituted carbon to yield *trans*-3-*p*-menthen-5-ol (**2**).

An examination of the molecular model of the *cis* isomer **1**, which is best represented by a twisted chair, shows that one of the C_5–H bonds in an α position to the oxirane oxygen lies parallel to the C_4–O bond of the oxirane, thus favoring β-proton elimination leading to the concerted formation of *trans*-3-*p*-menthen-5-ol (**2**).

Such a favorable conformation is not prevalent in the *trans* isomer **1a**, and more drastic conditions are required for the formation of *cis*-3-*p*-menthen-5-ol (**2a**). Under these conditions, a small amount of β deprotonation from the C_8–H bond affords, as an alternative, minor amounts of *cis*-pulegol (**5**), which was shown[2] to allylomerize to 3-*p*-menthen-8-ol (**6**) and dehydrate to **3** and **4**.



Steric factors may also account for the facile rearrangement of **1**, since the latter is rapidly converted into isomenthol by hydrogenation in the presence of Raney nickel catalyst, while the *trans* isomer **1a** is recovered unchanged.[3]

(1) Part I: E. H. Eschinasi, *Israel J. Chem.*, **6**, 713 (1968).
(2) E. H. Eschinasi, *J. Org. Chem.*, in press.
(3) E. H. Eschinasi, U. S. Patent 3,052,729 (1962).

TABLE I

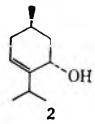
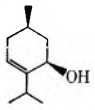
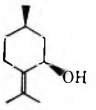
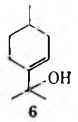
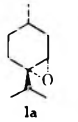
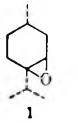
Temp, °C	3, %	4, %	1,[a] %	1a[a] %	X,[b] %	2, %	2a, %	5, %
25			48%	52				
100–125				46		49	>2	
155–165	7	4		15	4	53	17	
170	9	5		7	9	53	12	1
Cut 1	10	6		9	10	53	12	
Cut 2					3	55	39	3

[a] Vpc analysis of epoxide made on 10% 2,4-xyler.yl phosphate, 4 m × 0.125 in. column, accuracy ±5%. [b] X, 3-*p*-menthen-5-one.

AIP rearrangement product (15 g) corresponding to the composition of the 1st step was distilled at a reflux ratio of 200:1 and the following cuts were obtained: (1) 3,4-epoxy-*trans*-*p*-menthane (1a), yield 5 g, bp 86° (22 mm), $n^{20}D$ 1.4445, purity (vpc) 98 ± 5% (2,4-xylenyl phosphate column at 80°) (for nmr and ir spectral data see Table I); (2) pure *trans*-3-*p*-menthen-5-ol (2), yield 6 g, bp 73° (2 mm), $n^{20}D$ 1.4730, which was identified by vpc (20M column at 175°) and ir with the main isomer of the Meerwein-Pondorf-Verley reduction of 3-*p*-menthen-5-one (see Table I). Upon hydrogenation with Pd–C catalyst it afforded a mixture of 25% neomenthol, 60% isomenthol, and, a minor amount of menthol.

TABLE II

NMR[a] AND IR DATA

Compd	Vinylic protons	Protons geminal to OH, etc.	General protons, including allylic, methyl, etc.	Characteristic ir absorption, μ
 2	5.48 (br d, 1, J = 4Hz)	4.06–4.25 (br m, 1)	1.4–2.70 (br m, 7, includes OH) 0.85–1.16 (five-peak m, 9, with *gem*-dimethyl) 0.99–1.10 (d, J = 2 Hz)	8.5, 9.3, 10.3, 10.7, 13
 2a	5.48–5.6 (br, 1)	4.36 (br t, 1, J = 6 Hz)	1.35–2.99 (br m, 7, includes OH) 0.86–1.28 (m, 9, with *gem*-dimethyl) 0.99–1.10 (J = 1 Hz)	7.7, 8.85, 9.65, 10.45, 11.05, 11.7
 5		4.72 (br t, 1, J = 5 Hz)	1.33–1.85 (m, 12, with *gem*-dimethyl) 1.70–1.80 (s)	6.85, 7.9, 9.5, 9.8, 10, 10.25, 12, 13.1, 13.55
 6	5.61–5.86 (br, 1)	In deuterated DMSO, 4.24 (s, tertiary OH proton)	1.12–2.41 (m, 14, with *gem*-dimethyl) 1.31 (s) 0.97 (d, J = 5 Hz, CH_3CH)	6.91, 7.3, 7.4, 8.2, 8.5, 8.7, 8.9, 9, 9.05, 9.15, 11.2, 11.85, 12.32
 1a			2.93 (d, 1, J = 5 Hz, epoxide) 1.13–2.3 (m, 8) 0.72–1.1 (m, 9, methyls)	7.5, 8.65, 9.6, 10.1, 10.2, 10.55, 11.3, 11.7, 12.3, 13.2
 1			2.95 (t, 1, J = 1.5 Hz, epoxide) 1.19–2.32 (m, 8) 0.73–1.12 (m, 9, methyl)	8.1, 8.75, 9.5, 10.8, 11.55, 11.80, 13.05

[a] In δ units on a Varian A-60A spectrometer with TMS as internal standard.

Experimental Section

AIP Rearrangement of *cis*–*trans*-3,4-Epoxy-*p*-menthane (1).—3,4-Epoxy-*p*-menthane (10 g, 90% pure) consisting of a 1:1 mixture of 3,4-epoxy-*cis*- and -*trans*-*p*-menthane (as determined by vpc on a 4 m × 0.125 in. 2,4-xylenyl phosphate column at 80°) was added to a clear solution of 2.5 g of AIP in 10 g of dry isopropyl alcohol (IPA). The clear solution was heated in a small (50 ml) Vigreux flask at 85–90° for 5 min, and 11 g of IPA was collected. Heating was resumed and the pot temperature was gradually raised in three steps to 100 → 125°, 155 → 165°, and 170°. At each step the heating was maintained for 2 min while traces of IPA were distilled off 85–90° vapor temperature). Samples of the reaction mixture were quenched in 3 volumes of 30% NaOH and heated to 50–60° until all the aluminum salt dissolved, and the top organic layer was analyzed by vpc (20M column, 4 m × 0.125 in. at 175°). Finally, the reaction was cooled to 80° and high vacuum was applied to distil off a main cut (1), yield 6 g, bp 60–90° (2 mm), $n^{20}D$ 1.4715. The viscous residue was treated with 20 ml of 30% NaOH heated to 60° under agitation until a clear solution was obtained. The top layer was separated and distilled, yielding a second minor cut (2), yield 1.5 g, bp 80–90° (2 mm), $n^{20}D$ 1.4690.

The course of the reaction is given in Table I (vpc 20M at 175°).

Distillation in Nester–Faust Teflon Spinning-Band Column of AIP Rearrangement Products of 3,4-Epoxy-*cis*-*p*-menthane (1).—AIP rearrangement product (15 g) corresponding to the composition of the 1st step was distilled at a reflux ratio of 200:1 and the following cuts were obtained: (1) 3,4-epoxy-*trans*-*p*-menthane (1a), yield 5 g, bp 86° (22 mm), $n^{20}D$ 1.4445, purity (vpc) 98 ± 5% (2,4-xylenyl phosphate column at 80°) (for nmr and ir spectral data see Table I); (2) pure *trans*-3-*p*-menthen-5-ol (2), yield 6 g, bp 73° (2 mm), $n^{20}D$ 1.4730, which was identified by vpc (20M column at 175°) and ir with the main isomer of the Meerwein-Pondorf-Verley reduction of 3-*p*-menthen-5-one (see Table I). Upon hydrogenation with Pd–C catalyst it afforded a mixture of 25% neomenthol, 60% isomenthol, and, a minor amount of menthol.

Reaction of 3,4-Epoxy-*trans*-*p*-menthane (1a) with AIP.—3,4-Epoxy-*trans*-*p*-menthane (1a), yield 2.5 g, 95% pure, as recovered by Nester–Faust distillation from previous reaction, and 1 g of AIP were gradually heated to 100–155° and 170° within 5 min in a Claisen–Vigreux flask. Vacuum was gradually applied until it reached 2 mm, and 1.7 g, consisting mostly of unreacted epoxide 1a, was collected and showed no evidence of alcohols (by vpc and ir). The residue in the flask was decomposed with 30% NaOH and distilled to yield a second cut of 0.4 g. Vpc analysis of the two cuts showed the following composition: cut 1 (1.7 g), 3% 3, 5% 4, 92% 1a; cut 2 (0.4 g), 2% 3, 3% 4, 37% 1a, 15%[4] 2, 28%[5] 2a, >1% 6, 4% 5.

***cis*-3-*p*-Menthen-5-ol (2a) by Reduction of 3-*p*-Menthen-5-one with $LiAlH_4$.**—3-*p*-Menthen-5-one (8 g) in 20 ml of dry ether were fed within 0.5 hr into 0.6 g of $LiAlH_4$ in 25 ml of dry ether. The reaction mixture was stirred for an additional 0.5 hr and decomposed first with 2 ml of ethanol followed by 20 ml of water. The ether layer was separated and distilled in a Vigreux flask,

(4) The amount of *trans*-3-*p*-menthen-5-ol (2) present is due to a small amount (5–10%) of *cis*-epoxide 1 present in the starting material which could not be evaluated accurately by vpc (2,4-xylenyl phosphate column).

(5) *cis*-3-*p*-Menthen-5-ol (2a) was separated from the mixture by distillation through a Nester–Faust column, bp 80° (2 mm), $n^{20}D$ 1.4735. It was identical with the main reduction product of 3-*p*-menthen-5-one with $LiAlH_4$ (for nmr and ir data see Table II); it gave upon reduction with Pd–C 90% menthol.

yielding 6 g, bp 76–80° (2 mm), n^{20}D 1.4735. Vpc (20M column at 200°) showed the following composition: 6% *trans*-3-*p*-menthen-5-ol (2); 94% *cis*-3-*p*-menthen-5-ol (2a). For nmr and ir spectra see Table I.

***trans*-3-*p*-Menthen-5-ol (2) by Reduction of 3-*p*-Menthen-5-one with AlP (Meerwein–Pondorff–Verley).**[6]—3-*p*-Menthen-5-one (8 g) and 8 g of AlP were heated in a Claisen–Vigreux flask for 5 min at 130–140° while acetone distilled off. Analysis of the reaction product (vpc, 20M column at 200°) showed that 25% of the ketone was reduced, affording a mixture of 60% *trans*-3-*p*-menthen-5-ol (2) and 40% *cis*-3-*p*-menthen-5-ol (2a). The reaction mixture was quenched in 30% NaOH and separated. After boration with 1 g of B_2O_3 at 120–130°, the unreacted ketone (5 g) was recovered by distillation at 95° (5 mm). The borate ester residue was then decomposed with 30% NaOH and afforded 1 g of distillate, bp 80–85° (2 mm), n^{20}D 1.4650, which consisted of a mixture of 2 and 2a in a ratio of 60:40, respectively. The components of the mixture were identified by vpc with those obtained from the $LiAlH_4$ reduction and with pure samples obtained by Nester–Faust distillation of the rearrangement products of 3,4-epoxy-*cis*- and -*trans*-*p*-menthane (1 and 1a). Pure *trans*-3-*p*-menthen-5-ol (2), bp 102–108° (14 mm), n^{20}D 1.4712, has been previously described by Malcolm and Read.[6]

Catalytic Reductions.—The catalytic reductions of the various samples of the allylic alcohols were carried out in a 10% ethanolic solution using 2 g of substance and 0.5 g of catalyst. The hydrogenation was carried out in a Parr shaker at 50 psi hydrogen pressure at 30° and continued until the hydrogen absorption ceased. The results are given below.

cis-Pulegol (5) gave 3% neoisomenthol, 90% menthol, and 8% menthone.

trans-3-*p*-Menthen-5-ol (2) gave 25% neomenthol, 15% menthol, and 60% isomenthol.

cis-3-*p*-Menthen-5-ol (2a) gave 88% menthol and 12% menthones. 3-*p*-Menthen-8-ol (6) gave 60% *trans*-*p*-menthan-8-ol and 40% *cis*-*p*-menthan-8-ol.

α-Terpineol gave 60% *trans*-*p*-menthan-8-ol and 40% *cis*-*p*-menthan-8-ol.

Registry No.—1, 23602-11-1; 1a, 23602-12-2; 2, 22472-77-1; 2a, 22472-78-2; 5, 22472-80-6; 6, 18479-65-7.

(6) D. Malcolm and J. Read, *J. Chem. Soc.*, 1037 (1939).

A New and Useful Sulfur Ylide. Thetin Anions

JEROME ADAMS,[1] LEE HOFFMAN, JR., AND BARRY M. TROST[2]

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

Received September 16, 1969

A procedure for utilization of stabilized sulfur ylides in ketone condensations in good yields is described. The sodium salts of dimethylthetin anion and diphenylthetin anion condense with ketones to produce glycidic acids and with α,β-unsaturated ketones to produce cyclopropanecarboxylic acids. With 4-*t*-butylcyclohexanone, the formed glycidic acid was almost exclusively the *trans* isomer. Thermal decomposition of glycidic acids is known to give aldehydes with loss of CO_2. Thus this method allows easy chain extension by one or two carbon atoms.

The utilization of ylides in organic synthesis has exploded in the last few years. Although phosphorus ylides enjoy the most widespread use, interest into the applications of sulfur ylides to synthetic problems has been stimulated by the work of Corey and coworkers.[3] Utilization of all kinds of stabilized ylides has been hampered by the unreactivity of these synthetic intermediates. One solution to the problem with phosphorus ylides involves the use of a less electronegative phosphorus substituent. The decreased stabilization by phosphorus of the carbanionic center sufficiently enhanced the reactivity of the species to allow normal condensation with most carbonyl partners. A second approach involves reducing the ability of the substituent on carbon to stabilize an adjacent carbanionic center. We have explored this latter alternative to the solution of this problem in the area of sulfur ylides and wish to report our results at this time.

Dimethyl(carbomethoxymethylene)sulfuran (I) has been reported not to add to carbonyl groups of aldehydes and ketones, although its Michael condensation with α,β-unsaturated systems to produce cyclopropanes is well documented.[4,5] Conversion of the carbomethoxy group into a carboxy anion may sufficiently reduce the stabilization of the ylide to allow normal carbonyl condensations. To examine this possibility, the requisite betaines, IIIa[5a] and IIIb, were prepared from the corresponding sulfonium salts, IIa and IIb. Dimethylthetin (IIIa) was obtained by treatment of an aqueous solution of the sulfonium bromide with silver oxide at room temperature;[5a] diphenylthetin (IIIb) was obtained by treatment of the sulfonium fluoroborate with Amberlite resin at 25°. Other attempts to prepare IIIb led only to decomposition products.

Reaction of dimsylsodium with dimethylthetin generated a suspension of the anion in DMSO (see Scheme I). This suspension reacted with chalcone to produce two cyclopropanes in approximately equimolar amounts. Analysis of this mixture proceeded after conversion of the acids into their esters with diazomethane. Nmr allowed unambiguous assignment of stereochemistry to the two compounds. In cyclopropane V,[6] the cyclopropyl hydrogen adjacent to the benzoyl group had couplings to the adjacent protons of 5.0 and 10.0 Hz, the benzylic cyclopropyl hydrogen of 5.0 and 7.0 Hz, and the cyclopropyl hydrogen α to the ester of 7.0 and 10.0 Hz. In cyclopropane

$(CH_3)_2\overset{+}{S}\overset{-}{C}HCO_2CH_3$ (I) $\quad R_2\overset{+}{S}CH_2CO_2R^1\ X^-$ (II) $\quad R_2\overset{+}{S}CH_2CO_2^-$ (III) $\quad R_2\overset{+}{S}\overset{-}{C}HCO_2^-$ (IV)

a, R = CH_3

b, R = Ph

(1) NSF Undergraduate Research Participant, 1969.

(2) Alfred P. Sloan Foundation Fellow.

(3) E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, **89**, 3912 (1967), and references cited therein.

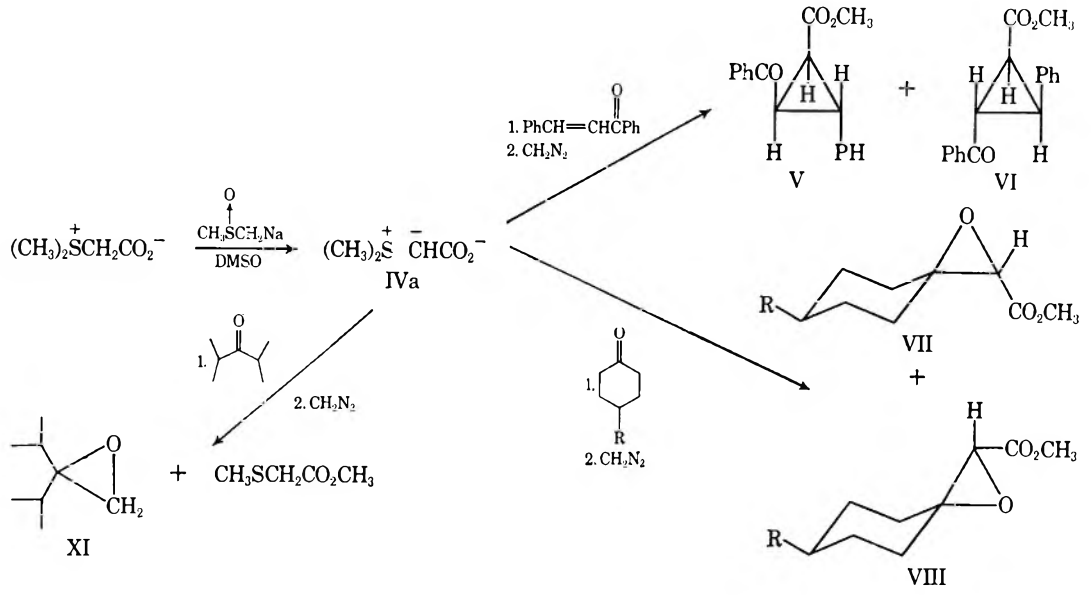
(4) (a) A. W. Johnson and R. T. Amel, *J. Org. Chem.*, **34**, 1240 (1969). (b) Similar reactivity has been reported for very closely related sulfuranylideneacetates. See H. Nozaki, D. Tunemoto, S. Matubara, and K. Kondo, *Tetrahedron*, **23**, 545 (1967).

(5) For preparation and properties of very closely related sulfuranylideneacetates, see (a) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966); (b) J. J. Tufariello, L. T. C. Lee, and P. Wojtkowski, *J. Amer. Chem. Soc.*, **89**, 6304 (1967); (c) J. Casanova and D. A. Rutolo, *Chem. Commun.*, 1224 (1967); (d) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967); (e) G. B. Payne, *ibid.*, **33**, 1284, 3517 (1968); (f) G. B. Payne and M. R. Johnson, *ibid.*, **33**, 1385 (1968); (g) H. Nozaki, M. Takaku, Y. Hayashi, and K. Kondo, *Tetrahedron*, **24**, 6536 (1968).

(6) In cyclopropanes, it has been established that *cis* couplings are larger than *trans*. See S. Sternhell, *Quart. Rev.* (London), **23**, 236 (1969); J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962).

Scheme I

Preparation and Reactions of Dimethylthetin Anion



VI,[6] the corresponding hydrogens had coupling constants of 4.5 and 6.5 Hz, 6.5 and 13.3 Hz, and 4.5 and 10.0 Hz. A similar reaction of I has been reported to yield cyclopropane(s) of undetermined stereochemistry.[4b]

Diphenylthetin anion (IVb) has been generated from the corresponding betaine either by treatment with dimsylsodium in DMSO or with *n*-butyllithium in hexamethylphosphoramide (HMPA). It reacted in identical fashion with chalcone to produce the cyclopropanes. Whereas, in the former reaction, the ratio of V to VI was *ca.* 1, in the latter it was *ca.* 1.5.

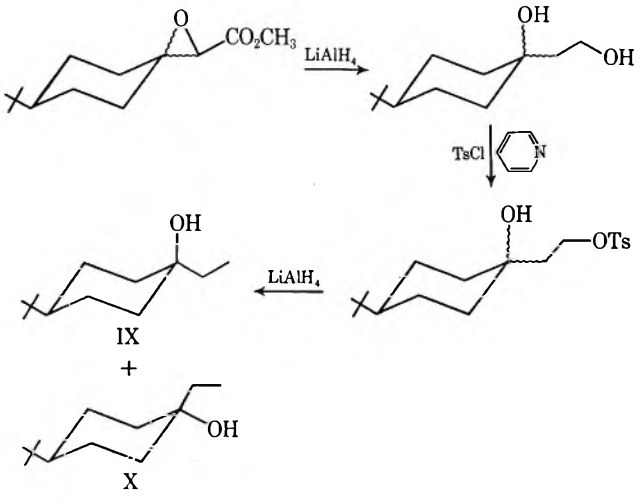
It is interesting to note the difference in reactions of chalcone with various sulfur ylides. Whereas the parent ylide, dimethylmethylenesulfurane, produces the epoxide exclusively,[7] less reactive ylides add in conjugative fashion exclusively. In this regard, we have found that dimethyl(phenacylene)sulfurane,[8] dimethyl(carbomethoxymethylene)sulfurane (I), sodium(dimethylsulfuranylidene)acetate (IVa), and dimethyl(vinylmethylene)sulfurane[9] produce only cyclopropane products with no detectable amounts of epoxides. There are two steps to this reaction—addition to the carbonyl or olefinic carbon followed by elimination to epoxide or cyclopropane. Since it is difficult to understand why elimination to epoxide would be very much slower than elimination to cyclopropane in each respective adduct, we attribute exclusive cyclopropane formation with the stabilized ylides to lack of carbonyl addition. With the most reactive ylide, the transition state of addition should more closely resemble reactant than product, leading ultimately *via* reaction at the most highly electron-deficient center to epoxide.[10] Stabilization of the carbanionic center even with a simple double bond moves the transition state sufficiently along the reaction coordinate so that the thermodynamically most favored adduct (Michael-type addition) is produced exclusively. Presumably, choice of an ylide intermediate in reactivity between dimethylmethylenesulfurane and dimethyl(vinylmethylene)sulfurane would yield mixtures of both types of products.

The condensation of dimethylthetin anion with cyclohexanone proceeded readily to produce after esterification a 60% yield of the glycidic ester (VII, R = H). Identification was made by comparison of its spectral properties with those reported in the literature.[11] Reaction of sulfonium ylides with cyclohexanones has been reported to proceed in a highly stereoselective fashion with production of the axial carbon–carbon bond.[7,12] For example, reaction of 4-*t*-butycyclohexanone with dimethylmethylenesulfurane produced 83% *cis* epoxide (axial C–C bond) and 17% *trans* epoxide (equatorial C–C bond).[7] On the other hand, the less reactive sulfoxonium ylides produce the opposite stereochemical preference. To determine if this difference is a function of the electronegativity of sulfur or the reactivity of the carbanionic center, the reaction of IV with 4-*t*-butylcyclohexanone was examined. The reaction gave a 56% isolated yield of glycidic esters after treatment with diazomethane. Vpc analysis showed essentially one isomer. Deduction of the stereochemistry proceeded as outlined in Scheme II. Lithium aluminum hydride reduction followed by tosylation and lithium aluminum hydride reduction produced a mixture of *cis*- (X) and *trans*-4-*t*-butyl-1-ethylcyclohexanol (IX) in 3 and 97% relative yields, respectively. The stereochemistries were established by comparison with authentic samples prepared by addition of ethylmagnesium bromide to 4-*t*-butylcyclohexanone.[13] In contradiction to the unstabilized sulfonium ylide, the thetin anion adds virtually exclusively *via* the least hindered route to produce an equatorial carbon–carbon bond, *i.e.*, VII.

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(8) B. M. Trost, *ibid.*, **89**, 138 (1967).
(9) R. W. LaRochelle, unpublished work in these laboratories.
(10) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(11) H. O. House and J. W. Blaker, *ibid.*, **80**, 6389 (1958).
(12) (a) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967); (b) R. S. Ely, C. M. DuBose, Jr., and G. B. Konizer, *ibid.*, **33**, 2188 (1968); (c) C. E. Cook, R. C. Corley, and M. E. Wall, *ibid.*, **33**, 2789 (1968).
(13) G. F. Hennion and F. X. O'Shea, *J. Amer. Chem. Soc.*, **80**, 614 (1968).

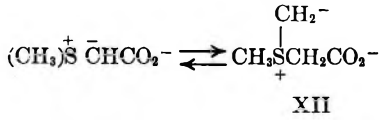
SCHEME II

DETERMINATION OF STEREOCHEMISTRY



The reasons for these stereochemical preferences remain unclear.

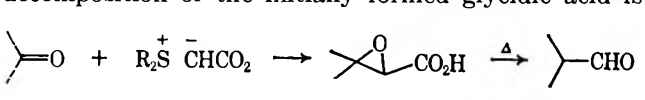
In an ancillary experiment, the extent to which the reactivity of the ylide IV has been increased was tested by examining the reaction of the anion with diisopropyl ketone. After the usual diazomethane work-up, vpc analysis revealed the presence of two materials. The first was identified as methyl methylthioacetate. The second product shows no carbonyl nor hydroxyl absorptions in the infrared spectrum. Its mass spectrum exhibits a parent peak at *m/e* 128 and its nmr spectrum exhibits absorptions at δ 2.45 (singlet, 2 H, epoxide methylene), 1.96 (multiplet, 2 H, isopropyl methines), 0.90 (doublet, 6 H, one set of isopropyl methyls), and 0.85 (doublet, 6 H, second set of isopropyl methyls). These data clearly indicate the structure to be 2-isopropyl-3-methyl-1-butene epoxide (XI). It appears that dimethylthetin anion IV is not reactive enough to add to the hindered carbonyl and that it equilibrates to the more reactive sulfoniummethylide XII before condensation. To



XII

obviate this reaction, we treated the diphenylthetin anion with diisopropyl ketone. However, no glycidic esters could be found. Thus, although the ylide IV is sufficiently more reactive than I to add to simple ketones, it remains unreactive enough not to add to hindered carbonyls.

The utilization of the thetin anion can also serve as a one carbon chain extension procedure, since the thermal decomposition of the initially formed glycidic acid is



known to produce the aldehyde.[14] This technique serves as an attractive alternative to acid-catalyzed rearrangement of epoxides formed from the methylenesulfonium ylides, to the Wittig procedure using the alkoxymethylene ylide, and to the normal Darzens procedure.

(14) M. S. Newmann and B. J. Magerlein, *Org. React.* **5**, 413 (1949). For a discussion of the problems encountered in the usual conversion of glycidic esters into aldehydes and a modification of that technique, see E. P. Blanchard, Jr., and G. Buchi, *J. Amer. Chem. Soc.*, **85**, 955 (1963).

Experimental Section[15]

Preparation of Dimethylthetin (IIIa).—The procedure of Ratts and Yao was employed.[5a] From 5.73 g (25 mmol) of dimethyl(carboethoxymethyl)sulfonium bromide was obtained 4.55 g (60%) of dimethylthetin, mp 138–140° dec (lit. mp 137–138°) after recrystallization from ethanol–ether and drying overnight *in vacuo* over phosphorus pentoxide. The nmr spectrum[16] showed singlets at δ 2.92 (6 H) and 4.15 (2 H). The latter signal slowly decreases and eventually disappears, indicating fairly facile H–D exchange.

Preparation of Diphenyl(carbomethoxymethyl)sulfonium Fluoroborate (IIb, R′ = CH₂).[17]—In a dry bag under a nitrogen atmosphere, a solution of 3.60 g (19.3 mmol) of diphenyl sulfide in 30 g (196 mmol) of methyl bromoacetate was prepared. With magnetic stirring, portionwise addition of 3.75 g (19.3 mmol) of anhydrous silver fluoroborate took place over a period of 0.5 hr. After having been stirred for an additional 2 hr and allowed to stand overnight, the mixture was diluted with methylene chloride and filtered by gravity. Concentration of the methylene chloride solution *in vacuo* produced an oil which crystallized after dissolving in ethanol and addition of ether. Recrystallization in similar fashion produced 3.13 g (47%) of colorless crystals, mp 87–88°. The infrared spectrum[18] showed absorptions at 1740 (carbonyl) and 1000–1100 cm⁻¹ (fluoroborate anion). The nmr spectrum[19] showed multiplets at δ 7.80–8.15 (4 H) and 7.50–7.80 (6 H) and singlets at δ 5.23 (2 H) and 3.66 (3 H).

Anal. Calcd for $C_{15}H_{15}O_2SBF_4$: C, 52.05; H, 4.37; S, 9.26. Found: C, 51.95; H, 4.30; S, 9.31.

Preparation of Diphenylthetin (IIIb).—Amberlite resin IRA-400 was converted into its hydroxide form by stirring a suspension in saturated sodium hydroxide solution for 1 week. After the resin had been separated by filtration, it was washed thoroughly with distilled water. A solution of 1.50 g (4.34 mmol) of diphenyl(carbomethoxymethyl)sulfonium fluoroborate in 100 ml of distilled water was treated with 8.5 ml of the above prepared resin. After the solution had been stirred for 1 hr at 25°, filtration removed the resin. Lyophilization *in vacuo* left 885 mg (84%) of white powder, mp 106–107° dec. The infrared spectrum[20] showed a carbonyl peak at 1630 cm⁻¹. The nmr spectrum[16] had a multiplet at δ 7.60–8.05 (10 H) and a singlet at δ 5.02 (2 H). The latter absorption slowly disappeared, indicating facile H–D exchange, in D_2O.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.70; H, 4.96; S, 12.98.

Preparation of Dimethylthetin Anion (IVa). Method A.—A solution of dimsylsodium in dimethyl sulfoxide was prepared by the method of Corey from 400 mg (9.16 mmol, 55% mineral oil dispersion) of sodium hydride in 25 ml of dry (freshly distilled from calcium hydride) dimethyl sulfoxide. Then 989 mg (8.3 mmol) of dimethylthetin was added portionwise under nitrogen through a pressure-equalizing solid addition funnel. Upon completion of the addition, the suspension was stirred for 1 hr at 25° to produce a thick, off-white suspension of dimethylthetin anion (IVa).

Method B.—A solution of dimsylsodium in dimethyl sulfoxide under nitrogen was prepared by the method of Corey from 1.5 g

(15) Melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer, and ultraviolet spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer fitted with a variable-temperature probe. Chemical shifts are given in parts per million relative to TMS as an internal standard. Mass spectra were taken on a CEC 103 C or a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Analyses were performed by Spang Microanalytical Laboratory and Micro-Tech Laboratories, Inc. Unless otherwise indicated, extractions were performed with chloroform and magnesium sulfate was employed as a drying agent. Vpc analyses were performed on an Aerograph Model 90P instrument.

(16) Determined as a solution in deuterium oxide.

(17) A modification of the procedure of Franzen and coworkers. See V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).

(18) Determined as a solution in chloroform.

(19) Determined as a solution in deuteriochloroform.

(20) Determined as a KBr pellet.

(35.4 mmol, 56.6% mineral oil dispersion) of sodium hydride in 50 ml of dry dimethyl sulfoxide. A few crystals of triphenylmethane were added to produce a brillant red solution. In a second flask fitted with a magnetic stirrer and two serum caps and flushed under nitrogen was placed 1.184 g (9.90 mmol) of dimethylthetin in 15 ml of dry dimethyl sulfoxide. To this suspension the red dimsylsodium solution was added dropwise *via* syringe until the red color persisted for 30 min.

Preparation of Diphenylthetin Anion (IVb).—This anion could be prepared by either of the above procedures. Alternatively, it was produced by treatment of diphenylthetin with *n*-butyllithium. In a nitrogen atmosphere, 0.47 ml (1.5 *M*, 0.70 mmol) of *n*-butyllithium in hexane was added to 2.0 ml of hexamethylphosphoramide (HMPA). A few crystals of triphenylmethane were added as an indicator. At this point, 0.171 g (0.70 mmol of diphenylthetin was added. A thick, gray slurry was produced.

Reaction of Dimethylthetin Anion with Chalcone.—In a nitrogen atmosphere, 2.08 g (10.0 mmol) of chalcone was added all at once to a solution of the anion generated from 1.24 g (10.3 mmol) of dimethylthetin. A brown solution formed and was stirred for 15.5 hr at 25°. The mixture was poured onto 50 g of ice and acidified to pH 1 with dilute aqueous hydrochloric acid. Ether extraction of the mixture followed by washing of the ether layers with water produced a pale yellow solution. After drying, the solution was treated with diazomethane and the excess diazomethane was destroyed by addition of acetic acid. Washing with aqueous potassium carbonate removed excess acetic acid. After the solution had been dried and concentrated *in vacuo*, the ether layers produced 2.48 g of crude product which showed three major spots on thin layer chromatography[21] utilizing 15% ethyl acetate in cyclohexane as eluent. The fastest moving spot (R_f *ca.* 0.39) was chalcone. The second spot (R_f *ca.* 0.3) was isolated by preparative thin layer chromatography.[21] From 112 mg of crude oil, 38.3 mg (30%) of this component was isolated. The infrared spectrum[22] showed absorptions at 1730 (ester carbonyl), 1672 (ketone carbonyl), and 1600, 1587, and 1500 cm^{-1} (aromatic rings). The ultraviolet spectrum[23] exhibited λ_{max} 247 nm (ϵ 17,000). The nmr spectrum[22] showed a multiplet (2 H) at δ 8.00–8.25, a multiplet (3 H) at δ 7.1–7.7 superimposed upon which is a singlet (5 H) at δ 7.25, three sets of doublets of doublets (1 H each) at δ 3.75 (J = 4.5 and 6.5 Hz), 3.14 (J = 6.5 and 10 Hz), and 2.77 (J = 4.5 and 10 Hz), and a singlet (3 H) at δ 3.50. Its mass spectrum exhibited a molecular ion at m/e 280 and intense peaks at m/e 249, 222, 221, 175, 115, 105 (base peak), 91, and 77. These data allow assignment of structure VI to this cyclopropane derivative.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.23; H, 5.66.

The third spot (R_f *ca.* 0.23) was also isolated by preparative thin layer chromatography. From 112 mg of crude oil, 36.6 mg (29%) of this component was isolated. The infrared spectrum[22] showed absorptions at 1725 (ester carbonyl), 1672 (ketone carbonyl), and 1600, 1584, and 1499 cm^{-1} (aromatic rings). The ultraviolet spectrum[23] showed λ_{max} 248 nm (ϵ 21,600). The nmr spectrum[22] exhibited a multiplet (2 H) at δ 7.80–8.05, a multiplet (3 H) at δ 7.19–7.60, a singlet (5 H) at δ 7.12, a singlet (3 H) at δ 3.75, and an ABC pattern for the cyclopropylhydrogens with H_A at δ 3.50, H_B at δ 3.26, and H_C at δ 3.20 (J_{AB} = 5.0 Hz, J_{AC} = 10.0 Hz, and J_{BC} = 7.0 Hz). The mass spectrum showed, in addition to a molecular ion at m/e 280, abundant peaks at m/e 221, 115, 105 (base peak), and 77. These data allow assignment of structure V to this compound.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.91; H, 5.76.

Reaction of Diphenylthetin Anion with Chalcones.—In a nitrogen atmosphere a suspension of the sodium salt of diphenylthetin anion prepared from 173 mg (9.77 mmol) of diphenylthetin in DMSO was prepared. To this mixture was added 143 mg (0.69 mmol) of chalcone all at once. After the mixture had been stirred at 25° for 20 hr, it was worked up as described above. Preparative thin layer separation of the products yielded, in addition to diphenyl sulfide, 173 mg (89%) of a mixture of V and VI. Nmr analysis[22] indicated the ratio of V to VI to be *ca.* 1.5.

Reaction of Dimethylthetin Anion with Cyclohexanone.—To a suspension of 6.6 mmol of IVa at 25° under nitrogen was added 612 mg (6.2 mmol) of cyclohexanone in one portion. The temperature rose slightly. After having been stirred for 3 hr at room temperature, the clear solution that evolved was cooled to 20°, poured onto ice, and acidified to pH 1 with hydrochloric acid. After ether extraction and drying, the ethereal solution was treated with diazomethane. Vpc analysis[24] of the oil that resulted after solvent removal utilizing ethyl phenylacetate as internal standard indicated 610 mg (60%) of glycidic ester VII (R = H). Comparison of its infrared spectrum with that of an authentic sample confirmed the structural assignment. The nmr spectrum[19] of the acid prior to diazomethane treatment showed the carboxyl proton at δ 10.10, the epoxide methine hydrogen as a singlet at δ 3.16, and the ring protons as a multiplet centered at δ 1.53.

Reaction of Dimethylthetin Anion with 4-*t*-Butylcyclohexanone.—In a nitrogen atmosphere, 772 mg (5.0 mmol) of 4-*t*-butylcyclohexanone in 2 ml of dry DMSO was added dropwise to a suspension of dimethylthetin anion in DMSO generated from 626 mg (5.22 mmol) of dimethylthetin. Upon completion of the addition, the mixture was stirred for 20 hr at 25°, poured onto ice, acidified to pH 1, and extracted with ether. After esterification with diazomethane and destruction of excess diazomethane with acetic acid, the solution was washed with aqueous potassium carbonate, dried, and concentrated *in vacuo*. Distillation at 73–78° (0.03 mm) generated 664 mg (57%) of a mixture of glycidic esters VII and VIII (R = t-C_4H_9). Vpc analysis[24] showed essentially one peak. Nmr analysis[22] also indicated great preponderance of one isomer over the other. The nmr spectrum exhibited singlets at δ 3.70 (3 H), 3.17 (1 H), and 0.88 (9 H) as well as complex absorption between δ 1.1 and 2.1 (9 H). The infrared spectrum[22] showed a doublet at 1730 and 1755 cm^{-1} characteristic of glycidic esters. The mass spectrum showed a molecular ion at m/e 226 and abundant peaks at m/e 168, 81, 67, 57 (base peak), and 55.

Anal. Calcd for $C_{13}H_{22}O_3$: mol wt 226.15688. Found: mol wt, 266.15674 ± 0.00439.

Conversion of Methyl β,β-(γ-*t*-Butylpentamethylene)glycidate (VII and VIII, R = *t*-C_4H_9) into 4-*t*-Butyl-1-ethylcyclohexanol. Reduction of Ester.[25]—A solution of 664 mg (2.91 mmol) of VII and VIII (R = t-C_4H_9) in 2.0 ml of dry ether was added slowly at 0° to a slurry of 230 mg (6.07 mmol) of lithium aluminum hydride in 5 ml of ether. After the mixture had been stirred for 7 hr, wet ether followed by water was added. Ether extraction, drying, and concentration *in vacuo* generated 501 mg (86%) of an isomeric mixture of 1-(2-hydroxyethyl)-1-hydroxy-4-*t*-butylcyclohexane. A small portion of this material was recrystallized from carbon tetrachloride–hexane to give colorless needles, mp 102–102.5°. The infrared spectrum[18] showed broad hydroxyl absorption at 3400 cm^{-1} and a sharper peak at 3630 cm^{-1}. The nmr spectrum[19] possessed a triplet (2 H) at δ 3.89 (J = 6.0 Hz), a broad singlet (2 H) at δ 3.00, a triplet at δ 1.67 (J = 6.0 Hz) superimposed on a complex multiplet at δ 0.9–2.0 (total 11 H), and a singlet (9 H) at δ 0.87. The mass spectrum showed no molecular ion but showed weak M − 1^+ and M − 2^+ peaks as well as abundant peaks at m/e 107, 93, 91, 79, 69, 57 (base peak), 56, 55, 45, and 43.

Anal. Calcd for $C_{11}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.01; H, 12.08.

Conversion of Diol into Monotosylate.—The crude diol mixture (396 mg, 2.0 mmol) was dissolved in 4 ml of pyridine and cooled to 0° with stirring in a nitrogen atmosphere. Addition of 420 mg (2.2 mmol) of *p*-toluenesulfonyl chloride in 3 ml of pyridine proceeded dropwise. After the addition, stirring was continued for 1.5 hr at 0° and 1.5 hr at 25°. After the solution had been poured onto ice, an oil resulted. The mixture was extracted with ether and the ether was washed with dilute aqueous hydrochloric acid and then water. Subsequent drying over sodium sulfate and concentration *in vacuo* produced 663 mg of crude monotosylate product. The nmr spectrum[19] possessed an AB pattern with H_A at δ 7.78 and H_B at δ 7.35 (J_{AB} = 8 Hz) and a singlet at δ 2.42 for the tosylate moiety. The remaining protons appeared as a triplet (2 H, J = 7 Hz) at δ 4.23, a triplet (2 H, J = 7 Hz) at δ 1.77, a singlet (1 H) at δ 2.44, a multiplet (9 H)

(21) Silical gel (Merck) PF 254 was employed.

(22) Determined as a solution in carbon tetrachloride.

(23) Determined as a solution in ethanol.

(24) A 5 ft × 0.25 in. 20% SE-30 on Chromosorb P column was employed for this analysis.

(25) For similar reductions of glycidic esters, see H. M. Walborsky and C. Colombini, *J. Org. Chem.*, **27**, 2387 (1962); M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1042 (1952).

at δ 0.9–1.8, and a singlet (9 H) at δ 0.83. The product was not purified further.

Reduction of Monotosylate.—In a nitrogen atmosphere, a solution of 379 mg (1.1 mmol) of crude monotosylate in 3 ml of dry tetrahydrofuran was added dropwise to a stirred slurry of 900 mg (24 mmol) of lithium aluminum hydride in 10 ml of dry tetrahydrofuran. After the mixture had been stirred for 1 hr at room temperature and 3 hr at reflux, addition of ethyl acetate at 0° destroyed excess lithium aluminum hydride. The mixture was diluted with 100 ml of water and extracted with ether. Subsequent drying and concentration *in vacuo* produced 230 mg of crude oil. Vpc analysis[26] of the crude mixture showed two peaks in the ratio of 97:3. The shorter retention time peak (97% isomer) was identified as 1-ethyl-*trans*-4-*t*-butylcyclohexanol (IX) by comparison of retention time and infrared spectrum with that of an authentic sample. The longer retention time peak (3% isomer) was identified as 1-ethyl-*cis*-4-*t*-butylcyclohexanol (X) by comparison of vpc retention time with that of an authentic sample and physical properties and infrared spectral data with the published information.[13]

Reaction of Dimethylthetin Anion with Diisopropyl Ketone.—To a solution of 6.5 mmol of dimethylthetin anion was added 775 mg of diisopropyl ketone. The resulting suspension was stirred for 16 hr at room temperature; however, the suspension remained. It was poured onto ice and acidified to pH 1 with hydrochloric acid. Ether extraction followed by drying and diazomethane treatment produced an oil which exhibited three peaks on vpc.[27] The first peak (73%) was diisopropyl ketone. The second peak (12%) showed no carbonyl group in its infrared spectrum.[22] The nmr spectrum[22] exhibited a singlet (2 H) at δ 2.45, a multiplet (2 H) at δ 1.96, a doublet (6 H) at δ 0.90 (J = 6.5 Hz), and a doublet (6 H) at δ 0.85 (J = 6.5 Hz). From this data, the compound is tentatively identified as 1,2-epoxy-2-isopropyl-3-methylbutane (XI).

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.75; H, 12.56.

The third component (14%) showed ester carbonyl stretching absorption (1740 cm^{-1}) in its infrared spectrum.[22] The nmr spectrum[19] exhibited three singlets at δ 3.72, 3.18, and 2.20 in the ratio 3:2:3. These data identify this material as methyl methylthioacetate; comparison with an authentic sample confirmed the assignment.

Registry No.—IIb, 23511-07-1; IIIb, 23511-06-0; V, 23511-08-2; VI, 23511-09-3; VII, 23511-10-6; VIII, 23511-11-7; XI, 23511-12-8; 1-(2-hydroxyethyl)-1-hydroxy-4-*t*-butylcyclohexane, 23511-13-9.

Acknowledgment.—We express our gratitude to the National Institutes of Health for generous support of this work. We also thank the National Science Foundation for an URP grant to the Department of Chemistry which provided summer support for one of us (J. A.).

(26) An 8 ft × 0.25 in. 20% diethylene glycol glutarate on Chromosorb P column was employed for this analysis.

(27) An 8 ft × 0.25 in. 20% Carbowax 20M on Chromosorb P column was employed for this analysis.

The Stereochemistry of Electroreductions. III. Carbon–Oxygen Single Bonds[1]

RONALD E. ERICKSON AND CHARLES M. FISCHER

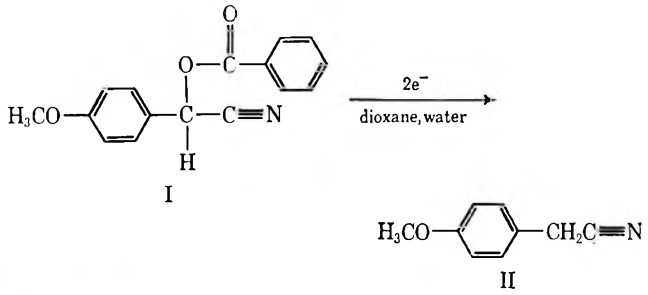
Department of Chemistry, University of Montana, Missoula, Montana 59801

Received September 8, 1969

Optically active O-benzoylatrolactic acid and methyl O-benzoylatrolactate are reduced electrochemically to 2-phenylpropionic acid with almost complete loss of optical activity. This is in sharp contrast with the electroreduction of the related 2-chloro-2-phenylpropionic acid, which has been reported to undergo reduction with 77–92% inversion of configuration. The exact mechanisms of the two processes must differ.

Numerous workers have investigated aspects of carbon–halogen bond electroreductions. Lambert[2] has attempted a quantitative correlation between polarographic half-wave potentials and Taft polar and steric constants. Several papers have been concerned with the effect of structure on half-wave potentials[3] and mass electrolysis data.[4] Annino, *et al.*,[1] have examined the stereochemical nature of these reductions using cyclopropyl halide derivatives. They explained their results on the basis of the formation and subsequent breakdown of an intermediate electrode complex.

In contrast to carbon–halogen bond reductions, the electroreduction of carbon–oxygen single bonds has received little attention. Wawzonek and Fredericksen[5] examined several mandelonitriles and mandelonitrile esters polarographically and reduced I to II in good yield by mass electrolysis. Kabaskalian and



I

II

McGlotten reduced a series of hydroxy keto steroids polarographically and followed this study with several controlled potential mass electrolyses.[6]

We report in this paper on the stereochemistry of the electroreduction of atrolactic acid derivatives. The compounds were chosen for initial stereochemical study because (a) analogy with Wawzonek and Fred-

(1) R. Annino, R. E. Erickson, J. Michalovic, and N. McKay, *J. Amer. Chem. Soc.*, **88**, 4424 (1966); R. E. Erickson, R. Annino, M. Scanlon, and G. Zon, *ibid.*, **91**, 1767 (1969).

(2) J. L. Lambert, *J. Org. Chem.*, **31**, 4184 (1966).

(3) F. L. Lambert and K. Kobayaski, *J. Amer. Chem. Soc.*, **82**, 5324 (1960); F. L. Lambert, A. H. Albert, and J. P. Hardy, *ibid.*, **86**, 3155 (1964); J. Zavada, J. Krupieka, and J. Sicher, *Collect. Czech. Chem. Commun.*, **28**, 1664 (1963); P. Zuman, *Talanta*, **12**, 1337 (1965); J. W. Sease, P. Chang, and J. L. Groth, *J. Amer. Chem. Soc.*, **86**, 3154 (1964).

(4) P. J. Elving, I. Rosenthal, and A. J. Martin, *ibid.*, **77**, 5218 (1955); S. Wawzonek, R. C. Duty, and J. H. Wagenknecht, *J. Electrochem. Soc.*, **111**, 74 (1964); G. Klopman, *Helv. Chim. Acta*, **44**, 1908 (1961).

(5) S. Wawzonek and J. D. Fredericksen, *J. Electrochem. Soc.*, **106**, 325 (1959).

(6) P. Kabaskalian and J. McGlotten, *Anal. Chem.*, **31**, 1091 (1959); P. Kabaskalian, J. McGlotten, A. Bosch, and M. D. Yuchs, *J. Org. Chem.*, **26**, 1738 (1961).

ericksen's mandelonitriles[5] suggested that the compounds would be reducible, (b) configurational relationships between atrolactic acid and its reduction product, 2-phenylpropionic acid, are known, and (c) the stereochemistry of the electroreduction of the related halide, 2-chloro-2-phenylpropionic acid, has been determined; therefore direct stereochemical comparisons can be made between carbon–oxygen and carbon–halogen single-bond reductions.

Experimental Section

Materials.—Eastman tetraethylammonium bromide (TEAB) was recrystallized several times from ethanol before use. Undenatured 95% ethanol was used without any further purification. Atrolactic acid was purchased from Pfaltz and Bauer and Aldrich chemical Co.

Atrolactic acid was resolved using α-phenylethylamine[7] (Aldrich) and esterified with diazomethane.[8]

Methyl O-Benzoylatrolactate.—The methyl ester was treated with benzoyl chloride (1:1) in pyridine at room temperature for 12 hr. The resulting solution was poured into water and extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and distilled under vacuum, bp 172° (2 mm). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.83; H, 5.64; O, 22.53.[9] Found: C, 71.68; H, 5.69; O, 22.63.

O-Benzoylatrolactic Acid.—O-Benzoylatrolactic acid was prepared by treating the parent acid with benzoyl chloride in pyridine as described above. The dried ether extracts were evaporated under vacuum yielding a white solid, mp 130.5–132°. *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.11; H, 5.19; O, 23.70. Found: C, 71.30; H, 5.38; O, 23.32.

Atrolactic acid, $[\alpha]^{25}D$ −31° (95% EtOH, 82% resolved),[10] upon esterification and subsequent benzoylation gave the methyl O-benzoylatrolactate derivative having $[\alpha]^{25}D$ −35.33° (95% EtOH). Atrolactic acid, $[\alpha]^{25}D$ 29.78° (95% EtOH, 78.9% resolved), gave an O-benzoyl derivative having $[\alpha]^{25}D$ 31.67° (95% EtOH).

Apparatus.—Polarographic analyses were performed on a Sargent Model XV polarograph in conjunction with a Sargent IR compensator. A Sargent three-electrode Arthur polarographic cell was employed in all determinations. Saturated ethanol calomel electrodes were directly prepared in this cell[11,12] and used as both reference and counter electrodes.

Cyclic voltammetry experiments were performed on a Chemtrix Model SSP-2 single-sweep polarographic analyzer.

In the controlled-potential electrolysis experiments, constant effective potential was maintained with a Model 557/SU potentiostat purchased from Amel Instrument Co., Milano, Italy. Coulometric data was obtained using an Amel Model 558 electronic integrator connected to the potentiostat. Two electrolysis cells, a double-diaphragm model described by Meites[13] and a Model 494 cell from Amel, were employed. The reference electrode in both cases was a commercial saturated calomel electrode. The counter electrode was either a platinum wire or platinum sheet electrode isolated from the sample compartment. A mercury pool electrode was employed as the cathode.

Nuclear magnetic resonance spectra were recorded on a Varian HA-60 recording spectrometer as approximately 15% solutions in chloroform-*d* ($CDCl_3$).

Optical rotations were measured on an O. C. Rudolph & Sons polarimeter, Model 80. All measurements were made in 95% ethanol using a 10-cm cell.

Polarographic Analysis.—Portions (75 ml) of 0.1 *M* TEAB in 95% ethanol were pipetted into the cell compartment and oxygen was removed by passing nitrogen through the solution for at least 30 min. A 2.00-ml portion of 0.015 *M* ethanolic solution of the compound to be analyzed was added and the solution was polarographed under a nitrogen atmosphere. All data were obtained directly from the recorded polarograms.

Controlled-Potential Electrolysis.—Electrolyte solution (0.1 *M* TEAB in 95% ethanol) was added to the cell and purged with nitrogen. The mercury pool–solution interface was kept in motion with a mechanical stirrer or a magnetic stirrer. The residual current was recorded at a number of control potentials and the potential at which significant discharge from the supporting electrolyte occurred was noted. The sample (0.5–1.0 g) was dissolved in a minimum amount of ethanol and added to the cell. The solution was again purged with nitrogen and then electrolyzed at the appropriate control voltage. The electrolysis was allowed to proceed until residual current was obtained.

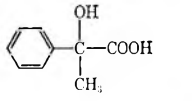
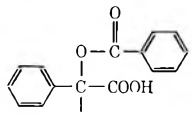
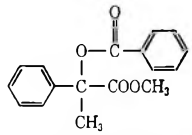
Product Analysis.—The electrolysis solution was poured into three times its volume of water and extracted with ether. In the case of the acid as starting material, the solution was made acidic with concentrated sulfuric acid before extraction. The ether extracts were dried over anhydrous magnesium sulfate and evaporated under vacuum. An nmr spectrum and optical rotation measurements, where appropriate, were obtained on this ether residue. The electrolysis product from O-benzoylatrolactic acid was first chromatographed on silica gel before optical measurement was obtained.

Results and Discussion

Table I summarizes the polarographic data obtained in this study.

TABLE I

POLAROGRAPHIC DATA FOR THE REDUCTION OF CARBON–OXYGEN SINGLE BONDS

Compd	$E_{1/2}$[a]	I_d[b]	Media
	−1.73		0.1 *M* TEAB in 95% EtOH
	−1.60	2.41	0.1 *M* TEAB in 95% EtOH
	−1.84		
	−1.86		0.1 *M* TEAB in 95% EtOH; equimolar base added
	−1.48		0.1 *M* TEAB in 95% EtOH;
	−1.84		equimolar acid added
	−1.82	2.03	0.1 *M* TEAB in 95% EtOH
	−1.82		0.1 *M* TEAB in 95% EtOH; equimolar base added
	−1.48		0.1 *M* TEAB in 95% EtOH;
	−1.82		equimolar acid added

[a] Potentials are in volts relative to saturated ethanol calomel electrode. [b] $I_d = i_d/Cm^{2/3}t^{1/6}$; i_d is the diffusion current measured at the maximum of the instantaneous current.

As can be seen, atrolactic acid exhibits a polarographic wave within the voltage range observed. This represents the reduction of the acidic proton to hydrogen. Polarographic experiments with O-benzoylatrolactic acid (III) and its methyl ester (IV) establish that the first wave in the reduction of III is indeed the reduction of the carboxylic acid proton. Wave height analysis[14] shows that the second wave in III and the wave in IV are both diffusion controlled.

The reductions of III and IV are irreversible as evidenced from cyclic voltammetry experiments. Scan reversal past the cathodic peak at speeds up to 5 V/sec resulted in no evidence of reoxidation.

(7) L. Smith, *J. Prakt. Chem.*, **84**, 731 (1911).

(8) "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250.

(9) All microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(10) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1020 (1910).

(11) P. Arthur and H. Lyons, *Anal. Chem.*, **24**, 1422 (1952).

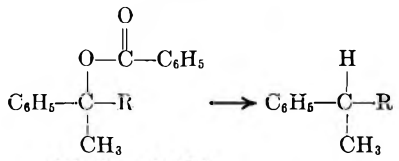
(12) P. Arthur, P. A. Lewis, N. A. Lloyd, and R. K. Vanderkam, *ibid.*, **33**, 488 (1961).

(13) L. Meites, *ibid.*, **27**, 1116 (1955).

(14) L. Meites, "Polarographic Techniques," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1965, Chapters 3 and 4.

Controlled-potential electrolysis of both III and IV resulted in cleavage of the carbon–oxygen bond and subsequent carbon–hydrogen bond formation. See Scheme I. Electrolysis of atrolactic acid yielded only the starting acid with no indication of carbon–oxygen bond cleavage.

SCHEME I

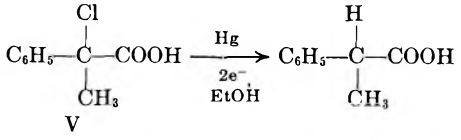


III, R = COOH
IV, R = $COOCH_3$

Potential was maintained at −1.80 V for the electrolysis of III and at −1.90 V for IV (*vs.* sce). Coulometric data for IV indicated that the reduction proceeded *via* $2e^-$/mol. The number of electrons involved for III were variable owing to the presence of the acid proton wave in this compound.

The products were identified from their respective nmr spectra. The spectrum resulting from reduction of III had a doublet at 1.42, a quartet at 3.63, and a singlet at 7.17 ppm. The spectrum also contained absorption at 8 ppm indicative of the presence of benzoic acid. A triplet at approximately 1.1 and a quartet appearing at 3.65 ppm were shown to represent impurity unrelated to the actual electrolysis product. The product from IV contained a doublet at 1.4 (3 H), an overlapping singlet and quartet at 3.55, (4 H), and a singlet at 7.2 ppm (5 H). The presence of a triplet at 1.15 and a quartet at 4.00 ppm was taken as evidence of ester exchange with concomitant formation of ethyl 2-phenylpropionate. Since the pH of the electrolysis solution varies from 6 to 9 during the reaction period, the assumption of ester interchange is reasonable. The stereochemical data obtained are given in Table II.

This is in contrast to our earlier reductions of cyclopropyl halides[1] in which moderately high stereospecificities (56% inversion to 38% retention) were found. However, analogies to cyclopropyl systems might not be valid owing to the special stereochemical characteristics of the cyclopropyl carbanion. More pertinent to an understanding of the mechanism of carbon–oxygen single bond reductions is a comparison to Czochraloka's work on compound V.[15]



V

TABLE II
STEREOCHEMICAL RESULTS

Compd	Electrolyte	$[\alpha]_D$ found, deg	$[\alpha]_D$ calcd,[a] deg	Lit. $[\alpha]_D$, deg
III	0.1 *M* TEAB in 95% EtOH	−1.0	±35.07[b]	±58[c–f]
IV	0.1 *M* TEAB in 95% EtOH	−0.15	±47.56[g]	±86.0[c,h]
IV	0.1 *M* TEAB in 95% EtOH	−0.50	±47.56	±86.0[h]
IV	0.1 *M* TEAB in 95% EtOH, dilute HAc added to control pH at *ca.* 7	−4.60	±47.56	±86.0[i]
IV	0.1 *M* TEAB in 95% EtOH, dilute HAc added to control pH at *ca.* 7	+0.76	±47.56	±86.0[i]

[a] Calculated based on literature value of ±58° and optical purity of starting material. [b] 77.7% resolved starting material. [c] W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *J. Amer. Chem. Soc.*, **74**, 5088 (1952). [d] E. L. Eliel and J. P. Freeman, *ibid.*, **74**, 923 (1952). [e] W. A. Bonner, *ibid.*, **74**, 1038 (1952). [f] References contained in footnotes *c–e*. Discrepancies for this value range from ±54.2 to ±81.0°. [g] 82% resolved starting material. [h] Product also contains ethyl 2-phenylpropionate. [i] No evidence of ethyl 2-phenylpropionate in nmr.

Czochraloka reported this electroreduction to proceed with 77–92% inversion of configuration and explained the result in terms of an SN2-type mechanism. We do not agree that initial attack is on the rear side of the carbon atom and have proposed a fairly complicated mechanism into which Czochraloka's data would fit.[1] *It is obvious, however, that, whatever the true picture of carbon–halogen bond electroreductions is, the mechanism of carbon–oxygen single-bond reductions is different.*

The most obvious difference in the electroreduction of carbon–halogen *vs.* carbon–oxygen bonds is in the nature of the leaving group. It may be that adsorption of benzoate ion on the electrode is an important factor but we would prefer to defer speculation until we have completed further stereochemical and polarographic investigations.[16]

Registry No.—(+)-O-Benzoylatrolactic acid, 23510-90-9; methyl (−)-O-benzoylatrolactate, 23510-91-0.

Acknowledgment.—The support of this work by the National Science Foundation is gratefully acknowledged.

(15) B. Czochraloka, *Chem. Phys. Lett.*, **1**, 239 (1967).

(16) Fry and Mitnick [A. J. Fry and M. A. E. Mitnick, *J. Org. Chem.*, **35**, 1232 (1970)] have shown that the stereochemistry of electroreduction of some geminal dihalonorbornanes varies with the addition of surface active species. We thank Professor Fry for a preprint of his publication.

Nuclear Magnetic Resonance Evidence for Restricted Nitrogen Inversion and Nonplanarity in Perfluoro-4-chloro-2-halo-1,2-oxazetidines[1]

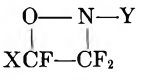
JOSEPHINE D. READIO

Thiokol Chemical Corporation, Reaction Motors Division, Denville, New Jersey 07834

Received July 1, 1969

Perfluoro-4-chloro-2-fluoro-1,2-oxazetidine and perfluoro-2,4-dichloro-1,2-oxazetidine have been prepared. Evidence for a high barrier to nitrogen inversion in these compounds is provided by ^{19}F nmr results, which demonstrate the presence at room temperature of *cis* and *trans* invertomers. Additional nmr studies have shown that the chemical-shift differences of the geminal fluorines of each invertomer are temperature dependent, indicating equilibrating nonplanar conformers. Values of ΔG for conformers of three invertomers have been determined. Assignments of nmr signals to specific fluorines are discussed.

The tendency of N-halo substituents, particularly bromine and chlorine, to retard inversion of nitrogen in three-membered ring systems has been demonstrated in recent studies involving N-haloaziridines.[2] We have reported[3] similar results for the perfluorooxazetidine system and have further found that fluorine is equally effective in restricting nitrogen inversion. This ability of fluorine was revealed in perfluoro-2-fluoro-1,2-oxazetidine (**1**) by the nonequivalence of the geminal fluorines in the ^{19}F nmr spectrum at 24°. Clearly, this nonequivalence could not be attributed to slow ring inversion, since at this temperature interconversions between possible nonplanar conformations would be rapid. A second manifestation of hindered nitrogen inversion in N-haloperfluorooxazetidines would be the likely detection of invertomers for those compounds in which X (structure below) is some group or atom other than fluorine.[4]



1, X = F; Y = F
2, X = Cl; Y = F
3, X = Cl; Y = Cl
4, X = F; Y = Cl
5, X = Cl; Y = H
6, X = Cl; Y = $CF_2CFClOEt$

We wish to present nmr evidence for the presence of two configurational isomers of perfluoro-4-chloro-2-fluoro-1,2-oxazetidine (**2**) and perfluoro-2,4-dichloro-1,2-oxazetidine (**3**) and thus further demonstrate that nitrogen inversion in these compounds even at room temperature has been effectively retarded.

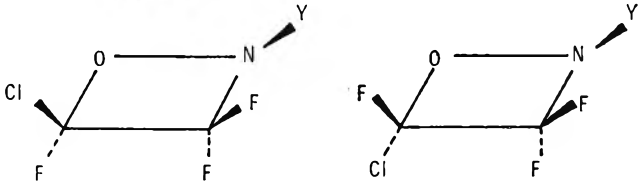
Nmr studies of certain substituted difluorocyclobutanes performed by Lambert and Roberts[5] indicated that the chemical-shift differences of the geminal fluorines were temperature dependent. These observations were interpreted in terms of a classical equilibrium between puckered ring conformations. We have reported similar evidence for the nonplanarity of the perfluorooxazetidines **1** and **4**[3] and in this paper will present low-temperature nmr data which suggest that the invertomers of **2** and **3** also exist as equilibrating nonplanar conformers.

Results and Discussion

Compounds **2** and **3** were prepared by fluorination and chlorination, respectively, of the parent amine, perfluoro-4-chloro-1,2-oxazetidine (**5**). This latter compound is generated on hydrolysis of the corresponding chloro ether **6**.[6] Preparative glpc was utilized to obtain pure samples of the N-halooxazetidine products with each collected as a single peak. In neither case did glpc provide evidence for invertomers. The structures of **2** and **3** were confirmed by infrared, mass spectral, and elemental analyses.

The ^{19}F nmr data from room-temperature spectra of **2** and **3** are listed in Table I. The spectrum of the CF_2N fluorines of **2** at −60° is reproduced in Figure 1, while these same fluorines of **3** at 24° are found in Figure 2. It is evident from these results that each collected sample of **2** and **3** does in fact consist of two configurational isomers, **2** showing a 65:35 invertomer distribution and **3** containing essentially equal quantities of the *cis* and *trans* isomers. These ratios are unchanged in spectra taken over the temperature range of 24 to −125°. The above evidence hence indicates a high barrier to nitrogen inversion in **2** and **3**.

TABLE I
CHEMICAL SHIFTS AND GEMINAL COUPLING CONSTANTS FROM THE ^{19}F NMR SPECTRA OF **2** AND **3** AT 24°



cis *trans*

2, Y = F
3, Y = Cl

Assignment	2, ϕ^* [a]	2, J_{F-F}, Hz	3, ϕ^* [a]	3, J_{F-F}, Hz
cis CF_2N	96.0, 98.2,[b] 102.9, 105.9	128	86.3, 88.2,[c] 96.7, 98.8	116
trans CF_2N	98.2, 100.6,[b] 102.4, 104.6	128	91.2	...
cis CFCl	62.4[b]	...	60.3[b]	...
trans CFCl	61.7[b]	...	63.0	...
cis N-F	−26.9	...		
trans N-F	−30.0	...		

[a] Chemical shift in parts per million with $CFCl_3$ as internal standard. [b] Each value represents center of doublet of doublets. [c] Each value represents center of doublet.

(1) This investigation was performed under Contract No. N00019-68-c-0372 for the Naval Air System Command, Department of the Navy, Washington, D. C. 20360, with Mr. John Gurtowski as Project Officer.

(2) S. J. Brois, *J. Amer. Chem. Soc.*, **90**, 506, 508 (1968); J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

(3) J. D. Readio and R. A. Falk, *J. Org. Chem.*, **35**, 927 (1970).

(4) Lee and Orrell observed the presence of invertomers of perfluoro-4-chloro-2-methyl-1,2-oxazetidine in a ^{19}F nmr spectrum obtained at −79°: J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **61**, 2342 (1965).

(5) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3710 (1963); **87**, 3884 (1965).

(6) R. A. Falk and J. D. Readio, *J. Org. Chem.*, **34**, 4088 (1969).

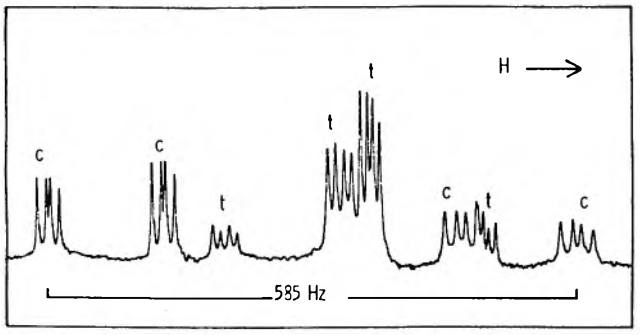


Figure 1.—^{19}F nmr spectrum of the CF_2N fluorines of **2** at −60°: c = *cis*; t = *trans*.

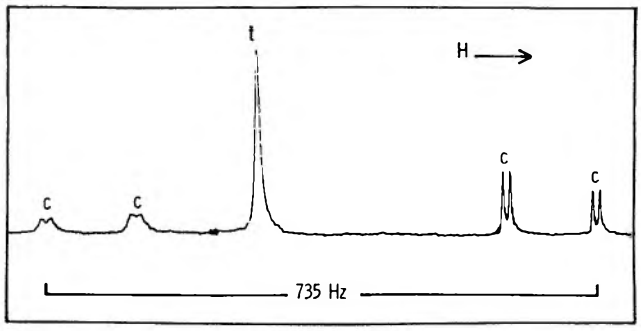


Figure 2.—^{19}F nmr spectrum of the CF_2N fluorines of **3** at 24°: c = *cis*; t = *trans*.

The specific assignment of peaks in the spectrum of **2** to the *cis* and *trans* invertomers was primarily based on nmr correlations which are discussed below. These interpretations were most consistent with the conclusion that the more prevalent isomer of **2** had the *trans* configuration. The nonequivalence of the CF_2N fluorines of **2** is indicated by the basic AB patterns in the spectrum (Figure 1). These patterns for both invertomers are clearly resolved at this lower temperature. In addition to the geminal coupling, the CF_2N fluorines also undergo coupling with the adjacent CFCl and N–F fluorines, and consequently each member of the AB quartets appears as a doublet of doublets. This same pattern is likewise observed for the CFCl fluorine of the *cis* invertomer and indicates coupling only with the vicinal CF_2N fluorines.[7] The CFCl fluorine of the *trans* invertomer of **2** gives a quartet pattern which will be discussed later. The N–F absorptions of the invertomers of **2** are broad and essentially structureless at room temperature, whereas at low temperature (−100°) quartet structures are discernible.

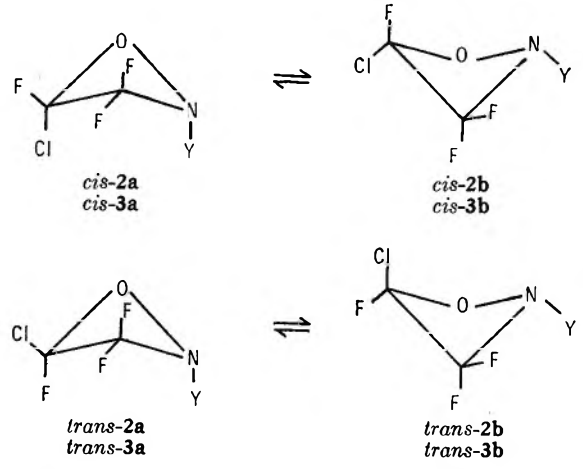
The data in Table I and the spectrum in Figure 2 clearly indicate that the geminal fluorines of one of the invertomers of compound **3** appear as a single unsplit absorption. The apparent equivalence of these fluorines suggests a certain degree of symmetry more likely encountered in the *trans* configuration; hence the single peak is attributed to the CF_2N fluorines of the *trans* invertomer. Assignment of the upfield CFCl peak to this same invertomer then follows and is based on the absence of appreciable splitting in this absorption. In Figure 2 it may be seen that the CF_2N fluorines assigned to *cis*-**3** are nonequivalent and show the basic AB pattern with each member appearing as a doublet owing to coupling with the adjacent CFCl. This latter fluorine of the same invertomer appears as a doublet of doublets. The coupling constants for the ABX system of *cis*-**3** were calculated: J_{AB} = 116 Hz, J_{AX} = 12.7 Hz, and J_{BX} = 10.0 Hz (spectrum at −58°).[8]

Low-temperature nmr studies of compounds **2** and **3** indicated that the chemical-shift difference, δ, of the geminal fluorines of the invertomers was temperature dependent. The observed values of δ at various temperatures are listed in Table II. As has been previously reported,[3,5] such effects in four-membered ring compounds may be interpreted in terms of equilibrating nonplanar conformers. Since interconversion of conformers is rapid, only an average signal is observed. The puckered conformers involved are represented as follows.

TABLE II
FLUORINE–FLUORINE CHEMICAL-SHIFT DIFFERENCES[a]

Temp, °C	*cis*-**2** δ CF_2N, Hz	*trans*-**2** δ CF_2N, Hz	*cis*-**3** δ CF_2N, Hz
24	362	191	586
−13	396	154	554
−33	420	127	534
−60	443	102	513
−80	470	80	488
−105	498	55	465
−125	518	—	445

[a] These values were found to be essentially independent of changes in concentration (see Experimental Section).



Although the *trans* invertomer of **3** is likely a mixture of twon onplanar conformers, the apparent equivalence of the geminal fluorines throughout the temperature range investigated precluded the determination of δ. However, the single absorption does undergo a change in chemical shift with lowering of temperature, thus suggesting that variations in conformer population are likewise occurring with this invertomer.

For the equilibria above, it is assumed that the a conformation is the less stable owing to destabilization from the 1,3-diaxial chloro–N-halo interaction. The fraction of molecules, p, in conformation b is thus related to the conformational free-energy difference, ΔG, by the expression

$$p/(1 - p) = K = e^{-\Delta G/RT}$$

(7) The corresponding CF_2O fluorines of **1** show coupling with both CF_2N and N–F fluorines and give an ABMXY pattern.[3]

(8) K. B. Wiberg and B. J. Nist, "Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., pp 21–27.

The fraction, p, is also related to the chemical-shift difference, since the observed δ is the weighted average of the chemical-shift differences, δ_a and δ_b, of the individual conformers.

$$\delta = \delta_a + p(\delta_b - \delta_a)$$

Values of p at those temperatures shown in Table II were calculated for a range of ΔG's and were plotted *vs.* δ at the corresponding temperatures. ΔG values for the equilibria were those for which the best linear relationships were obtained. Values of δ_a and δ_b were readily calculated from the slopes. The determined chemical-shift differences of the conformers and the free-energy differences are listed in Table III.[9,10]

TABLE III
CONFORMATIONAL DATA

	cis-**2**	*trans*-**2**	*cis*-**3**
δ_a, Hz	−610	+1265	+1374
δ_b, Hz	+572	−6	+382
ΔG, cal/mol	−900 ± 100	−1000 ± 100	−800 ± 100

Comparison of the ΔG values for the invertomers of **2** and **3** with those of −900 and −1000 cal/mol obtained for **1** and **4**, respectively,[3] does not reflect much variation. These results suggest that for those oxazetidines studied, the conformer composition at any temperature will be nearly the same for all compounds, with conformer b predominating even at room temperature. In all cases, the proportion of conformer b at −120° would be greater than 0.93.

The relationship between p and the chemical-shift difference, δ, for the invertomers is shown in Figure 3. The negative sign for δ indicates a reversal in relative signal positions of the geminal fluorines. As related to the conformer of *trans*-**2**, the data suggest that as the temperature is lowered and the population of the more stable conformer b increases, the value of δ would approach 0 and then become slightly negative at $p = 1$. A low-temperature (−100°) spectrum shows that the CF_2N fluorines of *trans*-**2** are in fact becoming equivalent, since the inner members of the AB quartet are partially coalesced and the outer members are very small. It is interesting to note that this signal at the lower temperature resembles that of *trans*-**3**. This fact is consistent with the proposed *trans* configuration of these two invertomers.

The assignment of the CF_2N fluorines of the invertomers to specific nmr peaks was based on considerations made previously for the similar assignment of fluorines of perfluoro-2-fluoro-1,2-oxazetidine (**1**).[3] In the case of **1**, it was assumed that the fluorine *cis* to the N–F group would experience the greater variation in chemical shift as the temperature was lowered and the equilibrium favored conformer b. This would result in an increase in the number of molecules having the *cis* fluorine in an axial position or

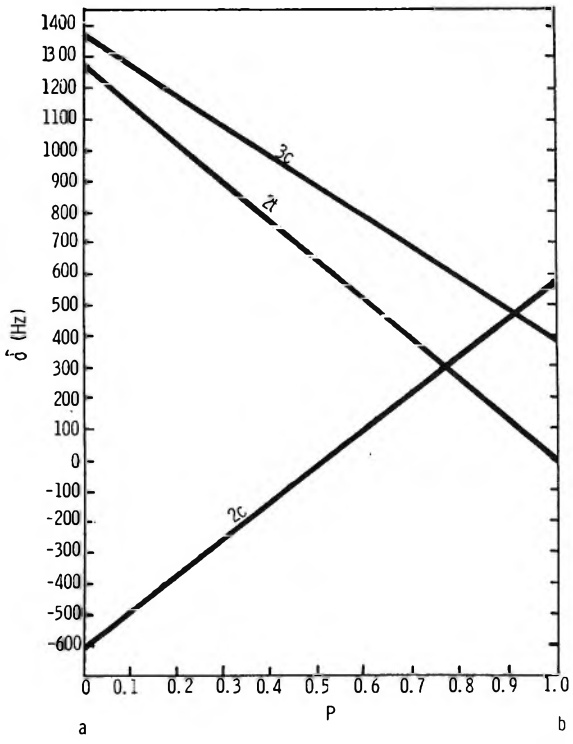


Figure 3.—Chemical-shift difference *vs.* conformer population.

situated axial and coplanar with the unshared pair of electrons on nitrogen. This particular steric relationship between a hydrogen and free electron pair has been reported to give rise to a pronounced upfield shift of the proton signal,[11] and hence might significantly affect the chemical shift of a similarly oriented fluorine. Since the broad unresolved upfield portion of the AB quartet of the CF_2N fluorines of **1** was essentially stationary over the temperature range studied (24 to −115°), the resolved downfield peaks which comprised the other half of the AB pattern and which underwent a substantial downfield shift on cooling were assigned to the *cis* fluorine As a result of the above, it further appeared that peak broadening provided another basis for configurational assignment.

The present results are completely consistent with the above observations and lend support to the assumptions made. Each AB quartet of the invertomers of **2** shows a noticeably broader portion, although the difference in peak broadness is not as pronounced as in **1**. The chemical shifts of the CF_2N fluorines obtained from spectra at several temperatures are given in Table IV, and when compared with the spectrum shown in Figure 1 indicate that the positions of the broader peaks of *cis*-**2** and *trans*-**2** are virtually unchanged over the temperature range studied.[12] Similarly evident from the data is the fact that the sharper members of the AB quartets of each invertomer move downfield as the temperature is lowered and the proportion of conformer b increases. These results allow for assignment of the fluorines *cis* to N–F to the sharper members and the *trans* fluorines to the broader members. Clearly the effect of temperature on δ for the

(9) It is assumed in this treatment that ΔG is constant over the temperature range studied, hence $\Delta S = 0$. Lambert and Roberts note[5] that although differences in conformer entropies may cause inaccuracies in determined values of ΔG, the demonstrated temperature dependence of δ still represents positive evidence for nonplanarity.

(10) ΔG for the conformers of *trans*-**3** could not be calculated. Since the observed chemical shift of the CFCl fluorine of this invertomer is also a weighted average of its shift in either conformer, the above treatment using this one absorption is theoretically possible. However, this signal of *trans*-**3** underwent only a very slight change over the temperature range, hence the above procedure was not applicable.

(11) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967).

(12) The differences in peak broadness are more pronounced in room-temperature spectra.

invertomers of **2** depends upon the relative signal positions of the *cis* and *trans* fluorines, since the *cis* fluorine moves downfield in each case.

The absence of coupling between the CFCl fluorine of *cis*-**2** and the fluorine on nitrogen has been noted. This fluorine thus appears as a doublet of doublets owing to coupling with the adjacent geminal fluorines.

TABLE IV

CF_2N FLUORINE PEAK POSITIONS AT SEVERAL TEMPERATURES[a]

Temp, °C	*cis*-**2**		*trans*-**2**		*cis*-**3**		*trans*-**2**
24	97.4	103.8	99.8	103.1	87.5	97.9	91.3
−60	96.0	103.8	99.9	101.7	87.4	96.4	90.6
−105	95.0	103.8	99.8	100.8	87.5	95.7	90.1
−125	94.7	103.8	...	...	87.5	95.4	89.6

[a] Determined chemical shift of each fluorine in parts per million with $CFCl_3$ as the internal standard.

The initial assignment of configuration to the invertomers of **2** is derived from the observation that the above doublet of doublet pattern resembles very closely that of the same fluorine in *cis*-**3**. Values of J, 10.6 and 12.7 Hz and 9.6 and 12.7 Hz, are obtained for the CFCl fluorines of *cis*-**2** and *cis*-**3**, respectively, from spectra at 24°. Since the proportion of conformers of each invertomer would be nearly the same, similarity of configuration is suggested. The pattern observed for the CFCl fluorine of *trans*-**2** suggests that this fluorine is coupled with the vicinal CF_2N fluorines as well as with N–F. Since invertomer *trans*-**2** is predominantly represented by conformer b at 24° and since the CF_2N fluorines in this conformer have essentially the same chemical shift, a triplet structure or a doublet of doublets with nearly equal values of J would be anticipated in the absence of NF coupling. The observed quartet (J = 11 Hz) therefore is more consistent with the interpretation that the CFCl fluorine undergoes equal coupling with the three neighboring fluorines.

As in the case of compound **1**,[3] the N–F signals for both *cis*-**2** and *trans*-**2** likewise experience a downfield shift with a lowering of temperature (ϕ −27.6 and −30.6, respectively, at −125°). This observed deshielding (0.7 and 0.6 ppm) may be interpreted as resulting from changes in the proportions of conformers a and b and further may be related to the increase in conformer b over the temperature range 24 to −125°. Thus approximate values representing the difference of the N–F chemical shift in the two possible conformations may be calculated. Values of 298 and 280 Hz for *cis*-**2** and *trans*-**2** invertomers, respectively, are estimated.[13]

The assignment of the nmr absorptions of the CF_2N fluorines of the invertomer *cis*-**3** was based on peak shape and chemical-shift change in a manner analogous to that used for the invertomers of **2**. The geminal fluorine AB pattern of *cis*-**3** consists of two broad downfield and two sharp upfield members, each of which appears as a doublet (Figure 2). The downfield portion which is attributed to the *trans* fluorine (relative to N–Cl) remained stationary, while the *cis* fluorine peaks moved downfield as the temperature was changed from 24 to −125° (Table IV). Coupling of each geminal fluorine with the adjacent CFCl results in the splitting at −58° of J(*trans*-F) = 12.7 Hz and J(*cis*-F) = 10.0 Hz. Since *cis*-**3** more closely resembles conformer b at this temperature, these values represent essentially the vicinal F–F equatorial–axial and axial–axial coupling constants, respectively. These results are consistent with those of Feeney, Sutcliffe, and Walker,[14] which related vicinal coupling constants to fluorine conformation as follows: equatorial–axial > axial–axial > equatorial–equatorial.

The single peak observed for the CF_2N fluorines of the invertomer *trans*-**3** at 24 and −125° clearly indicates that these fluorines have nearly the same chemical shift at both temperatures. The small value of δ at −125°, coupled with the assumption that *trans*-**3** is not too unlike the other three invertomers, hence leads to the conclusion that δ_b is small. That δ_a is likewise small is one manner in which the apparent equivalence of the geminal fluorines at 24° may be explained. In light of the relatively large differences in values of δ_a and δ_b for the other three invertomers, this explanation may at first appear to be somewhat unsatisfactory. However, it should be noted that whereas only one of the geminal fluorines of *cis*-**3** and *cis*- and *trans*-**2** undergo any significant change in chemical shift with variations in conformer population, both fluorines of *trans*-**3**, as represented by the single absorption, move upfield as the temperature is increased (Table IV). Similar behavior was observed for compound **4** and is reflected in the relatively small difference in the values of δ_a and δ_b (δ_a = 604 Hz and δ_b = 202 Hz).[3] In contrast are the values δ_a = −798 Hz and δ_b = 311 Hz[3] obtained for the CF_2N fluorines of **1**, fluorines whose chemical shifts respond to changes of conformer population as do those of the three invertomers. The absence of significant coupling between the fluorines of *trans*-**3** is not understood. There is only a suggestion of splitting in the CF_2N fluorine signal (<2 Hz), and the CFCl fluorine, which conceivably would appear as a triplet as a result of coupling with the nearly equivalent geminal fluorines, is at best a doublet (J = 3 Hz).

Experimental Section

Chromatographic preparative scale separations were accomplished with a Wilkens Autoprep Model A 700 utilizing a column (20 ft × 0.375 in.) containing 20% SF-96 on Chromosorb P.

The elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

Infrared spectra were obtained with a Perkin-Elmer Model 137 double-beam spectrophotometer. Spectra of gaseous samples were obtained with a 7.5-cm gas cell equipped with silver chloride windows.

A Bendix time-of-flight mass spectrometer (Model 12-101) with source elements S14-107 was employed to record the mass spectra at 70 eV.

The ^{19}F nmr spectra were obtained with a Varian Model V-4302B spectrometer operating at 56.4 MHz. The spectra were calibrated by the side-band modulation technique using a Hewlett-Packard wide-range oscillator. Chemical shifts and coupling constants represent the average of at least eight measurements. Errors of ±0.1 ppm and ±1 Hz, respectively, were estimated. For low-temperature studies, the variable-temperature accessory supplied by Varian was used. Temperature measurements were made both before and after recording spectra by means of a copper–constantan thermocouple immersed in a tube filled with a Kel-F oil. The temperature measurements are

(13) A value of 217 Hz was obtained for compound **1**.[3]

(14) J. Feeney, L. H. Sutcliffe, and S. M. Walker, *Trans. Faraday Soc.*, **62**, 2650 (1966).

believed to be accurate to ±1°. The chemical-shift differences (Table IV) obtained from nmr spectra of $CFCl_3$ solutions of **2** and **3** were essentially unchanged with the weight per cent of **2** varied from 30 to 75 and that of **3** varied from 35 to 75.

Perfluoro-4-chloro-1,2-oxazetidine (5) was prepared by hydrolysis of compound **6** as described previously.[3]

Perfluoro-4-chloro-2-fluoro-1,2-oxazetidine (2).—A 2-l. steel reactor (passivated with fluorine) was charged with NaF pellets (10 g), perfluoro-4-ehloro-1,2-oxazetidine (**5**, 5.0 g, 34 mmol), and fluorine (43 mmol) at −196°. The mixture was allowed to react for 5 hr and the excess fluorine was pumped off at −196°. Product **2** was collected as one peak by preparative glpc at 20°. Compound **3** could also be obtained from the reaction mixture, since it was initially present as an impurity in **5**. The infrared spectrum of **2** showed bands at 7.30 (s, ring), 7.75 (s), 8.3 (shoulder), 8.5 (s), 8.95 (s), 9.4 (s), 10.8 (w), and 12.3 μ (s). The mass spectrum of **2** showed peaks at *m/e* (rel intensity, ion) 130 (9.3, $C_2F_4NO^+$), 118 and 116 (10.6, 30.9, $C_2F_3Cl^+$), 97 (2.1, $C_2F_3O^+$), 87 and 85 (1.8, 5.3, CF_2Cl^+), 83 (4.6, CF_3N^+), 69 (10.1, CF_3^+), 66 (6.9, CF_2O^+), 64 (7.4, CF_2N^+), 50 (20.4, CF_2^+), 47 (100, COF^+), 45 (9.0, CFN^+), 37 and 35 (4.3, 14.9, Cl^+), 31 (62.8, CF^+), 30 (91.5, NO^+), and 26 (4.4, CN^+).

Anal. Calcd for C_2F_4ClNO: C, 14.52; H, 0.00; F, 45.92; N, 8.46. Found: C, 14.55; H, 0.00; F, 45.67; N, 8.10.

Perfluoro-2,4-dichloro-1,2-oxazetidine (3) was prepared by reaction of **5** (5.0 g, 34 mmol) and chlorine (32 mmol) in a 2-l. flask at room temperature for 5 hr. Product **3** was collected as one peak by preparative glpc at 20°. Its infrared spectrum showed bands at 7.40 (s, ring), 7.94 (s), 8.5 (s), 9.0 (s), 9.8 (s), 12.7 (m), and 13.3–13.4 μ (vs, broad). The mass spectrum of **3** showed peaks at *m/e* (rel intensity, ion) 181 (trace, $C_2F_3Cl_2NO^+$), 129 and 127 (0.6, 1.9, $C_2F_2ClNO^+$), 118 and 116 (6.2, 21.9, $C_2F_3Cl^+$), 101 and 99 (2.2, 7.5, CF_2NCl^+), 87 and 85 (1.1, 3.6, CF_2Cl^+), 82 and 80 (2.7, 7.5, $CFClO^+$), 69 (7.8, CF_3^+), 66 (2.2, CF_2O^+), 65 (0.6, $COCl^+$), 64 (8.0, CF_2N^+), 63 (2.6, $COCl^+$ or $CNCl^+$), 61 (2.4, $CNCl^+$), 50 (13.5, CF_2^+), 51 (2.4, CCl^+), 49 (9.6, NOF or CCl^+), 47 (100, COF^+), 45 (6.0, CFN^+), 37 and 35 (8.5, 30, Cl^+), 31 (40.6, CF^+), 30 (90, NO^+), and 26 (6.9 CN^+).

Anal. Calcd for $C_2F_3Cl_2NO$: C, 13.20; H, 0.00; F, 31.33; N, 7.70. Found: C, 13.45; H, 0.00; F, 31.60; N, 7.49.

Registry No.—*cis*-**2**, 23025-21-0; *trans*-**2**, 23025-22-1; *cis*-**3**, 23025-23-2; *trans*-**3**, 23025-24-3.

Acknowledgments.—The author wishes to thank Dr. Philip D. Readio for many helpful discussions, Mr. J. Bienvenue for his assistance in the preparation of the samples, and Mr. J. Christakos for the mass spectral determinations.

Organic Reactions in Liquid Hydrogen Fluoride. I. Synthetic Aspects of the Ritter Reaction in Hydrogen Fluoride[1]

JOHN R. NORELL

Phillips Research Center, Phillips Petroleum Company, Bartlesville, Oklahoma 74003

Received September 8, 1969

Liquid hydrogen fluoride effectively condenses an olefin and nitrile (Ritter reaction) to form N-substituted amides at ambient conditions. With linear monoolefins, *i.e.*, 1-octene and acetonitrile, three isomeric secondary amides are produced in yields of 80–90% when 0–10% water is present in the HF. Branched olefins, *i.e.*, 2-methyl-2-butene, which give tertiary carbonium ions, require 25–40% water in the reaction medium to obtain high yields of amides. With an olefin in which the tertiary carbon is remote from the point of unsaturation, as in the case of 3-methyl-1-butene, the major product is the amide derived from the tertiary carbonium ion *via* isomerization. The reaction has been applied to a variety of monoolefins and substituted nitriles, including HCN. Diolefins, in general, react poorly, giving viscous gums, although 2,5-dimethyl-1,5-hexadiene gave 2,5-diacetamido-2,5-dimethylhexane and norbornadiene gave N-3-nortricyclylacetamide.

Hydrogen fluoride, long known as a catalyst in alkylation reactions,[2] has received little attention as a solvent for organic reactions. This is undoubtedly due to the hazards associated with handling HF such as its toxicity and the rapid attack on glass. However, its volatility (bp 20°), its strong acid character ($H_0 = -9.9$), and the fact that it can be handled conveniently in polyethylene labware or Monel reactors suggest that HF could have distinct advantages over commonly used acid solvent systems such as sulfuric, polyphosphoric, etc.[2] We have examined several classes of reactions which normally are carried out in strong acids and wish to report our findings concerning the Ritter condensation of olefins and nitriles.

The acid condensation of an olefin, alcohol, or halide with a nitrile to form N-alkylamides has been extensively studied.[3] In most cases sulfuric acid was used either alone or with solvents such as acetic acid, but prior to this work no reports concerning the use of hydrogen fluoride as a solvent system has been noted.[4]

In the present study it was found that hydrogen fluoride is an excellent solvent system for the preparation of N-alkylamides and can be used at room temperature and atmospheric pressure for a variety of olefins and nitriles. Since conditions for optimum yields vary, these are discussed for linear olefins, which form secondary carbonium ions; branched olefins, which form tertiary carbonium ions; and cyclic and bicyclic olefins.

Results and Discussion

Linear Olefins.—Linear monolefins react smoothly with nitriles, including hydrogen cyanide, in hydrogen fluoride containing from 0 to 10% water to produce N-substituted amides at ambient conditions. Table

$$RCH{=}CHR' + R''CN \xrightarrow[H_2O]{HF} \underset{\displaystyle NHCOR''}{\overset{\displaystyle |}{RCHCH_2R'}}$$

(1) Portions of this paper were presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) G. A. Olah, "Friedel-Crafts and Related Reactions" Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1963, p 317 ff.

(3) (a) L. I. Krimen and D. J. Cota, *Org. Reactions*, **17**, 213 (1969); (b) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948); (c) E. N. Zil'berman, *Russ. Chem. Rev.* (Engl. Transl.), 311 (1960).

(4) During the course of this research, a patent was issued describing the use of hydrogen fluoride for preparing secondary alkyl, primary amines from linear olefins and nitriles: R. H. Potts, E. J. Miller, and A. Mais (to Armour and Co.), U. S. Patent 3,338,967 (1967).

TABLE I

REACTION OF LINEAR OLEFINS WITH NITRILES IN ANHYDROUS HYDROGEN FLUORIDE[a]

$$RCH{=}CH_2 + R'CN \xrightarrow{HF} \xrightarrow{H_2O} \text{amide}$$

R	R'	Yield, %	Amide produced	Compd no.	Bp, °C (mm)	$n^{20}D$	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	CH_3	4	N-Ethylacetamide	1	[b]							
CH_3	CH_3	23	N-Isopropylacetamide	2	93–94 (13)[c]	1.4297	59.35	10.98	13.84	58.55	11.10	13.78
n-C_3H_7	CH_3	72	N-(2- and 3-pentyl)acetamides	3	71–72 (0.3)	1.4394	65.07	11.70	10.84	64.92	11.86	10.70
n-C_6H_{11}	H[d]	40	Octylformamides	4	102–105 (0.6)	1.4473	68.74	12.18	8.90	68.56	11.94	8.70
n-$C_{16}H_{31}$	H	43	Octadecylformamides	5	186–194 (0.4)	[e]	76.67	13.24	4.71	77.00	13.50	4.86
n-C_6H_{11}	CH_3	92	N-(2-, 3-, and 4-octyl)acetamides	6	94–99 (0.3)	[e]	70.12	12.38	8.18	70.00	12.43	8.22
n-C_6H_{11}	CH_3OCH_2	61	N-(2-, 3-, and 4-octyl)methoxyacetamides	7	79–86 (0.3)	1.4479	66.53	11.51	6.96	65.59	11.48	6.90
n-C_6H_{11}	$ClCH_2$	65	N-(2-, 3-, and 4-octyl)chloroacetamides	8	93–96 (0.3)	1.4633	58.38	9.80	6.81	58.48	9.83	6.69
n-C_6H_{11}	Ph	71	N-(2-, 3-, and 4-octyl)benzamides	9	139–146 (0.3)	1.5125	77.21	9.93	6.00	77.15	9.78	6.04
n-$C_{10}H_{21}$	CH_3[f]	40	N-Dodecylacetamides	10	130–134 (0.3)	1.4515	73.95	12.86	6.16	74.74	12.68	5.95

[a] Reactions were run at 25–40° for 0.5–2 hr on a 0.10–0.50 *M* scale. [b] Not isolated in pure state, but determined by glpc comparison with an authentic sample. [c] Lit. bp 201–203°: B. T. Gillis, *J. Org. Chem.*, **24**, 1027 (1959). [d] HCN source was NaCN and SO_2 was employed as a cosolvent. [e] Solidified at room temperature. [f] SO_2 was employed as a cosolvent.

TABLE II

TEMPERATURE DEPENDENCE OF THE 1-OCTENE–ACETONITRILE CONDENSATION[a]

Temp, °C	Yield, %, of N-octyl-acetamides	Residue,[b] wt, g	Composition of residue, % 1-Octene	RF	Amides	"Heavies"	Other[c]	Isomer distribution of amides 2	3	4
−75	2	6.5	58	37	5	0	0	100	0	0
−50	8	7.7	0	76	18	4	2	87	10	3
−25	40	12.0	3	19	59	9	10	26	39	35
0	57	13.7	4	1	72	19	4	21	42	37
20	71	13.8	2	0	88	6	3	20	42	38
40	62	14.2	1	0	76	23	0	22	41	37
60	48	13.4	0	0	64	36	0	27	39	34
100	26	11.1	0	0	40	60	0	32	37	31

[a] Reaction was run with 0.10 mol each 1-octene and CH_3CN, with 48 ml of HF and 2 ml of H_2O for 2 hr. [b] Represents the "crude" weight of product produced after extraction with ether and flash evaporation; 100% yield of N-octylacetamides would be 17.1 g. [c] Represents unidentified volatile peaks on the glpc.

I illustrates a representative sampling of many of the nitrile–olefin combinations which were investigated. Significantly, when Ritter's original conditions of H_2SO_4–HOAc were employed, the olefins tabulated gave amides in very low yields (0–10%). Also to our knowledge, this is the first example of ethylene entering into an acid-catalyzed nitrile condensation, albeit in low yield.

Because of its ease of handling and availability, 1-octene was used as a model compound typifying a secondary olefin in the reaction with acetonitrile to demonstrate the effect of temperature and hydrogen fluoride/olefin ratios and to establish the extent of isomerization. With 1-octene, three N-octylacetamides are possible and all three are usually produced; the relative quantities are dependent upon conditions. Because of the carbonium ion nature of the reaction no 1 isomer was identified.

$$C_6H_{13}CH{=}CH_2 + CH_3CN \xrightarrow[H_2O]{HF}$$

$$CH_3\underset{\displaystyle NHCOCH_3}{\underset{|}{C}}HC_6H_{13} + C_2H_5\underset{\displaystyle NHCOCH_3}{\underset{|}{C}}HC_5H_{11} + C_3H_7\underset{\displaystyle NHCOCH_3}{\underset{|}{C}}HC_4H_9$$

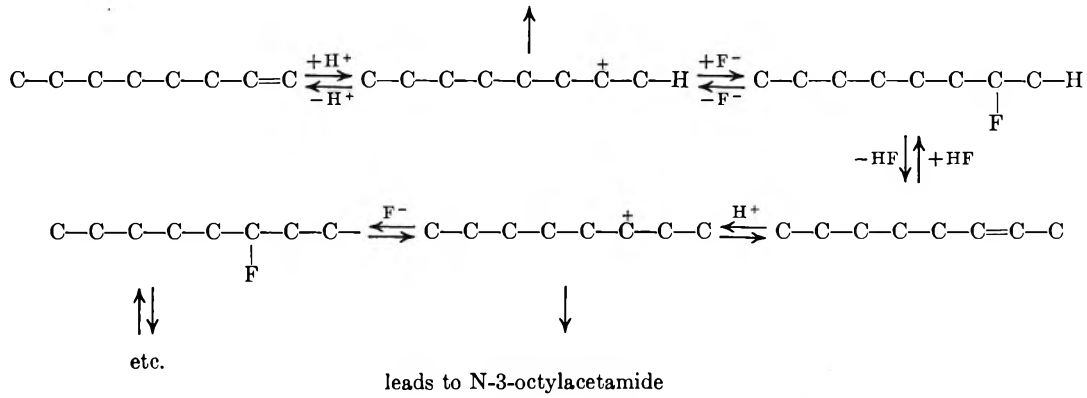
The reaction is temperature dependent (Table II) with the highest yields being produced near ambient conditions. In this study 4% water was present in the HF to minimize polymerization at the higher temperatures. The composition of the isolated residue was determined by glpc with an internal standard of dodecane to establish the amount of "heavies" present and was verified by distillation. Although the "heavies" could not be distilled, nitrogen was shown to be present by elemental analysis, and amidic groups were indicated by the infrared spectrum. It is significant that at low temperatures only octyl fluorides and unreacted octene were found along with a low yield of acetamides. The isomer distribution of the amides that were formed at low temperatures favored the 2 isomer, whereas at higher temperatures isomerization was more extensive.

High yields (80–85%) of N-octylacetamides are obtained when a mole ratio of hydrogen fluoride/1-octene is 10–30:1 with an isomer distribution of 2-, 3-, and 4-N-octylacetamides being about 1:2:2. With a mole ratio of 7.5:1 the yield drops to 56% and a 5:1 ratio gives a 33% yield; in both experiments a nearly 1:1:1 isomer distribution is obtained. The yield is only 7% with a 2.5:1 mole ratio and a 9:4:1 isomer ratio for the 2, 3, and 4 isomers is observed. A 1:1 mole ratio of hydrogen fluorido/1-octene gives no detectable N-octylacetamides. The lower yields indicate that insufficient HF is available for effectively carrying out the reaction as unreacted octene is recovered. Factors such as lowered dielectric constants or decreased H_0 values may be significant. Also HF has been shown by Wiechert, *et al.*,[5] to complex with acetonitrile in varying molar ratios [$CH_3CN/HF(HF)_n$] and a portion of the HF may be complexed in this manner thus decreasing the effective amount available for protonation at the lower concentrations. When 0–10% water is present in the HF, yields are optimal, but drop sharply at higher water concentrations (Figure 1) as will be discussed under Branched Olefins.

A small molar excess, preferably a 1.1:1.0 molar excess of nitrile/olefin, of either reactant does not

(5) K. Wiechert, H. H. Heilmann, and P. Mohr, *Z. Chem.*, **3**, 308 (1963).

SCHEME I



appear to be detrimental to the reaction (Table III). If a large excess of the olefin is employed, danger of polymerization is increased and on work-up the unreacted material is extracted with the product. Table III illustrates that when the nitrile/olefin ratio is

TABLE III
VARIATION OF NITRILE/OLEFIN RATIO

CH_3CN, g	1-Octene, g	CH_3CN/ 1-Octene	N-Octyl-acetamides	Isomer distribution 2	3	4
4.1	22.4	0.5	94	23	41	36
8.2	11.2	2.0	86	29	41	30
20.5	11.2	5.0	54	63	30	7
41.0	11.2	10.0	8	86	12	2

large (*ca.* 10), the nitrile acts as a solvent, decreases the yield, and alters the isomer distribution. The data shown were obtained at 25° with 2.5 mol of HF. A solvent such as liquid sulfur dioxide can be employed without adverse effects.

Yield and isomer distribution were insensitive to reaction time. When the reaction was run on a 0.10 *M* scale with a 25 *M* excess of HF at 25°, the yield remained at 82–88% over a time interval of 15–120 min. The isomer distribution of N-octylacetamides follows: 2 isomer, 26%; 3 isomer, 40%; and 4 isomer, 34%.

The initial location of the double bond in the octene has little effect on yield but alters the isomer composition to a small extent (Table IV).

TABLE IV
REACTION OF ISOMERIC OCTENES WITH ACETONITRILE IN HYDROGEN FLUORIDE

Olefin	Yield, %, of N-octyl-acetamides	Isomer distribution 2	3	4
1-Octene	87	32	38	30
2-Octene	85	21	46	33
3-Octene	83	23	45	32
4-Octene	85	18	49	33

Although anticipated, we observed no carbon-chain rearrangement as was found in the Koch carboxylation of olefins in strong acids.[6]

The variation of isomer distribution, *i.e.*, increased percentage of N-2-octylacetamide, appears to occur when the amount of HF is decreased and is always

(6) J. R. Norell, unpublished work; K. E. Moeller, *Angew. Chem. Intern. Ed. Engl.*, **2**, 719 (1963).

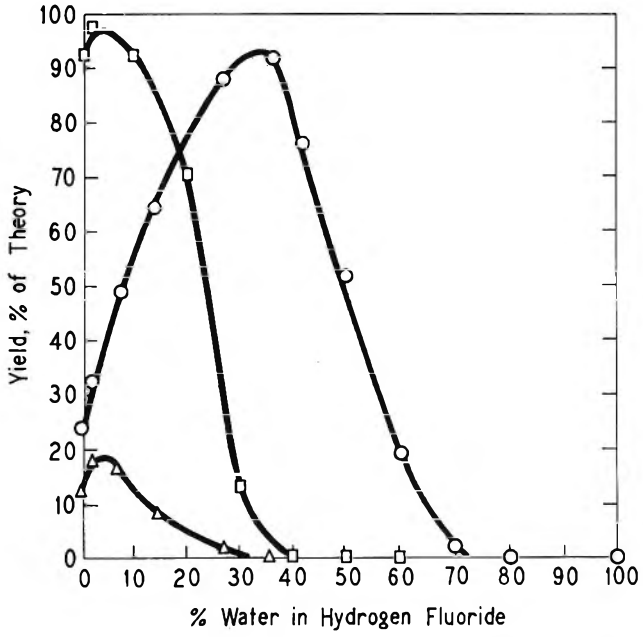


Figure 1.—Reaction of 2-methyl-2-butene and 1-octene with CH_3CN in aqueous HF at 40° for 2 hr using a total volume of 50 ml of H_2O–HF and 0.10 mol each of olefin and CH_3CN: □, N-octylacetamides from 1-octene; ○, *t*-amylacetamide from 2-methyl-2-butene; △, *t*-butylacetamide in crude product from reaction of 2-methyl-2-butene with CH_3CN.

accompanied by lower overall yield of the octylacetamides. Since the 2 isomer arises from stabilization of the 2-octyl carbonium ion, there is a strong indication that the isomerization occurs by a stepwise addition–elimination mechanism as suggested by Olson[7] in a similar study on the alkylation of aromatics with olefins, and not by a hydride migration (Scheme I). Under optimum conditions (*i.e.* large excess of HF) the free isomerized olefin is present only in transient amounts and the fluorooctane predominates as the nonnitrogen-containing intermediate. Furthermore the resulting loss of HF to form the isomerized olefin should be facilitated by the tendency to form HF_2^-. The preponderance of N-2-octylacetamide in media of low acid concentration may be due to two factors. (1) At lower acid concentrations the H_0 value is greatly decreased (100% HF = −9.9)[2] and hence the rate of protonation or the HF addition is much slower; thus, the rate of isomerization is decreased. (2) When

(7) A. C. Olson, *Ind. Eng. Chem.*, **52**, 833 (1960).

SO_2 or CH_3CN is present in excess the dielectric constant would be expected at be lower than that of pure HF (ϵ 85 at 0°) and hence the rate of ionization of the fluorooctane would decrease. Thus the rate-determining step for isomerization would seem to be ionization of the C–F bond, which would be less likely to occur in media of lower dielectric constant since the tendency of HF to form the HF_2^- ion should be less.

$$\underset{\underset{\text{F}}{|}}{\text{RCHCH}_3} + \text{HF} \longrightarrow \overset{+}{\text{R}}\text{CHCH}_3 + \text{HF}_2^-$$

Octyl alcohols or halides which may react as carbonium ion precursors were treated with acetonitrile in HF (Table V) to form N-octylacetamides. Under the specific conditions employed, primary alcohols and halides showed no tendency toward amide formation. Under these same conditions, the secondary chloro-, bromo-, and iodooctanes all gave either very low amide yields or no reaction at all, whereas 2-fluorooctane gave an amide yield comparable with that obtained with octene. 2-Octanol gave a high yield of amides and a "normal" isomer distribution.

TABLE V

VARIATION OF THE CARBONIUM ION SOURCE

$$C_8H_{17}X + CH_3CN \xrightarrow[2.\ H_2O]{1.\ HF,\ 25^\circ} C_8H_{17}NHCOCH_3$$

X	Yield, %, of acetamidooctanes	Recovered starting material, %
1-OH	0	80
2-OH	77	0
2-F	81	0
1-Cl	0	78
2-Cl	6	83
2-Br	0	99
2-I	0	92

The results appear at first glance to be inconsistent with the normally observed order of solvolysis rates for halides in that iodides solvolyze more readily than fluorides or chlorides because of the difference in bond strengths.[8] However, atoms which are strongly electronegative tend to be better leaving groups when they are in acidic media than when they are in neutral or basic solvents[9] because protonation and/or hydrogen bonding results in weakening of the C–X bond. Solvolysis of fluorides has been shown to be accelerated by acidic catalysts, whereas solvolysis of the other halides is not.[10] In this case, using HF as the acid catalyst gives an enhanced catalytic effect due to the tendency toward formation of the HF_2^-.[11] Thus the high yield of N-octylacetamide from 2-fluorooctane and not from the other halides is probably due to a combination of all the effects mentioned above.

Branched Olefins.—Table VI is representative of the branched olefins that were investigated with a variety of nitriles. As a convenient example of a branched olefin and precursor of tertiary carbonium ions, 2-methyl-2-butene was studied extensively in regard to its reaction with acetonitrile in various concentrations of aqueous HF to form *t*-amylacetamide (12). It was found that conditions that produce optimum yields of amides from a linear olefin, *i.e.*, 1-octene, give low yields with branched olefins and the converse is true. Several runs, which are displayed graphically in Figure 1, demonstrate that amide yields from branched olefins are optimized when 25–40% water is present in HF and that only 0–10% water should be present for linear olefin reactions.

A rationale for this striking difference seems to lie in the relative stabilities of the incipient carbonium ions which may be present during the course of the reaction. Three different carbonium ions are possible intermediates in this order of apparent stability: tertiary > imino > secondary.[12] For both linear and branched olefins there appear to be three distinct steps: protonation, nitrile attack, and hydrolysis and tautomerization. These are outlined in Scheme II for different situations, *i.e.*, linear olefins in concentrated HF and branched olefins in concentrated HF.

With linear systems in concentrated HF we have ready protonation, and nitrile attack is not extensively reversible because of the enhanced stability of the imino cation over a secondary carbonium ion.[12b] The hydrolysis proceeds in a normal fashion. However, when the acid is diluted, the protonating power to form secondary carbonium ions decreases and the first step in the reaction lies far to the left. Starting 1-octene is recovered along with little or no octyl fluoride, and traces of amidic products are obtained when 1-octene is allowed to react with acetonitrile in 60% aqueous HF.

Olefins with a branch on the olefinic carbon protonate readily even in dilute acid. We have found that conditions optimum for *t*-amylacetamide formation require 25–40% water in the HF (Figure 1). The nitrile attack is essentially nonreversible in aqueous acid because of the large amount of water present, which traps the adduct as the enol which in turn tautomerizes to the amide. In anhydrous conditions protonation is as extensive as in the linear system but now the reversibility of the nitrile attack is more pronounced. This reversal tends to build up concentrations of the *t*-amyl cation which in turn can dimerize with free olefin and then fragment to *t*-butyl and hexyl cations.[13] Both polymerized products and *t*-butylacetamide were observed but interestingly no N-hexylacetamide was found under our analytical techniques. Figure 1 shows the extent of *t*-butylacetamide formation arising from fragmentation of the *t*-amyl cation in very strong acid solutions. A maximum in amide yield is observed at a water concentration of about 40% (in HF). Since the initial reaction is protonation of the olefin, the latter concentration may be used as an indication of the cessation of the reaction of carbonium ion formation, which in turn, could conceivably be due to the acid strength of the system.

3-Methyl-1-butene reacted with acetonitrile and HF under "secondary carbonium ion" conditions to give

(8) E. S. Gould, "Mechanism and Structure of Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 261.

(9) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 50.

(10) W. T. Miller and T. Bernstein, *J. Amer. Chem. Soc.*, **70**, 3600 (1948).

(11) N. B. Chapman and J. L. Levy [*J. Chem. Soc.*, 1677 (1952)] have shown that the solvolysis of secondary alkyl fluorides is autocatalytic when the initial concentration of acid is low because of the generated HF.

(12) (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N Y., 1962, p 226; (b) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, p 169.

(13) S. H. Patinkin and B. S. Friedman in "Friedel-Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 48.

TABLE VI

REACTION OF BRANCHED OLEFINS WITH NITRILES IN HYDROGEN FLUORIDE[a]

Olefin	RCN	% HF concn	Yield, %[b]	Amides produced	Compd no.	Mp or bp (mm), °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2-Methyl-2-butene	HCN	70	70	$C_2H_5C(CH_3)_2NHCHO$	11	58–60 (0.5)	62.57	11.37	12.16	62.09	11.40	12.18
2-Methyl-2-butene	CH_3CN	64	91	$C_2H_5C(CH_3)_2NHCOCH_3$	12	78–79[c]						
2-Methyl-2-butene	CH_3CN	100	24	$C_2H_5C(CH_3)_2NHCOCH_3$	12	[d]						
			8	$(CH_3)_3CNHCOCH_3$	13							
3-Methyl-1-butene	CH_3CN	100	24	$C_2H_5C(CH_3)_2NHCOCH_3$	12	70–94[d]						
			4	$(CH_3)_2CHCH(CH_3)NHCOCH_3$	14							
2,3-Dimethyl-2-butene	CH_3CN	70	65	$(CH_3)_2CHC(CH_3)_2NHCOCH_3$	15	68–69	67.08	11.97	9.78	67.26	11.78	9.80
3,3-Dimethyl-1-butene	CH_3CN	100	50	$(CH_3)_2CHC(CH_3)_2NHCOCH_3$	15							
			12	$(CH_3)_3CCH(CH_3)NHCOCH_3$	16	69–76 (0.4)[e]						
Vinylcyclohexane	CH_3CN	80	60[f]	N-1-Ethylcyclohexylacetamide[d]	17							
1-Ethylcyclohexanol	CH_3CN	70	84	N-1-Ethylcyclohexylacetamide	17	69–70[g]						
2-Methyl-2-butene	$ClCH_2CN$	70	42	$C_2H_5C(CH_3)_2NHCOCH_2Cl$	18	49–51	[h]					
2-Methyl-2-butene	Cl_2CHCN	70	87	$C_2H_5C(CH_3)_2NHCOCHCl_2$	19	105–107	42.44	6.61	7.07	41.72	6.45	7.20
2-Methyl-2-butene	C_6H_5CN	70	70	$C_2H_5C(CH_3)_2NHCOC_6H_5$	20	92–93[i]	75.35	8.96	7.32	75.36	8.74	7.44
2-Methyl-2-butene	CH_3OCH_2CN	70	79	$C_2H_5C(CH_3)_2NHCOCH_2OCH_3$	21	55 (0.4)[j]	60.34	10.77	8.80	59.88	10.62	8.44

[a] Run at 25–40° for 2 hr. [b] No attempts were made to optimize the yields. [c] Lit.[35] mp 78–79°. [d] Composition was determined by glpc and comparison with authentic sample. [e] Composition was determined by nmr (see Experimental Section). Boiling point represents boiling point of the mixed amides. [f] Two isomeric but unidentified amides were present in 22% yield for a total amide yield of 82%. [g] Lit. mp 71–72°. N. K. Kochetkov, *et al.*, *Zh. Obshch. Khim.*, **29**, 3613 (1959). [h] Lit.[3b] bp 62–63° (1 mm). [i] Reference 3b cites mp 81–82° which we believe is in error. [j] $n^{20}D$ 1.4400.

SCHEME II

For linear olefins in concentrated HF

$$C_6CH{=}CH_2 + HF \rightleftharpoons C_6\overset{+}{C}H{-}CH_3 \rightleftharpoons C_6CHCH_3 \quad \text{(protonation)}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad F$$

$$C_6\overset{+}{C}HCH_3 + CH_3CN \rightleftharpoons C_6CHCH_3 \overset{F^-}{\rightleftharpoons} C_6CHCH_3 \quad \text{(nitrile attack)}$$
$$\qquad\qquad\qquad\qquad\qquad\quad N{=}\overset{+}{C}CH_3 \qquad\qquad N{=}CFCH_3$$

$$RN{=}CFCH_3 + H_2O \longrightarrow RN{=}\underset{OH}{C}CH_3 \longrightarrow RNHCOCH_3 \quad \text{(hydrolysis and tautomerization)}$$

For branched olefins in concentrated HF

$$(CH_3)_2C{=}CHCH_3 + HF \rightleftharpoons (CH_3)_2\overset{+}{C}CH_2CH_3 \rightleftharpoons (CH_3)_2CFCH_2CH_3 \quad \text{(protonation)}$$

$$(CH_3)_2\overset{+}{C}CH_2CH_3 + CH_3CN \rightleftharpoons (CH_3)_2CCH_2CH_3 \rightleftharpoons (CH_3)_2CCH_2CH_3 \quad \text{(nitrile attack)}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad N{=}\overset{+}{C}CH_3 \qquad\qquad N{=}CFCH_3$$

fragmentation and/or polymerization

$$R'N{=}CFCH_3 + H_2O \longrightarrow R'N{=}\underset{OH}{C}CH_3 \longrightarrow R'NHCOCH_3 \quad \text{(hydrolysis and tautomerization)}$$

the isomerized *t*-amylacetamide (**12**) and N-(1,2-dimethylpropyl)acetamide (**14**) in a ratio of 6.3:1 with an overall amide yield of only 28%. Employing "tertiary carbonium ion" conditions the yield was 10% and the ratio of migrated to nonmigrated amide was 12:1. This type of olefin presents a peculiar problem

$$\begin{matrix} C{-}C{-}C{=}C \\ \quad | \\ \quad C \end{matrix} + CH_3CN \xrightarrow{HF\text{–}H_2O}$$

$$\begin{matrix} \quad\quad\quad NHCOCH_3 \\ C{-}C{-}C{-}C \\ \quad | \\ \quad C \\ \quad\quad 12 \end{matrix} + \begin{matrix} \quad\quad NHCOCH_3 \\ C{-}C{-}C{-}C \\ \quad | \\ \quad C \\ \quad 14 \end{matrix}$$

in optimization of yields in that it is a secondary olefin but, after protonation, migration occurs and a tertiary carbonium ion is formed, which then tends to polymerize and fragment in the strong acid system. Under tertiary carbonium ion conditions, *i.e.*, dilute acid, the olefin is not protonated easily and hence the reaction proceeds very poorly.

2,3-Dimethyl-2-butene reacted smoothly with acetonitrile in HF under tertiary carbonium ion conditions to give the expected N-(1,1,2-trimethylpropyl)acetamide (**15**). Extensive methyl migration occurred with 3,3-dimethyl-1-butene; the ratio of migrated (**15**) to nonmigrated (**16**) amide was 4:1.

$$\begin{matrix} \quad C \\ \quad | \\ C{-}C{-}C{=}C \\ \quad | \\ \quad C \end{matrix} + CH_3CN \xrightarrow[2.\ H_2O]{1.\ HF}$$

$$\begin{matrix} \quad\quad C \\ \quad\quad | \\ C{-}C{-}C{-}C \\ \quad | \quad | \\ \quad C \quad NHCOCH_3 \\ \quad\quad\quad 16 \end{matrix} + \begin{matrix} \quad C \quad C \\ \quad | \quad | \\ C{-}C{-}C{-}C \\ \quad\quad | \\ \quad\quad NHCOCH_3 \\ \quad\quad\quad 15 \end{matrix}$$

As shown in Table VII a variety of nitriles react with 2-methyl-2-butene to give good yields of the respective amide at 40° with 70% aqueous HF.

TABLE VII

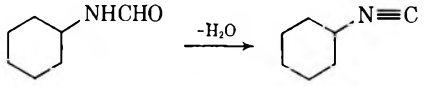
REACTION OF CYCLIC AND BICYCLIC OLEFINS WITH NITRILES IN ANHYDROUS HYDROGEN FLUORIDE[a]

Olefin	RCN	Yield, %	Amides produced	Compd no.	Mp or bp (mm), °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Cyclohexene	HCN[b]	67	Cyclohexylformamide	22	94–97 (0.4)	*c*					
Cyclopentene	CH_3CN	40	N-Cyclopentylacetamide	23	89–92 (0.5)	*d*					
1-Methylcyclohexene	CH_3CN[e]	80	N-1-Methylcyclohexylacetamide	24	84–86	*f*					
Cycloheptene	CH_3CN	62	N-Cycloheptylacetamide[g]	25	129–130 (0.8)	*h*					
Cyclododecene	CH_3CN[i]	85	N-Cyclododecylacetamide	26	141–142	74.66	12.00	6.22	74.29	12.24	6.16
Cyclohexene	CH_3CN	72	N-Cyclohexylacetamide	27	106–107	*j*					
Cyclohexene	$ClCH_2CN$	67	N-Cyclohexylchloroacetamide	28	106–108	*k*					
Cyclohexene	Cl_2CHCN	66	N-Cyclohexyldichloroacetamide	29	139–140	*l*					
Cyclohexene	C_6H_5CN	86	N-Cyclohexylbenzamide	30	148–150	*m*					
Cyclohexene	CH_3OCH_2CN	50	N-Cyclohexylmethoxyacetamide	31	60–62	63.12	10.01	8.18	63.82	9.96	8.12
Cyclohexene	$(CH_3)_3CCN$	67	N-Cyclohexylpivalamide	32	121–123	*n*					
Cyclohexene	CF_3CN	80	N-Cyclohexyltrifluoroacetamide	33	94–95	*o*					
Bicyclo[3.2.1]octene-2	CH_3CN	86	N-Bicyclo[3.2.1]oct-2-ylacetamide	34	132–134	*p*					
Norbornene	CH_3CN	74	N-2-Norbornylacetamide	35	140–141	*q*					
Norbornadiene	CH_3CN	Low	N-3-Nortricyclylacetamide	36	106–107	71.49	8.66	9.26	71.43	8.69	9.22
1,5-Cyclooctadiene	CH_3CN	Low	N-(*cis*-2-Bicyclo[3.3.0]octyl)acetamide	37	135–136	71.92	10.26	8.39	71.76	10.35	8.40

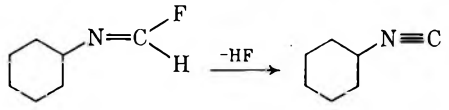
[a] All reactions were run at room temperature (25°) for 0.5–2 hr with 100% HF. [b] Run at 54° for 5 hr in 85% HF. [c] Lit. bp 150–158° (18 mm): H. E. Albert, U. S. Patent 2,819,306 (1958). [d] Lit. bp 146–149° (22 mm): E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950). [e] Used 85% HF at 40°. [f] Lit. mp 84–85°: H. E. Baumgarten, F. A. Bower, R. A. Setterquist, and R. E. Allen, *J. Amer. Chem. Soc.*, **80**, 4588 (1958). [g] No evidence for ring contraction by glpc. [h] Lit. bp 147–148° (3 mm): M. Murakami, K. Akagi, and Y. Mori, *Bull. Chem. Soc. Jap.*, **35**, 11 (1962). [i] Temperature 10°. [j] Lit. mp 107–109°: E. K. Harville, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 622 (1950). [k] Lit. mp 105–106°: M. Baker, *Compt. Rend.*, **233**, 66 (1951). [l] Lit. mp 140°: B. J. H. Heywood, British Patent 712,745 (1954). [m] Lit. mp 148–149°: D. B. Denney and G. Feig, *J. Amer. Chem. Soc.*, **81**, 227 (1959). [n] Lit. mp 122.5°: W. M. Degnan and C. J. Shoemaker, *ibid.*, **68**, 104 (1946). [o] Lit. mp 93–94°: E. J. Bourne, S. H. Henry, C. E. N. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952). [p] Lit. mp 134°: F. Derich and H. Bueren, German Patent 1,167,337 (1964). [q] Lit. mp 143–144° for *exo* amide, 131–132° for *endo* amide: J. A. Berson and D. A. Ben-Effraim, *J. Amer. Chem. Soc.*, **81**, 4094 (1959).

Cyclic and Bicyclic Olefins.—Cyclic olefins behave similarly to linear systems with no evidence of ring contraction being observed. Table VII illustrates that cyclohexane, cycloheptene, cyclopentene, and cyclododecene all give fair to good yields of the respective amides when run in 90–100% HF (secondary carbonium ion conditions). With cycloheptene, ring contraction was expected[14] but no N-1-methylcyclohexylacetamide (**24**) was found. 1-Methylcyclohexene reacted smoothly as a tertiary olefin to give an 80% yield of the expected amide (**24**) when run in 72% HF.

With hydrogen cyanide, cyclohexene gave the best yield (67%) of cyclohexylformamide (**22**) when run in 85% HF at 54° for 5 hr on a 2.0 *M* scale. If 100% HF is employed, only traces of the formamide are obtained along with a fair yield of N,N′-dicyclohexyl-2-cyclohexylaminomalonamide and polymeric material.[15] Hence, even though cyclohexene is a secondary olefin, it is preferable to use about 15% water and heat to 40–60° when preparing formamides from HCN. The source of HCN can be either the pure acid or formation *in situ* from the sodium or potassium salt. In this case, when the reaction is not run to completion, *i.e.*, shorter time (2 hr) and decreased temperature (16°), reaction intermediates and by-products can be identified. The composition of that portion of the reaction product which could be distilled contained 35% cyclohexyl fluoride, 6% cyclohexyl formate, 9% cyclohexanol, 50% cyclohexylformamide, and a trace of cyclohexylisonitrile. The fluoride, alcohol, and formamide are all readily explained, and cyclohexyl formate may arise by addition of formic acid (*via* HCN hydrolysis) to cyclohexene. Cyclohexylisonitrile may arise *via* two routes: (a) The dehydration of cyclohexylformamide by HF (the dehydration of formamides by P_2O_5 and other strongly dehydrating agents is a well-known method for preparing isonitriles[16] and HF has long been noted as a strong dehydrating agent);[2] (b) an alternative route is *via* dehydrofluorination of the

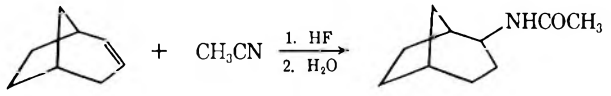


intermediate imidoyl fluoride by an α elimination of HF. The isonitrile was first observed by its foul odor



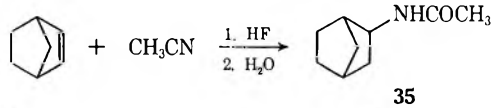
and then independently prepared by the method of Ugi, *et al.*,[16] and characterized in the mixture.

Although not extensively studied, the bicyclic olefins norbornene and bicyclo[3.2.1]oct-2-ene gave the respective amides with no detectable rearrangement. The amide isolated from norbornene appeared to be chiefly the *exo* isomer from melting point characteristics (see Table VII). The bicyclic diene

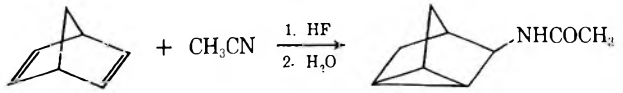


34

norbornadiene gave N-3-nortricyclylacetamide [N-3-tricyclo[2.2.1.0^{2,6}]heptyl)acetamide] (**36**) in low yield.



35



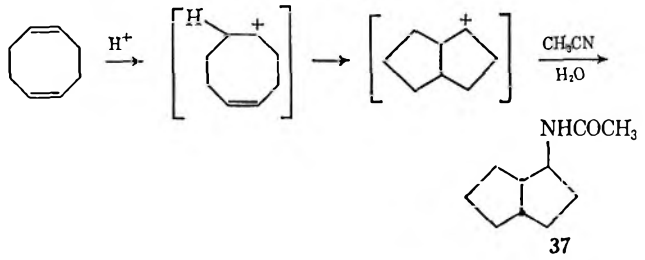
36

(14) R. Jacquier and H. Christol, *Bull. Soc. Chim. Fr.*, 596 (1957).

(15) The reaction of an olefin with HCN in HF represents a new synthesis for 2-aminomalonamides and is the subject of another paper: J. R. Norell, *J. Org. Chem.*, **35**, 1619 (1970).

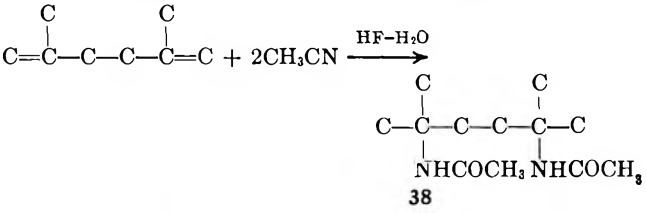
(16) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offenum, *Angew. Chem. Intern. Ed. Engl.*, **4**, 472 (1965).

Another transannular reaction occurred with 1,5-cyclooctadiene which gave N-(*cis*-2-bicyclo[3.3.0]octyl)-acetamide (**37**) in low yield. In general diolefins



37

react rather poorly in this reaction, forming a polymeric gum, high in nitrogen content. One exception was 2,5-dimethyl-1,5-hexadiene which gave 2,5-diacetamido-2,5-dimethylhexane (**38**) in 22% yield.



38

All the amides prepared in this work were characterized by comparison with known compounds or the structure was established by elemental analyses and infrared and nmr spectroscopy and the purity was checked by gas chromatography.

In summary, it has been found that N-substituted amides are conveniently prepared from linear or branched olefins by reaction with a nitrile or hydrogen cyanide in a hydrogen fluoride solvent. Yields are optimal for linear olefins when the HF contains 0–10% water, whereas, for branched olefins, 25–40% water is required, and temperatures of 20–40° are favored.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord, nmr spectra were run on a Varian A-60 spectrometer, and the mass spectra were obtained on a high resolution CEC mass spectrometer, Model 21-110. Purity of the amides produced was determined on an F & M Model 500 gas chromatograph using a 9-ft Apiezon L on Chromosorb W column programmed from 75 to 275° at 15°/min with a He flow rate of 80 cc/min.

Chemicals.—*CAUTION!* When handling anhydrous HF, a face shield, rubber gloves with plastic arm bands, and a protective apron are worn, using excellent hood facilities. Colorless hydrogen fluoride (99.9% from Air Products, Inc., Allentown, Pa.) is withdrawn in the liquid phase by inverting the cylinder and taking off the liquid HF through a Monel Hoke valve in addition to the cylinder valve. The liquid is allowed to drip directly into a polyethylene graduate where it readily condenses as a fuming liquid and is then poured into one of the two reaction vessels. No special precautions are taken to exclude moisture and air. All olefins and nitriles were commercially available and were distilled when the purity was in doubt. Hydrogen cyanide was obtained from E. I. du Pont de Nemours and Co. and was stabilized with P_2O_5.

Apparatus.—For reactions at room temperature or below, a reaction vessel was fabricated from high-density polyethylene into the shape of a cylinder (*ca.* 500 ml) with the bottom beveled so that an egg-shaped magnetic stirring bar could be inserted. Atop the cylinder were "welded" two female sections of Polycone (obtained from Cole-Parmer, Inc., Chicago, Ill.). A polyethylene plug containing a Weston stainless steel thermometer was inserted in one of the standard tapered openings. To a polyethylene separatory funnel was "welded" the male section of a Polycone so that a snug fit could be made into the other opening of the reactor. This ensured a reaction system which was completely inert to attack by HF. For reactions above room temperature or where a gas was involved, a 300-ml Monel reactor was used which was fitted with a pressure gauge and a thermocouple and could be shaken in a heated bath.

General Method for Preparation of N-Alkylamides.—One of the reaction vessels was cooled in ice and charged with a total of 50 ml of water and HF depending on the percentage acid concentration desired. The nitrile (0.10–0.25 mol) was added, followed by dropwise addition of the olefin (0.10–0.20 mol), and the reactor was capped and maintained at the desired temperature for the indicated time. The contents were poured on ice water (*ca.* 300 ml) and made strongly basic with an excess of concentrated NH_4OH. The amides were extracted with CH_2Cl_2 or ether, dried ($MgSO_4$-K_2CO_3), concentrated, and purified by distillation or recrystallization (hexane or hexane–ethanol). Tables I, VI, and VII list the physical properties for the amides obtained. Where the reaction was not so straightforward as described above, amplification of the procedure is given below.

N-Ethylacetamide (1).—HF (75 ml) and CH_3CN (0.55 mol) were placed in the Monel reactor and pressured to 400 psig with ethylene at 20°. The pressure dropped to 250 psig (*ca.* 1 hr) and was repressured to 400 psig; the process was repeated until 0.57 mol had been added. The reactor was shaken an additional 17 hr and the pressure dropped to 150 psig. On work-up (extraction with CH_2Cl_2) 2.9 g of a yellow oil was obtained containing 50% 1 as determined by glpc comparison with an authentic sample.

N-Isopropylacetamide (2).—HF (75 ml) and CH_3CN (0.55 mol) were placed in the Monel reactor and pressured with propylene, and the reactor was shaken at 10°. The pressure rapidly fell to 10 psig and was repressured to 100 psig; this process was repeated 12 times to give 0.52 mol of propylene. Isolated yield was low (23%) because of difficulties in extracting the highly water-soluble amide.

N-(2- and 3-Pentyl)acetamides (3).—1-Pentene (0.20 mol), CH_3CN (0.26 mol), and HF (50 ml) gave 15.6 g of distilled acetamidopentanes. The 2 and 3 isomers could not be separated by our glpc technique and were independently prepared by acetylation of the corresponding amines, N-2-pentylacetamide, bp 70° (0.2 mm), and N-3-pentylacetamide, mp 69–70°. The carbon-migrated N-*t*-amylacetamide was likewise independently synthesized, mp 78–79°, and was readily distinguished from the other isomers by glpc. None of the latter compound was found in the reaction mixture with 1-pentane.

N-(2-, 3-, and 4-Octyl)acetamides (6).—As described in the discussion these were prepared by a variety of conditions from octenes, CH_3CN, and HF. The mixture of the 2, 3, and 4 isomers was a liquid which solidified on prolonged standing. The individual isomers were independently prepared from the ketone *via* the oxime followed by $LiAlH_4$ reduction according to the method of Geiseler, *et al.*[17]

N-Dodecylacetamides (10).—1-Dodecene (0.10 mol), CH_3CN (0.11 mol), HF (25 ml), and SO_2 (75 ml) gave a 40% purified yield of the mixed dodecylacetamides.

Reaction of 3,3-Dimethyl-1-butene with CH_3CN in HF–SO_2.—3,3-Dimethyl-1-butene (0.10 mol), CH_3CN (0.10 mol), and 25 ml of HF in 50 ml of SO_2 gave 9.0 g of a crude amide mixture which was distilled, bp 69–76° (0.4 mm), and solidified to white crystals, mp 54–56°. Glpc analysis indicated only one peak; however, the nmr spectrum indicated that 80% of the material was the carbon-migrated compound, N-(1,1,2-trimethylpropyl)-acetamide (**15**), and 20% was N-(1,2,2-trimethylpropyl)acetamide (**16**). Three observations in the nmr spectrum point to this conclusion: (1) a very small but detectable N–H doublet is present at δ 7.92 in addition to the strong N–H singlet at 7.59 of **15**; (2) a small rise in the integral occurs at δ 3.80 indicative of $HCNHCOCH_3$ of **16** which is not present in pure **15**; (3) two $-COCH_3$ bands occur at 8.1 μ. The methyl band at 9.08 μ is greatly enhanced in area. Elemental analysis of the mixture gave the correct percentages (see Table VI).

Reaction of 3-Methyl-1-butene with CH_3CN–HF.—HF (50 ml) and CH_3CN (0.20 mol) were placed in the polyethylene reactor and cooled in an ice bath. 3-Methyl-1-butene (0.20 mol) which had been condensed in a Dry Ice bath was added slowly by means of a cooled pipet, and the mixture was allowed to gradually warm

(17) G. Geiseler, F. Asinger, and G. Henning, *Chem. Ber.*, **94** 1008 (1961).

to room temperature. The contents were poured on ice, neutralized with NH_4OH, dried (K_2CO_3), extracted with ether, and concentrated to give 11.45 g of a yellow oil. Glpc analysis of the oil indicated the following components (%): ether (5); *t*-amyl alcohol (29), arising from hydrolysis of the intermediate *t*-amyl fluoride; unknown (2); *t*-amylacetamide (54); and N-(1,2-dimethylpropyl)acetamide (9). The ratio of *t*-amylacetamide to N-(1,2-dimethylpropyl)acetamide was 6.3 with the yield of amidic products being 7.23 g (28% yield). The mixture was recrystallized from hexane to a white crystalline mixture, mp 70–74°.

N-Cyclohexylformamide (22).—A 1-l. Monel autoclave with a bottom tap was charged with HF (14.5 mol), water (2.8 mol), and liquid HCN (2.4 mol) and the temperature was maintained at 16° with circulating cooling water. Cyclohexene (2.0 mol) was added over a period of 45 min at 16° and the reactor was then heated to 54° for 5 hr. The reaction mixture was discharged through the bottom tap, poured on ice water, neutralized with NH_4OH, extracted (Et_2O), dried ($MgSO_4$), and concentrated to give 242.6 g of a light brown liquid. Glpc analysis indicated the following (%): ether (5); cyclohexanol (trace); cyclohexyl formate (9); and cyclohexylformamide (86). Distillation gave the pure formamide, bp 95–97° (0.4 mm).

In a similar run at 16° for 2 hr in addition to the above-mentioned materials cyclohexyl fluoride and cyclohexyl isonitrile were also isolated.

N-Cycloheptylacetamide (23).—Cycloheptene (0.20 mol) was added to a mixture of HF (50 ml) and CH_3CN (0.30 mol) at 10°. After warming to room temperature, the mixture was stirred for 30 min, poured on ice, neutralized with NH_4OH, extracted (Et_2O), dried ($MgSO_4$), and concentrated to give 25.0 g of crude amide. Glpc analysis indicated only one peak. Distillation gave the pure amide, bp 126–129° (0.8 mm), which melted at 51–55°. None of the ring-contracted material, N-1-methylcyclohexylacetamide, was found as determined by independently synthesizing the material and spiking the mixture prior to glpc analysis. Also the nmr spectrum indicated no ring contraction ($CDCl_3$), δ 7.50 (d, 1, J = 9.5 Hz, N–H), 3.90 (m, 1, ring H α to nitrogen), 1.82 (s, 3, $COCH_3$), and 1.53 (m, 16, ring hydrogens).

N-Cyclohexyltrifluoroacetamide (33).—A 300-ml Monel reactor was charged with 50 ml of HF, cooled in a Dry Ice bath, and charged with trifluoroacetonitrile (0.28 mol), bp −64°, by pressuring the gas into the reactor until the desired loss in weight was achieved. Cyclohexene (0.25 mol) was placed in a stainless steel bomb, pressured to 100 psig with N_2, and attached to the Monel reactor in such a way that the olefin could slowly be added to acid mixture. The reaction mixture was then shaken at 30° for 4 hr. After the material was poured on ice, neutralization, extraction, drying, and concentration gave 38.9 g of red-orange, low melting crystals. The material that was distilled [bp 77° (3.0 mm)] solidified to a crystalline mass, mp 93.5–94.5° (hexane).

N-(*cis*-2-Bicyclo[3.3.0]octyl)acetamide (37).—A mixture of HF (75 ml) and acetonitrile (0.60 mol) was cooled to −50° and 1,5-cyclooctadiene (0.20 mol) was added slowly. The mixture was allowed to warm to 0° over a period of 40 min and poured on ice. Neutralization, extraction, drying, and contration gave 28.1 g of a yellow viscous residue which could not be distilled but could be recrystallized from cyclohexane or pentane or sublimed [150–220° (0.2 mm)] to give white crystals, mp 135–136°. Infrared spectrum indicated the normal amide bands at 3.1 (N–H) and 6.1 μ (C=O); glpc analysis suggested only one component; and the nmr spectrum ($CDCl_3$) consisted of δ 6.78 (d, N–H), 1.92 (s, 3, $COCH_3$), and 1.8 (m, 13, ring protons).

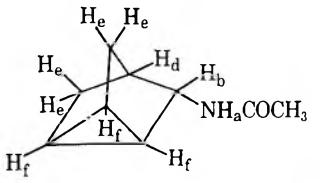
2,5-Diacetamido-2,5-dimethylhexane (38).—A mixture of HF (75 ml) and CH_3CN (0.60 mol) was cooled to −50° and 2,5-dimethyl-1,5-hexadiene was added over a period of 5 min. After the mixture warmed to 0° over a period of 30 min, it was poured on ice and neutralized with NH_4OH. White solids formed, which floated to the top and were filtered and air dried to give 31 g of crude diamide. Recrystallization (EtOH), followed by washing with ether, gave 10 g of white crystals, mp 226–228°. No attempt was made to recover additional product. The diamide exhibited interesting solubility characteristics in that it was insoluble (0.3 g in 1–2 ml of solvent) in $CHCl_3$, acetone, dimethyl sulfoxide, dimethylformamide, benzene, pyridine, and water and was soluble in MeOH, hot EtOH, warm dimethylformamide, dilute HCl, CH_3CO_2H, CF_3CO_2H, and concentrated H_2SO_4. The infrared spectrum (Nujol) consisted of 3.14 (N–H) and 6.15 μ (C=O); nmr (CF_3CO_2H) δ 8.28 (s, 2, N–H), 2.47 (s, 6, $COCH_3$), 1.94 (s, 4, $-CH_2-$), 1.50 [s, 12, $-C(CH_3)_2$].

Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.21; H, 10.61; N, 12.29. Found: C, 63.28; H, 10.55; N, 11.85.

N-3-Nortricyclylacetamide (36).—HF (60 ml), CH_3CN (15 g), and water (5 g) were placed in a polyethylene reaction vessel and cooled to 0°. Freshly distilled norbornadiene (0.20 mol) was added slowly (30 min) at a rate such that the temperature never rose above 10° and was allowed to stir an additional 25 min at 0–10°. The yellow mixture was poured on ice, forming a viscous gum. The aqueous mixture was neutralized with concentrated NH_4OH and extracted with ether (*ca.* 1 l.), dried ($MgSO_4$), and concentrated to give 5.0 g of an oil which tended to crystallize. Four recrystallizations (hexane) gave white needles (0.45 g), mp 106–107° (2% yield). The structure of **36** is further supported by the following spectroscopic data: infrared (Nujol) exhibited the characteristic nortricyclyl absorbances[18] at 12.4, 7.7, 6.8, and 3.3 μ in addition to the usual amide absorbances. The nmr data are given in Table VIII. Pertinent peaks in the mass spectrum (70 eV) are as follows: *m/e* (rel intensity), 151 (48, parent ion, M), 108 (48, M − $COCH_3$), 94 (54, nortricyclyl radical ion), and 43 (100, O=C—CH_3^+).

TABLE VIII

NMR SPECTRUM FOR N-3-NORTRICYCLYLACETAMIDE



Proton	Chemical shift	Area	Multiplicity
H_a	5.7 –6.5	1	Broad
H_b	3.65–3.95	1	Broad doublet
$H_{c,d}$	1.8 –2.5	4	Singlet at 1.98 represents a $-CH_3$ group and is overlapped by a broad resonance due to H_d
H_e	1.25–1.75	4	Multiplet
H_f	1.00–1.25	3	Multiplet characteristic of the cyclopropyl portion of nortricyclene

Registry No.—Hydrogen fluoride, 7664-39-3; **3** (2-pentyl), 23601-98-1; **3** (3-pentyl), 23601-99-2; **6** (2-octyl), 23602-00-8; **6** (3-octyl), 23602-01-9; **6** (4-octyl), 23601-97-0; **7** (2-octyl), 23601-96-9; **7** (3-octyl), 23602-02-0; **7** (4-octyl), 23602-03-1; **8** (2-octyl), 23602-04-2; **8** (3-octyl), 23602-05-3; **8** (4-octyl), 23602-06-4; **9** (2-octyl), 23602-07-5; **9** (3-octyl), 23602-08-6; **9** (4-octyl), 23602-09-7; **11**, 23602-10-0; **15**, 23602-16-6; **16**, 23602-17-7; **19**, 23604-67-3; **20**, 23645-72-2; **21**, 23604-68-4; **31**, 23604-69-5; **36**, 23645-73-3; **37**, 23602-18-8; **38**, 23604-70-8.

Acknowledgment.—The assistance of Mr. Bill Loffer in performing many of the experiments is gratefully recognized.

(18) D. J. Trecker and J. P. Henry [*J. Amer. Chem. Soc.*, **85**, 3204 (1963)] cite a band at 12.4 μ as very characteristic of the nortricyclene ring system, a band at 3.3 μ due to the cyclopropyl portion, and doublets at 6.8 and 7.7 μ which were always present in the derivatives studied.

Organic Reactions in Liquid Hydrogen Fluoride. II. Synthesis of Imidoyl Fluorides and N,N'-Dialkyl-2-alkylaminomalonamides[1,2]

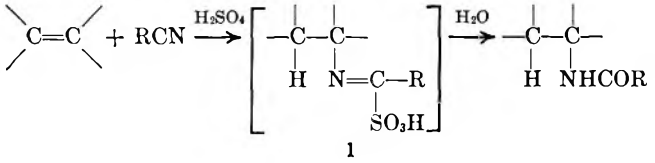
JOHN R. NORELL

Phillips Research Center, Phillips Petroleum Company, Bartlesville, Oklahoma 74003

Received September 8, 1969

Imidoyl fluorides (RN=CFR') have been isolated for the first time as intermediates in the condensation of olefins with nitriles (Ritter reaction) using liquid hydrogen fluoride as a solvent. When hydrogen cyanide is employed as the nitrile, no imidoyl fluorides are obtained but, instead, novel N,N'-dialkyl-2-alkylaminomalonamides are isolated in low yield.

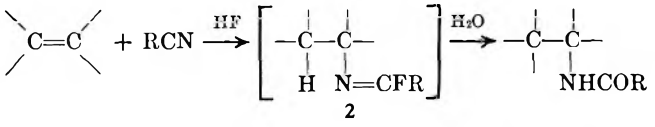
The Ritter condensation between an olefin and nitrile in liquid hydrogen fluoride was discussed in the preceding paper;[2] however, little emphasis was placed on the nature of the reaction intermediate. Since the initial suggestion of Ritter and Minieri[3] of an intermediate iminosulfate **1** in the condensation of olefins or alcohols with nitrile to produce amides in sulfuric acid systems, numerous reports have appeared concerning attempts toward its isolation,[4,5] kinetic data[6] to establish its existence, and mere speculation[3,7,8] on its intermediacy. Recently Glikmans, *et al.*,[4] have reported isolating the iminosulfate intermediate **1** from



1

the reaction of isobutylene with acrylonitrile in an acetic–sulfuric acid mixture.

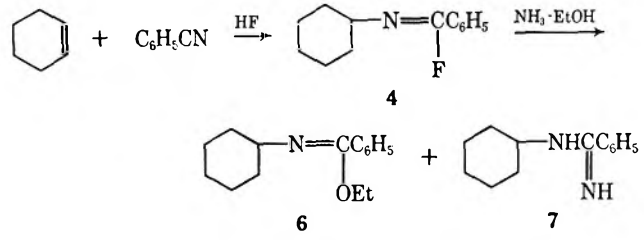
Since hydrogen fluoride is much more volatile (bp 19.6°) than sulfuric acid and readily effects the condensation of an olefin and nitrile,[2] it was found that



2

the novel intermediate imidoyl fluorides **2** could be isolated in the pure state.

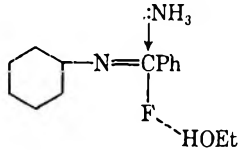
The properties and yields of the various imidoyl fluorides produced are listed in Table I, whereas the analytical and spectroscopic data are detailed in the Experimental Section. The reaction is carried out under anhydrous conditions since any water will instantly yield the amide and can be generalized as follows: A "secondary" olefin, *i.e.*, one not capable of forming a tertiary carbonium ion, is added under anhydrous conditions to a mixture of the nitrile and HF. The reaction is allowed to proceed from 30 min to 2 hr at 0–40° and excess HF is removed by distillation *in vacuo*. An aprotic solvent, such as ethyl ether, is added and gaseous ammonia is passed into the solution. The precipitated ammonium fluoride is removed by filtration and the product is isolated by vacuum distillation after evaporation of the solvent. Care must be exercised during the reaction, work-up, and storage to maintain anhydrous conditions because of the tendency of imidoyl fluorides toward hydrolysis. In the case of N-cyclohexylbenzimidoyl fluoride (**4**), when a protic solvent, such as ethanol, is employed in place of ether prior to neutralization, a mixture of imido ester **6** and amidine **7** is formed. No imidoyl fluoride is observed. However, using ether, good yields (50–70%) of **4** are obtained. A possible rationalization is that



4

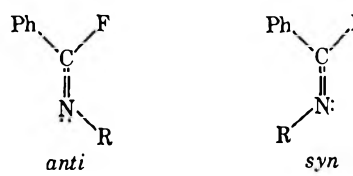
6 **7**

the fluorine, by hydrogen bonding, combines with the proton in ethanol thus weakening the C–F bond and facilitating nucleophilic attack by ammonia. No such solvating effect exists with ether which enables a facile isolation of **4**.



Cyclohexene reacts with acetonitrile to form N-cyclohexylacetimidoyl fluoride (**3**), a very reactive, fuming liquid. It attacks glass, stopcock grease, and metal cap liners and appears to attack stainless steel needles during glpc analysis. Extreme care and speed is required to obtain a satisfactory analysis because the product is hydrolyzed by moisture in the air to N-cyclohexylacetamide and HF.

1-Pentene, an example of a linear olefin, reacted with benzonitrile to produce N-pentylbenzimidoyl fluoride (**5**). Although the product should exist as a mixture of the 2 and 3 isomers,[2] the proton nmr spectrum indicated mostly the 2 isomer. The ^{19}F nmr spectrum displayed two singlet peaks which may be interpreted as "*syn*" and "*anti*" isomers of the imidoyl fluorides.



anti *syn*

(1) Portions of this paper were presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) Paper I: J. R. Norell *J. Org. Chem.*, **35**, 1611 (1970).

(3) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

(4) G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1376 (1966).

(5) T. Clarke, J. Devine, and D. W. Dicker, *J. Amer. Oil Chem. Soc.*, **41**, 78 (1964).

(6) G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1383 (1966).

(7) J. J. Ritter, *J. Amer. Chem. Soc.*, **70**, 4253 (1948).

(8) F. R. Benson and J. J. Ritter, *ibid.*, **71**, 4128 (1949).

TABLE I
IMIDOYL FLUORIDES FROM OLEFINS AND NITRILES

No.	Compound	Olefin	Nitrile	Yield, %	Bp (mm), °C	$n^{20}D$
3	N-Cyclohexyl-acetimidoyl fluoride	Cyclohexene	CH_3CN	33	40–42 (4.0)	1.4390
4	N-Cyclohexyl-benzimidoyl fluoride	Cyclohexene	C_6H_5CN	59	89–92 (0.55)	1.5268
5	N-(2- and 3-pentyl)-benzimidoyl fluoride	1-Pentene	C_6H_5CN	62	53–62 (0.25)	1.4960
		2-Methyl-2-butene	C_6H_5CN	0		
		Cyclohexene	HCN	0		

TABLE II
REACTION PARAMETERS AND YIELD DATA FOR N,N'-DIALKYL-2-ALKYLAMINOMALONAMIDES

Olefin	Olefin, mol	HCN, mol	HF, mol	Olefin addn time, min	Reaction time, hr	Temp, °C	Purified yield, %	Recryst solvent	Mp, °C	Compd no.
Propylene	1.1	1.2	8.0	12	2.0	50	23.3	Pentane	103–104	9
Cyclopentene	1.0	1.2	8.0	35	2.5	44–50	10	Hexane	126–128	10
Cyclohexene	2.0	2.4	8.0	38	4.0	45	19.4	85% Me_2CO	120–122	8
Cyclododecene	1.0	1.2	10.0	52	2.0	50	14.0	Isopropyl ether–benzene	153–154.5	11
1-Pentene	1.0	1.2	8.0	42	2.0	45–50	3.9	Hexane	76–78	12
Norbornene	0.5	0.6	4.1	37	5.0	0–20	10.6	Hexane–EtOH	180.5–182	13

No imidoyl fluorides were obtained using a "tertiary" olefin, such as 2-methyl-2-butene. This observation supports our earlier premise[2] that for tertiary carbonium ions dilute acid is required for amide formation because of the reversibility of the reaction forming the intermediate imino cation. In strong acid the imidoyl fluoride tends to revert to the more stable tertiary carbonium ion which then polymerizes or fragments, whereas, when the system contains water, the imino carbonium ion or fluoride is trapped as the enol and yields the amide.

The imidoyl fluorides are essentially an unknown class of compounds; however, N-*n*-butyl-α-chloro-α-fluoroacetimidoyl fluoride has been reported by Pruett, *et al.*,[9] as arising from an addition of *n*-butylamine to chlorotrifluoroethylene followed by elimination of HF. Wiechert, *et al.*,[10] have reported that condensation of HF and acetonitrile at 100° forms a complex saltlike material which they postulate to be

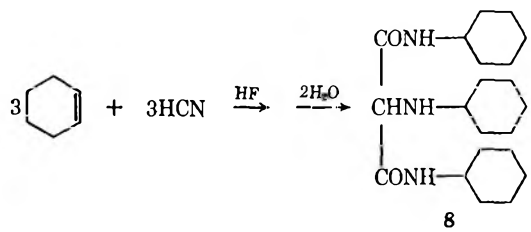
$$CH_3C(F)=\overset{+}{N}H_2\cdot(HF)_{n-1}F^-$$

No analysis or thorough characterization was obtained nor was the free base isolated. Most recently, Merritt and Johnson[11] have reported the transient existence of N-(2-pentyl)benzimidoyl fluoride arising from the elemental fluorination of benzilidene-2-pentylamine. The compound was observed only in the crude state by nmr and could not be isolated by their technique.

In general the chemistry of imidoyl fluorides should resemble that of the imidoyl chlorides, but the fluorides are probably more resistant to hydrolysis and other forms of nucleophilic attack. Analogous to the chlorides, alkyl imidoyl fluorides are less stable than the aryl derivatives. In addition to hydrolysis to amides (Ritter-type reaction), these compounds should readily form imino ethers, amidines, thioamides, etc., and under proper conditions react with most nucleophiles.

$$RN{=}CR'(F) + X: \longrightarrow RN{=}CR'(X) + F^-$$

Noteworthy in the foregoing discussion is that no imidoyl fluorides were isolated from the reaction of HCN and an olefin in HF. During our early studies of imidoyl fluorides only "tar" was obtained in reactions with HCN. It was later found that white crystals could be isolated which were identified as N,N'-dialkyl-2-alkylaminomalonamides. The reaction has the following stoichiometry: 3 mol of olefin, 3 mol of HCN, and 2 mol of water combine to form the malonamide, which for cyclohexene is formulated as follows.



8

Reaction conditions follow: 0–50° for 1–2 hr using 8–10 mol of HF, 1.0–2.5 mol of olefin, and a slight molar excess of hydrogen cyanide. Table II lists the olefins which underwent reaction, with the properties of

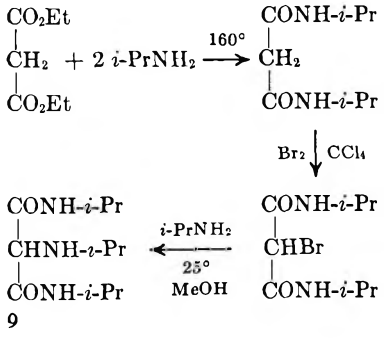
(9) R. L. Pruett, *et al.*, *J. Amer. Chem. Soc.*, **72**, 3646 (1950).
(10) K. Wiechert, H. H. Heilmann, and P. Mohr, *Z. Chem.*, **3**, 308 (1963).
(11) R. F. Merritt and F. A. Johnson, *J. Org. Chem.*, **32**, 416 (1967).

the resulting N,N′-dialkyl-2-alkylaminomalonamides. Yields are low, *ca.* 20% maximum; however, the crude yields are all quite high. In most cases the reaction was not run to optimize purified yields but rather to explore its scope, and the products were isolated by repeated crystallizations from the tars.

As Table II illustrates, identifiable adducts were obtained with propylene, cyclopentene, cyclohexene, cyclododecene, 1-pentene, and norbornene. Under the specific conditions employed, no adduct was isolated from the reaction of 1-octene and 7-tetradecene, although the infrared spectra of the reaction products indicated the presence of amides. No product was isolated from the reaction of ethylene, under the conditions employed, although some ethylene was absorbed. 2-Methyl-2-butene, a tertiary olefin, did not yield any malonamide, which is not too surprising from our work on attempted isolation of imidoyl fluorides from such olefins. This is probably due to relative stabilities of intermediate carbonium ions and reversible processes occurring as was explained earlier.[2] 4-Vinyl-1-cyclohexene gave extensive formation of higher molecular weight products.

An attempt was made to determine if the new synthesis could be used with sulfuric acid in place of hydrogen fluoride. It was found, however, in a nearly disastrous circumstance, that liquid HCN and H_2SO_4 are not compatible under our conditions. At 0° the two materials can be mixed without any noticeable reaction; however, when removed from the ice bath, the mixture will slowly warm to 30–40°. Once this temperature is attained the mixture suddenly heats to about 140° with almost explosive force.[12]

As described in the Experimental Section, proof of structure was based on an elemental analysis and infrared, nmr, and mass spectroscopy. In the case of propylene, N,N′-diisopropyl-2-isopropylaminomalonamide (**9**) was independently synthesized by the following series of reactions.



9

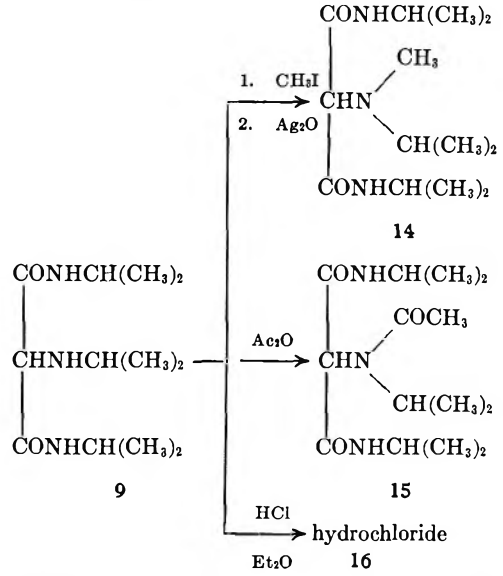
Compound **9** could not be prepared directly from diethyl bromomalonate and 3 mol of isopropylamine because of complex condensations which are known to occur.[15]

(12) This observation is not well documented in the literature or in monographs on hydrogen cyanide. Normally strong acids are thought to stabilize HCN and bases will promote a dangerous polymerization reaction. In a major source book[13] on HCN a chapter is devoted to the action of strong mineral acids on nitriles and only a reference is made to an old article on the interaction of HCN–H_2SO_4 with no implications as to its hazards. The early reference,[14] however, cites this rapid heat buildup which we observed. No such heating was noted with HCN and HF.

(13) V. Migridichian, "The Chemistry of Organic Cyanogen Compounds," ACS Monograph Series, No. 105, Van Nostrand-Reinhold Co., Princeton, N. J., 1947, p 57.

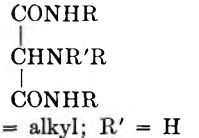
(14) A. W. Cobb and J. H. Walton, *J. Phys. Chem.*, **41**, 351 (1937).

As part of our proof of structure the following chemical reactions were observed with **9**, which in turn produced new derivatives.



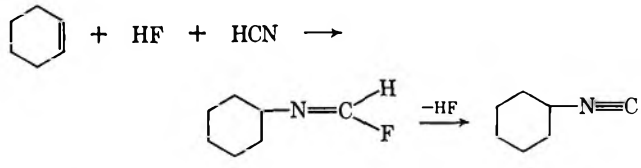
No reduction by $LiAlH_4$ of the amide groups on either compound **8** or **9** could be detected. The 2-alkylamino group does not undergo some of the classical tests for secondary amines such as the Hinsberg test or reaction with phenyl isothiocyanate.

Similar to the imidoyl fluorides, the substituted aminomalonamides are not a well-known class of compounds; the N,N′-dialkyl-2-alkylaminomalonamides have been prepared in the past by rather elaborate synthetic schemes.[15] Very few compounds have been reported where the 2-amino group contains an active hydrogen, *i.e.*, arises from a nucleophilic displacement of a halogen by a primary amine on a 2-halomalonamide to form **17**, but usually those such as **18** have been reported *via* displacement with secondary amines.



17, R = alkyl; R′ = H
18, R = alkyl; R′ = alkyl

Several mechanisms for formation of the malonamides have been considered. We suggest the following as one plausible rationalization. In our work during a large-scale preparation of cyclohexylformamide from HF and HCN, we observed the formation of cyclohexyl isocyanide and postulated its formation as follows.[2]

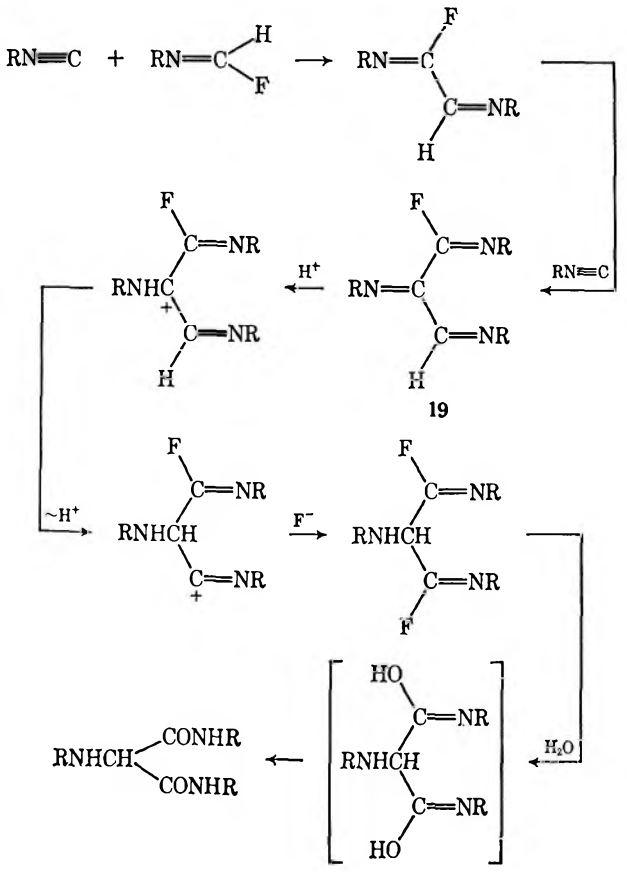


Similarly in our malonamide syntheses the odor of isocyanides is prevalent. Recently Ito, Okano, and Oder[16] disclosed that isocyanides react with N,N-dialkylamide chlorides to give N,N′-dialkyl-2-dialkyl-

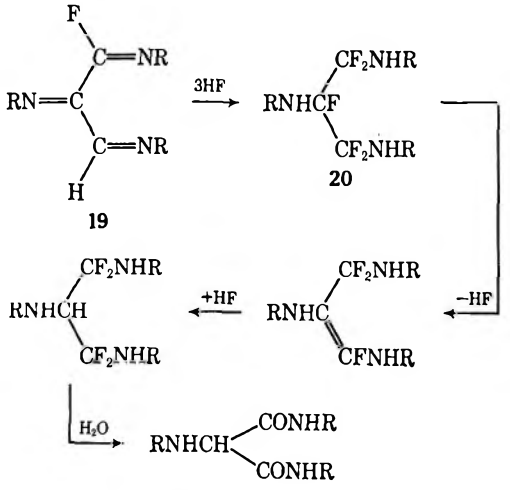
(15) (a) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **117**, 980 (1956); (b) R. W. West, *J. Chem. Soc.*, **127**, 748 (1925); (c) F. C. Uhle and L. S. Harris, *J. Amer. Chem. Soc.*, **78**, 381 (1956).

(16) Y. Ito, M. Okano, and R. Oder, *Tetrahedron*, **22**, 447 (1966).

aminomalonamides **18**. By invoking their reasoning, a similar type of mechanism involving imidoyl fluorides and isonitriles would provide a possible route to the aminomalonamides.



It is also possible that intermediate **19** could add 3 mol of HF to give **20** and then an elimination–readdition sequence could occur.



Since these reactions are carried out in anhydrous HF ($H_0 = -9.9$), such strong acidity would lead to highly cationic species involving numerous rearrangements and hydride transfers, as well as numerous protonated species not shown in the mechanism.

Experimental Section

Materials.—Colorless 99.9% hydrogen fluoride was obtained from Air Products, Inc., Allentown, Pa., and was withdrawn in the liquid phase by inverting the cylinder and taking off the HF through Monel valves as described in our previous paper.[2] *CAUTION!* When handling anhydrous HF, a face shield, rubber gloves with plastic arm bands, and a protective apron are worn, using excellent hood facilities. All olefins were Phillips pure grade and the nitriles were Eastman White Label with the hydrogen cyanide being obtained from Du Pont and stabilized with P_2O_5. The nmr spectra were obtained on a Varian A-60 spectrometer for the proton spectra and a HR-60 for ^{19}F resonance. Mass spectra were run on a high resolution CEC mass spectrometer, Model 21-110. Molecular weights were determined by osmometry and the infrared spectra were recorded on a Perkin-Elmer Infracord Model 127. Melting points were obtained on a Hoover–Thomas capillary melting point apparatus and are uncorrected.

N-Cyclohexylacetimidoyl Fluoride (3). Run 1.—A 300-ml Monel reactor was dried at 120° and cooled in ice under a nitrogen flow. Anhydrous HF (48.6 g, 2.43 mol) was added by means of a plastic graduate followed by CH_3CN (10.0 g, 0.26 mol). Cyclohexene (16.4 g, 0.20 mol) was added dropwise and the reactor was capped and shaken at room temperature (*ca.* 25°) for 30 min. The excess HF was removed by attaching a short piece of Monel tubing to a second 300-ml bomb immersed in Dry Ice–acetone and pulling a water-pump vacuum on the system through the second vessel to distil the excess HF. Between the second bomb and water pump a vacuum flask containing NaOH pellets was inserted to prevent any HF from escaping into the drains. Hoke valves were placed on both sides of the second bomb so that it could be easily removed and the weight of distilled HF could be determined. When this system was used and the reaction bomb was heated in warm water, a total of 36.0 g of HF was removed over a period of about 1 hr. After the vessel was cooled in ice, the pressure gauge assembly was removed under a nitrogen flow and 150 ml of ether was added. The bomb was capped and attached to a second 300-ml Monel vessel containing about 50 g of liquid ammonia at 100 psig. The two vessels were placed in a shaker, the reaction vessel was pressured slowly (to prevent overheating because of heat of neutralization) to 100 psig with NH_3 and allowed to fall to *ca.* 20 psig, and the process was repeated until no more NH_3 was absorbed. The reactor was shaken at *ca.* 30° for 1.5 hr after a total of 16 g of NH_3 had been added. The mixture was filtered under nitrogen to remove the precipitated ammonium fluoride and washed with ether. Concentration of the filtrate left 16.6 g (64% crude yield) of a fuming, bubbling liquid. Distillation of 14.1 g of the amber-colored liquid gave 8.0 g of the colorless product, bp 40–42° (4.0 mm), with 3.4 g of residue remaining in the still pot.

The infrared spectrum (neat) showed no N—H or amide bands; however, a significant band at 5.78 μ indicated the presence of the >C=N– linkage. The nmr spectrum (CCl_4) was in good agreement with the assigned structure **3**: δ 1.90 (d, 3, J = 10.5 Hz, =CFCH$_3$), 1.48 (m, 10, ring protons), and 3.65 (m, 1, ring proton α to N). The ^{19}F resonance exhibited a well-defined quartet, 2995 cps from CF_3CO_2H giving δ_F (from CF_3CO_2H) 49.9. This compares favorably with a δ_F 52.7 for the boldface fluorine in C_3F_7N=CF**C**F$_3$.[17]

Run 2.—The reaction was repeated using 51.6 g (2.58 mol) of HF and after the reaction 34.0 g of the HF was removed. After work-up 19.0 g (66%) of the crude product was obtained which was immediately distilled in a flame-dried apparatus at 33° (2.0 mm). After the product was stored overnight in a glass-stoppered distillation receiver, it was redistilled at 34° (2.5 mm) and taken immediately to the Analytical Section. The transfer of samples for the elemental analyses was made in a drybox under a blanket of nitrogen and the analyses were run shortly after the second distillation.

Anal. Calcd for $C_8H_{14}FN$: C, 67.10; H, 9.85; N, 9.75; F, 13.3; mol wt, 143. Found: C, 66.84; H, 9.86; N, 9.70; F, 13.4; mol wt, 142 (obtained by extrapolation to infinite dilution in benzene).

The compound yellowed rapidly on standing and attacked glass, stopcock grease, polyethylene film, and metal cap liners. When shaken with 5% NaOH, N-cyclohexylacetamide precipitated, mp 105–106° (lit.[18] mp 104°).

(17) N. Muller, P. C. Lauterbaur, and G. F. Svatos, *J. Amer. Chem. Soc.*, **79**, 1807 (1957).

(18) 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 288.

N-(2- and 3-Pentyl)benzimidoyl Fluoride (5).—The reaction was run similarly to the foregoing experiment except that 46.4 g (2.32 mol) of HF, 20.6 g (0.20 mol) of benzonitrile, and 14.0 g (0.20 mol) of 1-pentene were used with 30.0 g of the HF being removed by distillation after the reaction was completed. In this case 13 g of ammonia was pressured into the reactor and ether (150 ml) was added followed by an additional 8 g of NH_3. The solution was filtered and concentrated to give 32.5 g (83% crude) of an amber-colored nonviscous oil. The infrared spectrum showed a trace of N—H and a small amount of –CN indicative of unreacted benzonitrile as well as the characteristic C=N band at 5.78 μ. Distillation gave 23.3 g (62% yield) of colorless product, bp 53–62° (0.25 mm); the distillation residue weighed 2.5 g. For analysis the product was redistilled at 54–55° (0.20 mm), $n^{20}D$ 1.4960.

Anal. Calcd for $C_{12}H_{16}FN$: C, 74.57; H, 8.34; F, 9.83; N, 7.25; mol wt, 193. Found: C, 74.37; H, 8.52; F, 9.70; N, 7.25; mol wt, 196.

The fluorine nmr spectrum exhibited a strong "doublet" with J = 43 Hz. These peaks were of equal intensity suggesting existence of *syn* and *anti* isomerism. Proton nmr spectra indicated the product was mostly N-2-pentylbenzimidoyl fluoride with some 3 isomer.

N-Cyclohexylbenzimidoyl Fluoride (4).—The reaction was run similarly to the foregoing experiment except that 59.5 g (3.0 mol) of HF, 20.6 g (0.20 mol) of benzonitrile, and 16.4 g (0.20 mol) of cyclohexene were used and the reaction mixture was shaken for 80 min at room temperature (30°). Following removal of the HF (40.5 g) the mixture was treated with ether and ammonia (16 g) and was shaken overnight at 30° under ammonia pressure (100 psig). Filtration and evaporation of the ether gave 35.3 g (yield, 86%) of the crude imidoyl fluoride.

A portion (22.9 g) of the crude product when distilled gave 15.8 g of a pale yellow distillate boilng at 89–92° (0.5 mm); an analytical sample was obtained by redistillation, 87–88° (0.4 mm), $n^{20}D$ 1.5268.

Anal. Calcd for $C_{13}H_{16}FN$: C, 76.06; H, 7.86; F, 9.26; N, 6.82; mol wt, 205. Found: C, 76.23; H, 7.93; F, 9.25; N, 6.62; mol wt, 212 (osmometer).

The infrared spectrum indicated very little N—H and the C=N band at 5.9 μ was present. The nmr spectrum (50% in $CDCl_3$) exhibited δ 7.5 (m, 5, aromatic protons), 1.6 (m, 10, cyclohexyl protons), and 3.9 (m, 1, CHN=CF–). Two of the aromatic protons exhibited coupling with the fluorine. The ^{19}F resonance indicated a singlet, 1682 Hz from CF_3CO_2H. The mass spectrum showed no parent peak; however, the cracking pattern was consistent with the assigned structure since benzonitrile and cyclohexene fragments were observed. The compound decomposed on the column when subjected to glpc analysis.

Ethyl N-Cyclohexylbenzimidate (6) and N-Cyclohexylbenzamidine (7).—The reaction was carried out in apparatus similar to those described previously with 60 ml of HF, 20.6 (0.20 mol) of benzonitrile, and 16.4 g (0.20 mol) of cyclohexene being used. A total of 41.9 g of HF was removed by distillation. In place of ether, 150 ml of absolute ethanol was added and cooled to 0°. Ammonia gas was bubbled into the solution at a rate such that the temperature did not exceed 45°. A heavy precipitate formed which was filtered and washed with ethanol; concentration of the filtrate left 34.4 g of a liquid residue. This was triturated with a mixture of ether (100 ml) and acetone (200 ml) giving 8.70 g of a gummy white solid, N-cyclohexylbenzamidine hydrofluoride. Dissolution in 150 ml of water followed by 50 ml of 10% NaOH liberated the free base as a precipitate and recrystallization (hexane–EtOH) gave 4.9 g of white crystalline N-cyclohexylbenzamidine, mp 116–117.5° (lit.[19] mp 116–116.5°); the picrate melted at 142–143.5° (lit.[19] mp 143°).

The ether–acetone triturating solvent was evaporated to give 23.9 g of a red-brown residue which on distillation gave 12.9 g of ethyl N-cyclohexylbenzimidate (6) as a colorless liquid, bp 105–109° (0.6 mm), $n^{20}D$ 1.5189.

The infrared spectrum (Nujol) indicated the following: 6.02 (>C=N), 6.29 (aromatic), and 9.05 μ (ROR) with no bands present at 3.0 μ describing the absence of N—H bonds. The nmr spectrum (30% in $CDCl_3$) exhibited δ 7.30 (s, 5, aromatic protons), 4.22 (q, 2, $-OCH_2CH_3$) 3.18 (m, 1, ring H α to N), and 1.52 and 1.28 (m and t, 13, cyclohexyl protons and $-OCH_2-CH_3$).

(19) P. Oxley and W. F. Short, *J. Chem. Soc.*, 449 (1949).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05; mol wt, 231. Found: C, 77.76; H, 9.40; N, 6.20; mol wt, 230.

Reaction of 2-Methyl-2-butene with Benzonitrile in HF.—The reaction was run similarly to the preceding experiment except that 47.4 g of HF, 20.6 g (0.20 mol) of 2-methyl-2-butene, and 20.6 g (0.20 mol) of benzonitrile were employed. After the mixture was shaken for 30 min at 30°, the HF was removed with a resultant loss in weight of 58 g. This loss was 10.6 g more than the original amount of HF added indicating loss of 2-methyl-2-butene or *t*-amyl fluoride. The yellow residue in the reaction vessel was poured on ice, neutralized with NH_4OH, and extracted with ether. Removal of the ether left 20.9 g of a yellow residue, which by glpc analysis indicated mostly benzonitrile with traces of oligomers. By the foregoing procedure, no evidence for imidoyl fluoride formation was noted. The HF that was distilled into the second bomb was worked up similarly and was found to contain 8.2 g of benzonitrile and oligomers of 2-methylbutene indicative of free 2-methyl-2-butene or *t*-amyl fluoride being flashed over and subsequently polymerizing.

N,N'-Diisopropyl-2-isopropylaminomalonamide (9).—Hydrogen fluoride (160 ml, 8.0 mol) was placed in a 300-ml Monel reactor and cooled in ice water; addition of liquid hydrogen cyanide (48 ml, 33 g, 1.22 mol) followed. The reactor was capped and pressured with N_2 (*ca.* 150 psig) and the contents were transferred into a 1-l. Monel autoclave by means of a dip tube. Propylene (45 g, 1.07 mol) was condensed in a stainless steel bomb, which was fitted to the large reactor. Propylene, at 150 psig, was bled into the HF–HCN mixture at 23–29° with vigorous stirring over a period of 12 min. The autoclave was heated to 50° and stirred an additional 2 hr. After cooling, 300 ml of water followed by 200 ml of CH_2Cl_2 were pumped into the autoclave for an "*in situ* extraction." After being stirred an additional 15 min, the contents were drained into a polyethylene separatory funnel and the HF–H_2O layer extracted once with 150 ml of CH_2Cl_2. The combined CH_2Cl_2 layers were made basic with aqueous NaOH, dried over $MgSO_4$, and concentrated to give 6.1 g of a foul-smelling yellow oil which was discarded. The initial HF–aqueous layer was made basic with 40% NaOH and allowed to stand overnight. Silky crystals formed which when filtered and air dried gave 45.3 g (53% crude yield) of yellow solids. The material was recrystallized once from 200 ml of 75% acetone–25% water and then twice from 200 ml of pentane to give two crops of crystals; 10.95 g, mp 102.5–104°, and 9.29 g, mp 103–104°, for a total yield of 20.24 g (23.3% yield).

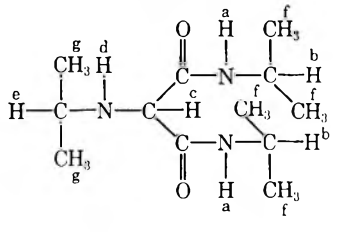
The product is soluble in pentane and very soluble in CCl_4, MeOH, EtOH, dilute HCl, pyridine, C_6H_6, $CHCl_3$, and Et_2O. It is soluble in hot water after a few drops of EtOH have been added and is insoluble in dilute NaOH.

Structure Determination. The structure of compound 9 was determined in the following manner.

Anal. Calcd for $C_{12}H_{25}N_3O_2$: C, 59.23; H, 10.36; N, 17.27; O, 13.2; mol wt, 243. Found: C, 59.08; H, 10.44; N, 16.93; O, 12.9; mol wt, 257; equiv wt, 243 (when titrated with $HClO_4$–HOAc).

A. Spectroscopic Data.—The nmr spectrum (described in Table III) provides a clear picture of the structure.

TABLE III



Proton	Chemical shift, δ	Appearance	Obsd no. of protons	No. of protons required
a	7.4–7.8	Broad singlet	2.0	2
b	3.8–4.2	Heptet	2.0	2
c	3.6	Singlet	1.0	1
d	2.7–2.9	Broad multiplet	2.0	1
e	2.7–2.9	Broad multiplet		1
f	1.1–1.3	Doublet, overlapping	18.0	12
g	1.0–1.2	Doublet, overlapping		6

Protons a and d are active protons as required by the structure since addition of D_2O to a solution of the sample in acetone-d_6 causes the corresponding peaks to shift to τ 5.2 because of rapid exchange with D_2O.

The infrared spectrum (Nujol) exhibited 6.08 and 6.12 (C=O), 3.08 (N—H), and other medium bands at 3.25, 6.50, 7.98, 8.58, and 11.67 μ.

B. Chemical Reactivity Data. 1. Reaction with Methyl Iodide.—Compound 9 (1.5 g) was heated at reflux in 20 ml of methyl iodide for 18 hr, giving a yellow solution which on evaporation left a crystalline mass. Recrystallization from hexane–ethanol gave 1.54 g of yellow crystals, mp 204–205°.

Anal. Calcd for $C_{13}H_{28}IN_3O_2$: C, 40.53; H, 7.32; N, 10.91. Found: C, 40.26; H, 7.47; N, 10.67.

The iodide salt (1.4 g) was dissolved in 30 ml of H_2O and 2 g of freshly prepared Ag_2O was added. The slurry was stirred at room temperature for 2 hr. Filtration, water washing, extraction with ether, and drying over $MgSO_4$ gave **14** (white crystals) which melted at 132–133° after recrystallization from *n*-hexane. Analysis indicated addition of *one* methyl group.

Anal. Calcd for $C_{13}H_{27}N_3O_2$: C, 60.66; H, 10.58; N, 16.33; mol wt, 257. Found: C, 60.60; H, 10.64; N, 16.24; mol wt, 244.

2. Acetylation.—Compound 9 (1.0 g) was heated at 100–110° with 15 ml of acetic anhydride for 3 hr. The solution turned dark red-brown. Excess Ac_2O was removed *in vacuo* and the residue was heated in hot hexane. The mixture was filtered and cooled to give brownish crystals; a second recrystallization from hexane gave **15** (white crystals), mp 125–126°. Analysis indicated the introduction of one acetyl group.

Anal. Calcd for $C_{14}H_{27}N_3O_3$: C, 58.92; H, 9.54; N, 14.72. Found: C, 58.74; H, 9.55; N, 14.76.

3. HCl Salt.—Compound 9 (1.0 g) was dissolved in 100 ml of ether and anhydrous HCl was bubbled into the solution, forming a fine precipitate. Nitrogen was swept through the system to remove the excess HCl. Filtering and drying gave 1.1 g of the very finely powdered hydrochloride **16**, mp 266–267° dec.

Anal. Calcd for $C_{12}H_{26}ClN_3O_2$: C, 51.51; H, 9.37; N, 15.02. Found: C, 51.28; H, 9.30; N, 14.62.

4. Sodium Hydroxide Fusion.—When a small portion of the adduct was placed in powdered NaOH and heated, isopropylamine evolved.

C. Independent Synthesis of 9. a. N,N′-Diisopropylmalonamide.—Diethyl malonate (32.0 g, 0.20 mol) and isopropylamine (100 g, 1.7 mol) were placed in a 300-ml Monel reactor and heated at 160° (275 psig developed) for 20 hr. The excess liquid was removed *in vacuo* leaving a 36.8 g (99% crude) of pale greenish white solids. Recrystallization from *n*-hexane–ethanol gave 22.7 g of white crystals, mp 117–119°, 61% purified yield (lit.[20] mp 114°).

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.30; H, 9.63; N, 15.00.

b. 2-Bromo-N,N′-diisopropylmalonamide.—N,N′-Diisopropylmalonamide (9.3 g, 0.50 mol) dissolved in 50 ml of HOAc was heated to reflux and Br_2 (8.2 g, 0.05 mol) in 25 ml of HOAc was added dropwise. Heating was continued for 2 hr. After cooling and concentration, a portion of the residue was recrystallized (hexane–EtOH) to give 6.3 g, mp 200–202°, of product (lit.[20] mp 204°). An additional recrystallization of the residue gave 1.4 g of product of lower purity, mp 195–197°. The total yield was 7.7 g (58%).

Anal. Calcd for $C_9H_{17}BrN_2O_2$: C, 40.77; H, 6.46; N, 10.56. Found: C, 40.90; H, 6.44; N, 10.12.

c. Compound 9.—Methanol (60 ml), isopropylamine (18 g, 0.3 mol), and 2-bromo-N,N′-diisopropylmalonamide (6.0 g, 0.02 mol) were placed in a 300-ml Monel reactor. The reactor was capped and shaken for 15 hr at room temperature. The mixture was evaporated to dryness and made basic with 3% NaOH, and the precipitated solids were filtered and washed with water. Recrystallization from *n*-pentane yielded two small crops of white crystals which totaled less than 1 g, mp 103–104°.

A mixture melting point with the product obtained from propylene, HCN, and HF showed no depression (mp 103.5–104.5°). The infrared spectrum (Nujol) and the nmr spectrum of the independently synthesized material were completely superimposable on the spectrum from the HCN–HF–propylene product.

N,N′-Dicyclohexyl-2-cyclohexylaminomalonamide (8).—A 1-l. Monel autoclave was charged with a mixture of HF (160 g, 8.0 mol) and HCN (66 g, 96 ml, 2.4 mol) and then was pressurized with N_2 to 800 psig. Cyclohexene (164 g, 2.0 mol) was pumped into the reactor over a period of 38 min at 20° and the mixture was heated at 45° for 4 hr with vigorous stirring. The mixture was cooled, CH_2Cl_2 (250 ml) was pumped into the reactor, and the contents were drained into an ice bath. After this mixture was stirred vigorously, the bottom organic layer was made basic by shaking with NaOH solution and dried over $MgSO_4$. Concentration gave 258.4 g of a viscous red-brown tar. To obtain a crystalline material from this residue is strictly an art and the description below points out the conditions which we found to be most satisfactory. The initial residue was chilled in a refrigerator for 2–4 hr and then allowed to stand at room temperature until it crystallized which usually took at least 1.5 days. Seeding seemed to make the crystals form faster. The solidified mass was triturated with 85% acetone–15% water and placed in a beaker and chilled. The mixture was filtered and washed with small amounts of cold 85% acetone. The solids were dried, preferably by pressing between paper towels, and then air dried. Recrystallization of the tan solids from 85% acetone gave 47.0 g (0.13 mol or 19.4% yield) of **8**: mp 120–122°; uv max (cyclohexane) 238 μ ($\epsilon \approx 150$); ir ($CHCl_3$) 2.82 (sh, N—H), 3.10 (N—H), 6.10 (C=O), and 6.49 μ (C=O); nmr ($CDCl_3$) δ 7.6–7.9 (m, 2, $-CONH-$), 3.5–3.9 (m, 2, ring protons α to amide), 3.68 (s, 1, $-COCHCO-$), 2.8–3.0 (m, 1, amino proton), 2.8–3.0 (m, 1, ring H α to amino group), and 7.5–9.0 (m, 30, ring protons).

Anal. Calcd for $C_{21}H_{37}N_3O_2$: C, 69.38; H, 10.26; N, 11.56, mol wt, 363. Found: C, 69.44; H, 10.54; N, 11.90; mol wt, 344.

A. Chemical Reactivity Data. 1. Acetylation.—Ac_2O (15 ml) and **8** (1.5 g) were heated at reflux for 3 hr. The excess Ac_2O was removed *in vacuo* and the residue was poured on ice. Ether was added which formed a crystalline precipitate at the interface. These crystals were of high purity, mp 175–177°, and represented introduction of one acetyl group.

Anal. Calcd for $C_{23}H_{39}N_3O_3$: C, 68.15; H, 9.65; N, 10.36. Found: C, 67.90; H, 10.04; N, 10.25.

2. Acid Hydrolysis.—Compound **8** (8.0 g) was dissolved in 150 g of 60% H_2SO_4 and heated at 130° for 3 days. The solution was greenish black and clear; extraction with CH_2Cl_2 gave no residue. The mixture was poured on cold concentrated NaOH with care being taken so that the temperature was never above 40°. When the mixture was strongly basic it was extracted with other and dried over $MgSO_4$–K_2CO_3. Removal of the solvent left 2.7 g of cyclohexylamine which was confirmed by ir and glpc, on comparison with an authentic sample.

N,N-Dicyclopentyl-2-cyclopentylaminomalonamide (10).—A 1-l. autoclave was charged with 160 ml (8.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN and pressured to 1000 psig with CO. Cyclopentene (68 g, 1.0 mol) was pumped into the stirred reactor at a rate of 3–4 ml/min over a period of 35 min at 20–22°. The reactor was heated to 44–50° and stirred 2.5 hr. No drop in pressure was noted. The reactor was cooled to 22°, the pressure was released, and 300 ml of H_2O and 200 ml of $CHCl_3$ were pumped into the reactor. After drainage into plastic separatory funnels, the aqueous acid layer was extracted twice with $CHCl_3$ and the extracts were combined with the $CHCl_3$ layer initially pumped into the reactor. The aqueous layer was discarded and the red-brown $CHCl_3$ layer was poured on ice and made basic with NaOH solution. An emulsion formed and filtration was necessary to produce a workable mixture. The $CHCl_3$ layer was dried over $MgSO_4$ and removal of the solvent left 95.3 g of a very dark oil which tended to crystallize on standing. An analytical sample was prepared by triturating 16.0 g of the residue in 5 ml of 90% acetone and filtering to give 2.55 g of crystals which, when recrystallized fron hexane, gave 1.70 g of **10**, mp 126–128°.

Anal. Calcd for $C_{18}H_{31}N_3O_2$: C, 67.23; H, 9.73; N, 13.08; mol wt, 321. Found: C, 67.12; H, 10.22; N, 13.11; mol wt, 319 (osmometer).

N,N′-Dicyclododecyl-2-cyclodecylaminomalonamide (11).—A 1-l. autoclave was charged with 200 ml (10.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN. Cyclododecene (85% pure from Columbia Organic Chemicals Co.; the remaining 15% was cyclododecane and cyclododecadiene) (166 g, 1.0 mole) was pumped into the reactor at 16° over a period of 52 min. The mixture was heated with stirring at 50° for an additional 2 hr. The reactor was cooled and 300 ml of H_2O was added followed by 200 ml of CH_2Cl_2. The mixture was drained from the reactor and extracted further with CH_2Cl_2. Solvent removal left 204.7 g of

(20) R. W. West, *J. Chem. Soc.*, **127**, 748 (1925).

red-brown solids possessing a waxy appearance. The residue was suspended in acetone and filtered, the solids were then further leached of impurities with hexane (100 ml), and absolute EtOH (500 ml) was added to the boiling suspension. Cooling and filtration gave 56.7 g of buff-colored solids, mp 152–155°.

Recrystallization was effected by suspending the solid in isopropyl ether (600 ml), heating the suspension to boiling, and adding benzene dropwise to the hot solution until solution was complete. When this was cooled, 28.5 g of off-white crystals were obtained, mp 153–154.5°, representing a 14% yield; however, no attempts were made to optimize the yield.

Anal. Calcd for $C_{39}H_{73}N_3O_2$: C, 76.04; H, 11.94; N, 6.83; mol wt, 616. Found: C, 76.13; H, 12.06; N, 6.72; mol wt could not be determined because of insolubility in the available solvents.

N,N′-Dinorbornyl-2-norbornylaminomalonamide (13).—A 1-l. Monel beaker with a polyethylene cover containing apertures for an addition funnel and thermometer and provided with a magnetic stirrer was charged with 80 ml (4.0 mol) of HF and 25 ml (17.2 g, 0.64 mol) of HCN and cooled in an ice bath to 0°. Norbornene (47.0 g, 0.50 mol) was added by means of a spatula over a period of 37 min. Five hours later, 150 ml of water was added followed by 100 ml of CH_2Cl_2. The CH_2Cl_2 layer was shaken with dilute NaOH until neutral, and removal of the solvent left 60.0 g of a viscous amber liquid. A portion of the material was triturated with 85% acetone to give **13** which, when recrystallized from *n*-hexane and ethanol, melted at 180.5–182°. A total of 7.1 g of product was obtained.

Anal. Calcd for $C_{24}H_{37}N_3O_2$: C, 72.14; H, 9.33; N, 10.52; mol wt, 399.6. Found: C, 71.94; H, 9.32; N, 10.23; mol wt, 419.

The infrared and nmr spectra were consistent with the structure postulated.

N,N′-Dipentyl-2-pentylaminomalonamide (12).—A 1-l. Monel autoclave was charged with 160 ml (8.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN. 1-Pentene (70 g, 1.0 mol) was pumped into the reactor at 18° over a period of 42 min. It was then heated at 45–50° for 2 hr; the heating was followed by cooling and addition of 300 ml of water and 200 ml of CH_2Cl_2. The CH_2Cl_2 layer was collected and the aqueous acid layer was extracted with CH_2Cl_2. The organic layers were combined and shaken with NaOH–H_2O giving an emulsion which was broken by filtration. Removal of the CH_2Cl_2 after separation and drying over $MgSO_4$ gave 90.4 g of a brown viscous liquid. Crystallization was achieved by immersing the flask in ice and adding 150 ml of hexane. Filtration and two additional crystallizations (hexane) gave a total of 4.2 g of white crystals, mp 76–78°.

Anal. Calcd for $C_{18}H_{37}N_3O_2$: C, 66.01; H, 11.39; N, 12.83; mol wt, 327. Found: C, 66.16; H, 11.42; N, 12.86; mol wt, 324 (osmometry).

Reaction of Ethylene with HCN–HF.—The 1-l. autoclave was charged with 160 ml of HF and 50 ml of HCN and pressured to 500 psig (39 g) with ethylene. The mixture was heated at 50° for 3 hr and the pressure dropped to 280 psig at 51°. It was repressured to 500 psig (21 g) and stirred an additional 1 hr. Work-up was similar to those described previously with only 2.5 g being obtained on various extractions with CH_2Cl_2. Possibly the product which would arise would be very water soluble and not be extractable by these methods.

Reaction of 1-Octene with HCN–HF.—When 160 ml of HF, 48 ml of HCN, and 112 g (1.0 mol) of 1-octene were used under conditions described above, 139.5 g of a dark viscous residue was obtained. No identifiable materials, except a small amount of N-octylformamide, could be detected either by crystallization or distillation procedures.

Reaction of 2-Methyl-2-butene with HCN–HF.—Using 160 ml of HF, 48 ml of HCN, and 70.0 g (1.0 mol) of 2-methyl-2-butene under conditions described above, 30.5 g of a black tar was isolated. No identifiable products could be isolated.

Registry No.—Hydrogen fluoride, 7664-39-3; **3**, 23604-71-9; **4**, 23604-72-0; **5** (2-pentyl), 23604-73-1; **5** (3-pentyl), 23604-84-4; **6**, 23604-74-2; **8**, 23604-75-3; **8** (acetylated), 23604-76-4; **9**, 23604-77-5; **9** (methiodide), 23758-69-2; **10**, 23604-78-6; **11**, 23604-79-7; **12**, 23604-80-0; **14**, 23604-81-1; **15**, 23604-82-2; **16** (HCl), 23604-83-3.

Acknowledgment.—The author wishes to acknowledge the capable laboratory assistance of Mr. Bill Loffer and is indebted to Dr. D. S. Weinberg for assistance in obtaining and interpreting some of the spectra cited.

Crystal Structure of 10-Methylisoalloxazinium Bromide Dihydrate

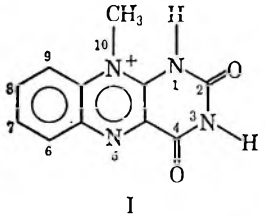
R. B. Bates, T. C. Sneath, and D. N. Stephens

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received September 8, 1969

The title compound, a model for protonated riboflavin, exists in the crystal in the tautomeric form I. There is minor deviation from copolanarity in the ring system, with a slight general bow along the long axis. The molecules are arranged in sheets of P_g symmetry with intrasheet hydrogen bonding.

In spite of the importance of riboflavin and its derivatives FMN and FAD in biological redox systems, bond parameters have been measured on only a few substances containing the riboflavin ring system.[1] This is undoubtedly due to the failure of many derivatives of interest to form crystals suitable for X-ray study. The title substance, however, which contains the cation depicted below, forms excellent crystals, and we wish to report the results of an X-ray study on them.[2]



I

Experimental Section

Cooling of a solution of 10-methylisoalloxazine in concentrated hydrobromic acid gave many-faced, olive green crystals of 10-methylisoalloxazinium bromide dihydrate.

Anal. Calcd for $C_{11}H_{13}N_4O_4Br$: C, 38.51; H, 3.86; N, 16.10; O, 18.54; Br, 23.89. Found: C, 38.29; H, 3.79; N, 16.24; O, 18.55; Br, 23.16.

(1) (a) P. Kierkegaard, *et al.*, *Chem. Commun.*, 288 (1967); (b) N. Tanaka, *et al.*, *Bull. Chem. Soc. Jap.*, **40**, 1739 (1967); (c) C. J. Fritchie, Jr., and B. L. Trus, *Chem. Commun.*, 1486 (1968).

(2) Fritchie and Trus[1c] have communicated their results on the same substance, and our parameters appear to be in close agreement with theirs. Our preliminary results with this structure (not then fully refined) were reported: Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. O-149.

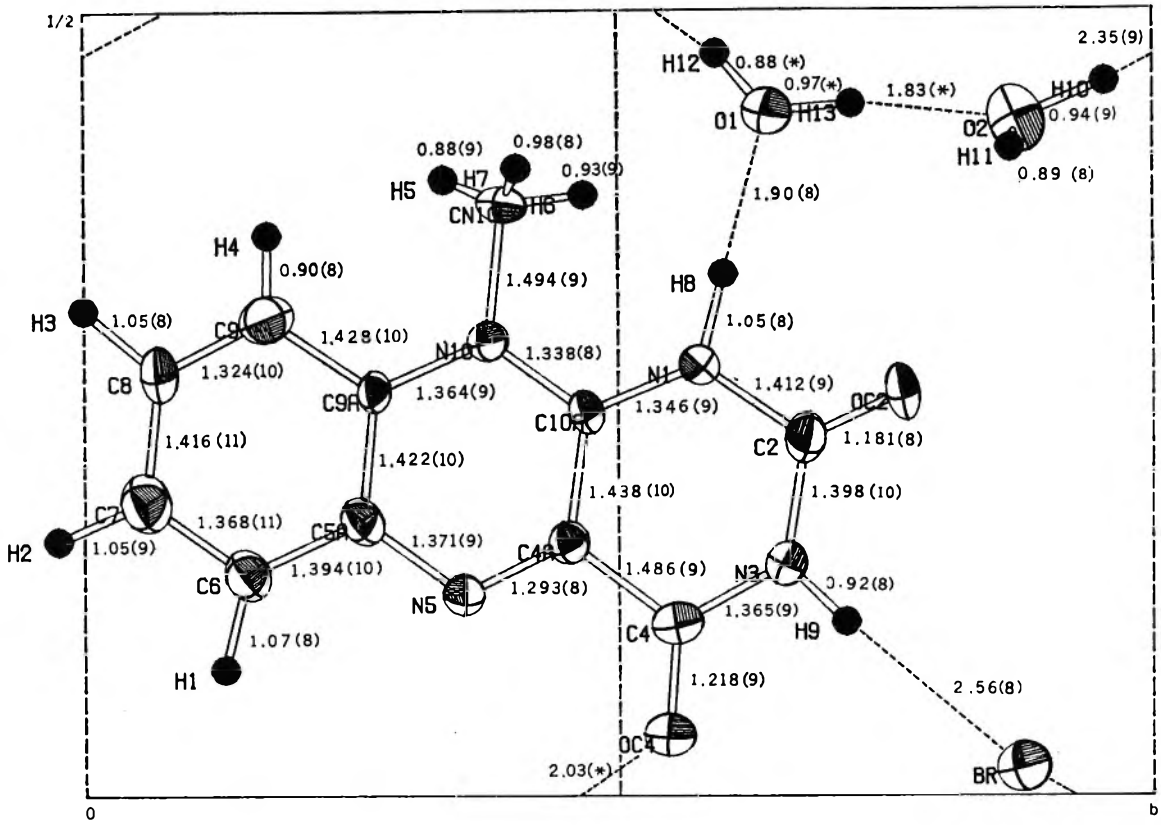


Figure 1.—An ORTEP plot of an asymmetric unit, viewed perpendicular to the 102 plane. Bond distances and their standard deviations are given in angstroms, and the intrasheet hydrogen bonds are shown as dotted lines. Standard deviations were not available in the starred cases owing to the failure of H-12 and H-13 to refine satisfactorily. Thermal ellipsoids enclose 50% probability.

Cell constants, determined from oscillation and Weissenberg photographs using a traveling microscope, follow: a = 9.38 Å (3), b = 11.77 Å (3), c = 13.57 Å (3), and β = 118.26° (10). The space group is $P2_1/c$. The unit cell volume calculated from these data is 1320 Å^3, and the density based on Z = 4 is 1.737 g/cm^3; the crystal density measured by flotation was 1.724 g/cm^3.

Intensity data were collected around the b axis of a 0.2 × 0.3 × 0.3 mm crystal on a Supper automatic diffractometer using a fine-focus Cu tube with a Ni filter. A 3° scan at 2°/min was used, with 45-sec background counts before and after. Reflections were accepted if the intensity was at least twice the square root of the sum of the scan and background counts. On levels 0–9, 1624 of a possible 2102 reflections (77%) were observed.[3] No absorption corrections were made.

The bromine atom was readily located on a three-dimensional Patterson map, and structure factors based on this atom gave an R of 39.9. All of the atoms except the hydrogens were clearly visible in the first Fourier map, and their inclusion in structure factor calculations lowered R to 22.4. Isotropic refinement gave an R of 12.3, which was lowered to 10.3 by anisotropic refinement.[4] A difference map revealed all of the hydrogens except H-13. At this point a data-processing error was corrected; isotropic refinement—including hydrogens—gave an R of 7.3, and anisotropic refinement led to a final R of 5.3. In these refinements, hydrogens were given the same temperature factors as the atoms to which they were attached, and hydrogen temperature factors were not refined. All of the hydrogen positions refined satisfactorily except for H-12 and H-13, which refined into O-1 and a position roughly halfway between O-1 and O-2, respectively. As the most reasonable hydrogen-bonding scheme

TABLE I

BOND ANGLES

Angle	Degrees	Angle	Degrees
C-10a–N-1–C-2	123.6 (5)	OC-4–C-4–N-3	122.2 (6)
N-1–C-2–N-3	115.6 (6)	OC-4–C-4–C-4a	122.3 (6)
C-2–N-3–C-4	126.7 (6)	C-4–C-4a–N-5	117.5 (6)
N-3–C-4–C-4a	115.4 (5)	N-5–C-5a–C-6	119.4 (6)
C-4–C-4a–C-10a	118.6 (6)	H-1–C-6–C-5a	129 (5)
C-4a–C-10a–N-1	119.9 (5)	H-1–C-6–C-7	111 (5)
C-10a–C-4a–N-5	123.8 (6)	H-2–C-7–C-6	121 (4)
C-4a–N-5–C-5a	118.2 (5)	H-2–C-7–C-8	120 (4)
N-5–C-5a–C-9a	120.5 (6)	H-3–C-8–C-7	124 (6)
C-5a–C-9a–N-10	119.0 (5)	H-3–C-8–C-9	114 (5)
C-9a–N-10–C-10a	120.4 (5)	H-4–C-9–C-8	117 (5)
N-10–C-10a–C-4a	117.9 (6)	H-4–C-9–C-9a	123 (5)
C-9a–C-5a–C-6	120.1 (6)	C-9–C-9a–N-10	122.8 (6)
C-5a–C-6–C-7	120.3 (6)	CN-10–N-10–C-9a	119.6 (5)
C-6–C-7–C-8	119.2 (7)	CN-10–N-10–C-10a	119.8 (6)
C-7–C-8–C-9	122.5 (7)	N-10–C-10a–N-1	122.2 (6)
C-8–C-9–C-9a	119.8 (6)	N-10–CN-10–C-5	106 (5)
C-9–C-9a–C-5a	118.2 (6)	N-10–CN-10–C-6	103 (5)
H-8–N-1–C-10a	125 (5)	N-10–CN-10–C-7	112 (5)
H-8–N-1–C-2	110 (5)	C-5–CN-10–C-6	114 (8)
OC-2–C-2–N-1	121.1 (6)	C-5–CN-10–C-7	122 (8)
OC-2–C-2–N-3	123.3 (6)	C-6–CN-10–C-7	98 (9)
H-9–N-3–C-2	123 (6)	H-10–O-1–H-11	111 (12)
H-9–N-3–C-4	108 (7)	H-12–O-2–H-13	119 (*a*)

[a] The standard deviation in this angle is unknown, since H-12 and H-13 did not refine satisfactorily.

(3) Listings of structure factors, coordinates, anisotropic temperature factors, least-squares plane deviations, and packing diagrams have been deposited with the American Documentation Institute, Document NAPS-00740 from ASIS National Auxiliary Publication Service, % CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and by remitting $1.00 for microfiche or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to CCMI-NAPS.

(4) Up to this point, the differential synthesis program of R. Shiono (File No. 7.5.003, Program Information Department, IBM) was used; the later refinements were by full matrix least squares with the ORFLS program of W. R. Busing, K. O. Martin, and H. A. Levy (ORNL-TM-305, Oak Ridge National Laboratory, 1962). Unit weights were used. Form factors were obtained by graphical interpolation of those in the International Tables for X-ray Crystallography, Vol. III, Table 3.3.1A, except for hydrogen, for which the form factors of R. F. Stewart, E. R. Davidson, and W. T. Simpson [*J. Chem. Phys.*, **42**, 3175 (1965)] were used.

requires H-12 and H-13 to be in the positions shown, they were placed there for the final refinement cycles and for Figure 1.

Bond lengths calculated using ORFFE[5] are given on an ORTEP[6] plot in Figure 1, and bond angles are listed in Table I.

Discussion

In the crystals under study, as has been postulated for solutions,[7] 10-methylisoalloxazine is protonated on N-1. Other riboflavin derivatives have also been shown to be protonated at this position in the crystalline state.[1]

The bond lengths found for the cation are very close to those reported by Fritchie and Trus[1c] and close to those in related structures.[1a,b] The long C-4–C-4a bond and the short C-4a–N-5 bond have been observed in all three of these structures.

All of the atoms except H-11 lie close to sheets of P_g symmetry parallel to the 102 plane. There are parts of six such sheets in the unit cell chosen, spaced 3.264 Å apart, starting from 408. The least squares plane calculated from the 17 nonhydrogen atoms of the cation is inclined 1.6° from the 102 plane. The standard deviation of the atoms defining the plane from the plane is only 0.053, with the deviations occurring primarily as a slight bow along the long axis of the molecule. This bow, which is quite possibly absent in solution, is probably present in the crystal to permit reasonable distances between bromide ion and N-3 in adjacent sheets [these atoms are 3.463(9) Å apart] and bromide and N-10 in adjacent sheets in the other direction [3.364(9) Å apart].

Figure 1 shows the intrasheet hydrogen bonds as dotted lines. The distances between nonhydrogen atoms joined through hydrogen bonds are unexceptional. The values in angstroms are: N-1–O-1, 2.883 (13); O-1–O(C-4), 2.886 (10); O-1–O-2, 2.767 (11); N-3–Br, 3.433 (10); O-2–Br, 3.291 (10).

The stacking arrangement of the sheets is governed primarily by the intersheet hydrogen bond involving H-11. The formation of strong intersheet hydrogen bonds requires the water oxygens to move closer to one another [intersheet O-1–O-2 distance, 2.983 (11) Å; H-11–O-1 distance, 2.09 (8) Å], and accounts for their large deviations from the molecular plane. O-1 moves farther out of the plane than O-2, presumably to give both oxygens better tetrahedral coordination [the fourth coordination for O-2 is provided by interaction with N-10, 3.235 (10) Å away]. The bromine is sandwiched between two nitrogens with partial positive charges, N-3 and N-10, as noted above. It also serves as a hydrogen-bond acceptor for N-3 and O-2, giving it roughly square-planar coordination. An H-2 and H-4 in the same sheet are nearly close enough [2.79 (8) and 2.85 (8) Å, respectively] and at the right angle to complete an octahedral arrangement around bromide ion.

Registry No.—I, 23653-16-9.

Acknowledgments.—We thank G. Tollin and D. E. Fleischman of this Department for suggesting this problem and furnishing the crystals; the University of Pittsburgh Crystallography Laboratory and the Oak Ridge National Laboratory for programs; H. S. Craig and R. D. and S. H. Jay for assistance with programming; the Numerical Analysis Laboratory of the University of Arizona for computer time; and the PHS (GM-12447), Sloan Foundation (Fellowship to R. B. B.), and NSF (URP support to T. C. S.) for financial assistance.

(5) W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-306, Oak Ridge National Laboratory, 1964.

(6) C. K. Johnson, ORNL-3794.

(7) K. Dudley, A. Ehrenberg, P. Henmerich, and F. Muller, *Helv. Chim. Acta*, **47**, 1354 (1964).

Conversion of Some Bicycloheptanols into Chlorides Using Triphenylphosphine–Carbon Tetrachloride. Stereochemistry and Mechanistic Implications

RICHARD G. WEISS AND E. I. SNYDER[1a]

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06268

Received August 25, 1969

The reaction of triphenylphosphine and carbon tetrachloride with *exo,exo*-2,3-dideuterio-*anti*-7-hydroxybicyclo[2.2.1]heptane affords *exo,exo*-2,3-dideuterio-*syn*-7-chlorobicyclo[2.2.1]heptane, exclusively. The isolated products from *exo,exo*-3,4-dideuterio-*exo*-2-hydroxybicyclo[3.2.0]heptane are *exo,exo*-3,4-dideuterio-*endo*-2-chlorobicyclo[3.2.0]heptane and *exo,exo*-2,3-dideuterio-*anti*-7-chlorobicyclo[2.2.1]heptane. With the aid of a comparison between the inversion found in these reactions and the predominant retention of configuration found in the products of solvolysis of the esters of the above alcohols, a *tentative* mechanistic rationale is presented to account for our observations.

A previous report[1b] has demonstrated that the reaction of triphenylphosphine and carbon tetrachloride with alcohols to give alkyl chlorides has remarkable

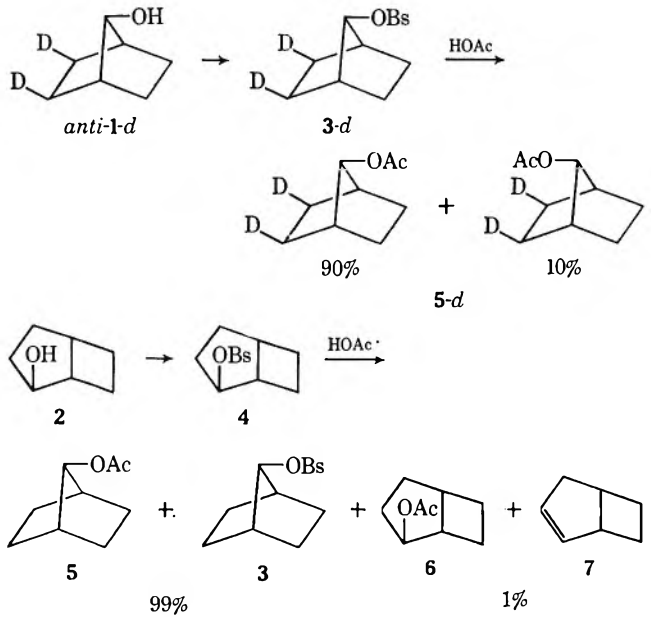
$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + CHCl_3$$

tendency for inversion, even in cases where solvolysis of the corresponding esters is largely or completely assisted and the solvolysis products exhibit retained configurations. It is known also that such conversions occur with little or no skeletal rearrangement in those systems where SN1 reactions afford extensively rearranged products.[1b,2] To further elucidate the scope of this reaction, the course of reaction with alcohols **1** and **2** was determined.

(1) (a) To whom correspondence should be addressed: East Tennessee State University, Johnson City, Tenn. 37601. (b) R. G. Weiss and E. I. Snyder, *Chem. Commun.*, 1358 (1968).

(2) R. G. Weiss, Ph.D. Thesis, University of Connecticut, 1969; I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind.* (London), 900 (1966).

The acetolysis of **3**-*d* has been shown to proceed with 90% retention of configuration,[3,4] whereas that of **4** leads to a predominance of **5** and traces of **6** and **7**.[5] Both **3** and **4** share the same reaction coordinate during much of the acetolysis reaction, as has been discussed by Winstein and coworkers[5] and Miles.[3]

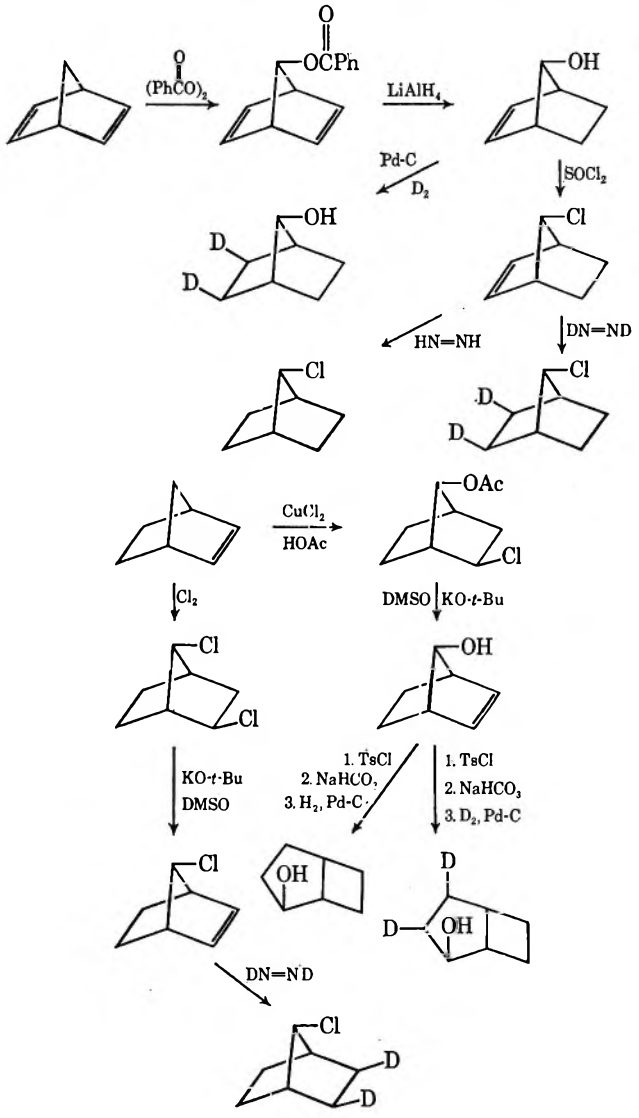


Results

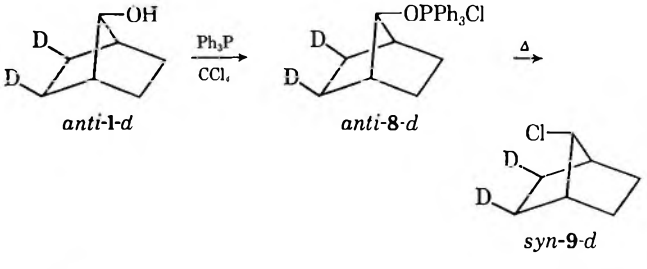
Reactions of 1.—Reaction of equimolar quantities of **1** and triphenylphosphine in carbon tetrachloride produces **8** as an oil which solidifies when solvent is removed. The structure of **8** was ascertained from its pyrolysis products, **9** and triphenylphosphine oxide, from its nmr spectrum,[6] and by analogy to work of Schaefer and Weinberg[8] on the Wiley[9] reaction. The structure of **9** was confirmed by comparison of its melting point, vpc retention time, and nmr and infrared spectra with those of an authentic sample. Consistently, 50–60% yields of **9** were obtained, although optimum reaction conditions were not sought.

The stereochemistry of the conversion **1** → **9** was determined using *exo,exo*-2,3-dideuterated alcohol. The route to dideuterated alcohol *anti*-**1**-*d* (Scheme I) assures the absence of *syn*-**1**-*d*. Independent synthesis of the isomeric dideuterated chlorides *syn*- and *anti*-**9**-*d* was achieved as shown in Scheme I. Facile differentiation of the *syn* and *anti* isomers of **9**-*d* was permitted by their distinct deuterium-decoupled nmr spectra (see Figure 1). The product from *anti*-**1**-*d* is obviously *syn*-**9**-*d* (Figure 1c). Independent control experiments showed that ≥5% *anti*-**9**-*d* is readily detected in a *syn–anti* mixture of chlorides **9**-*d*, so that reaction has proceeded with ≥95% inversion. When the decomposition of intermediate **8** was monitored, both its rate of disappearance and the rate of formation of **9** were roughly first order in **8**.

SCHEME I
SYNTHESES OF DEUTERIUM-LABELED COMPOUNDS



Reactions of 2.—In our hands, the method of Winstein[10] did not result in pure **2** despite numerous attempts. Alcohol, ≥90% pure by nmr, vpc, and in-



(3) F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 1265 (1968).

(4) P. G. Gassman and J. M. Hornback, *ibid.*, **89**, 2487 (1967).

(5) S. Winstein, F. Gadient, E. T. Stafford, and P. E. Klinedinst, Jr., *ibid.*, **80**, 5895 (1958).

(6) The nmr spectrum in either D_2O or $CDCl_3$ showed high-field resonances clearly attributable to a 7-substituted bicyclo[3.3.1]heptane and low-field resonances in the phenyl region. Denney, Denney, and Wilson[7] have found $J_{POCH} \cong 7$ cps (CH_2Cl_2) for the pentacovalent structure i and for the ionic compounds ii and iii. In both D_2O and $CDCl_3$, $J_{POCH} \cong 7$ cps for **8**.

$Ph_3P(OEt)_2$ (i) $[Ph_3POEt]^+BF_4$ (ii) $[Bu_3POEt]^+BF_4^-$ (iii)

(7) D. B. Denney, D. Z. Denney, and L. A. Wilson, *Tetrahedron Lett.*, 85 (1968).

(8) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635, 2639 (1965). Compound iv was isolated and purified when **1** and bromotriphenylphosphonium bromide were mixed in triglyme. Upon pyrolysis above its melting point, iv produced triphenylphosphine oxide and 7-bromobicyclo-[2.2.1]heptane. Halophosphoranes of *endo*-2-hydroxybicyclo[2,2,1]heptane and 1-hydroxybicyclo[2.2.1]heptane[12] have been isolated and pyrolyzed to the corresponding phosphine oxides and alkyl halides.

(9) G. Wiley, B. Rein, and R. Hershkowitz, *Tetrahedron Lett.*, 2509 (1964); G. Wiley, R. Hershkowitz, B. Rein, and B. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(10) S. Winstein and E. T. Stafford, *ibid.*, **79**, 505 (1957).

frared analyses, containing residual *exo*-2-hydroxybicyclo[3.2.0]hept-3-ene and a carbonyl-bearing compound, was used.[11]

Reaction of **2** with Ph_3P–CCl_4 at 65° for short periods ($\leq$4 hr) followed by solvent removal leaves a white solid whose structure is inferred from previous work[8,12] (see above) and from its pyrolysis products (triphenylphosphine oxide, **9**, and **10**) to be a mixture of **8** and **11**. The presence of *syn*-**8**-*d* during the reaction of **2**-*d* is inferred from the observation that *anti*-**9**-*d* comprises at least 90% of the rearranged chloride (see Figure 1d)[13] and the knowledge from the previous section that decomposition of *anti*-**8**-*d* occurs with inversion of configuration.

The ratio of **10**:**9** obtained from the pyrolyses of the residue from **2**, triphenylphosphine, and carbon tetrachloride appears to be a function of pyrolysis temperature and duration. The results are summarized in Table I.[14]

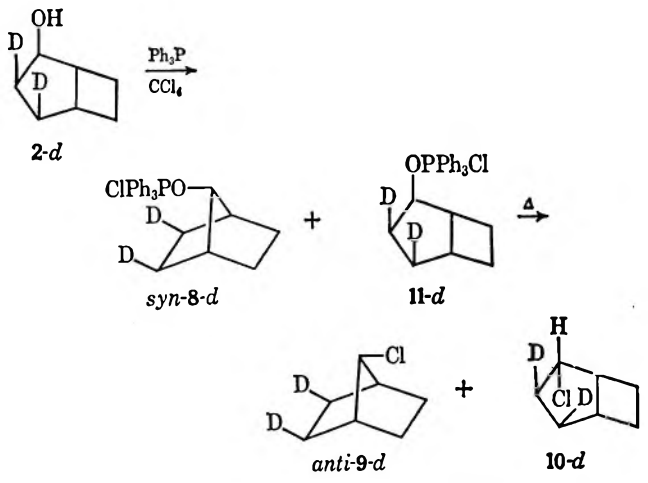


TABLE I

REACTIONS OF 2 WITH TRIPHENYLPHOSPHINE AND CARBON TETRACHLORIDE

Run	Reaction time, hr	Temp, °C	Pyrolysis of salts: Temp, °C	Pyrolysis of salts: Time, min	Product ratio[a] 10 to 9
1	65	Ambient room			33:7.5[b]
2	3.5	60–65	80–160	30	3:97[c]
3	3.5	60–65	70–180	15	1:3
4	6	60			1.83:1[b]
			60–135		3:8
5[d]	3.5	60–65	70–180	20	13:87

[a] Ratios were determined by direct comparison of vpc peak weights. [b] Ratio of 10 to 9 present in the reaction solvent prior to pyrolysis of the residue. [d] Deuterated substrate, **2**-*d*. [c] Contained a third, unidentified product.

The stereochemistry of the catalytic deuteration of *exo*-2-hydroxybicyclo[3.2.0]hept-3-ene is not known.

(11) The role of the impurities during reaction of **2**-*d* is not known. Although they are not expected to alter the product stereochemistry, they may have influenced the ratio of *anti*-**9**-*d* to **10**-*d*.

(12) D. B. Denney and R. R. DiLeone, *J. Amer. Chem. Soc.*, **84**, 4737 (1962).

(13) Control experiments showed that 10% *syn* **9**-*d* is detected in a *syn*–*anti* mixture of chlorides **9**-*d*.

(14) The results from reaction of **2** with Ph_3P–CCl_4 at $\leq$65° over extended times are puzzling. Although rearranged chloride, **9**, is formed, other experiments suggest that the oxyphosphorane **8** is thermally stable under these conditions. If both statements above are valid, then the sequence **2** → **8** → **9** cannot be correct, at least at these temperatures. We note that the absolute yields of **9** formed under these conditions is small, and that we have insufficient data to resolve this point at present.

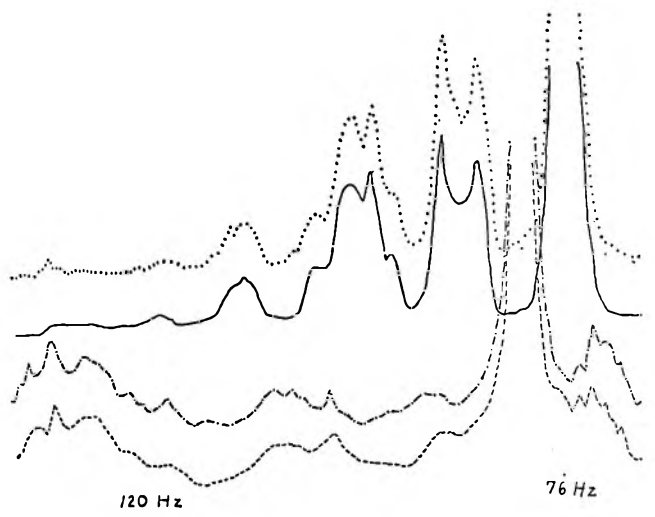
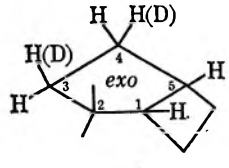


Figure 1.—Nmr spectra of *exo,exo*-2,3-dideuterio-*syn*-7-chloro[2.2.1]heptane (. . . .), chloride from *exo,exo*-2,3-dideuterio-*anti*-7-hydroxybicyclo[2.2.1]heptane (——), *exo,exo*-2,3-dideuterio-*anti*-7-chlorobicyclo[2.2.1]heptane (-·-·), and chloride from *exo,exo*-3,4-dideuterio-*exo*-2-hydroxybicyclo[3.2.0]heptane (– – – –).

By analogy to the deuteration of bicyclo[2.2.1]heptene[15] and from comparison of the nmr spectra of deuterated and undeuterated **2** (see below), the deuteriums are assigned as 3,4-*exo* in **2**-*d*.

Chloride products from runs 3 and 5 were isolated by vpc. The compound of shorter retention time in run 3 was identified as **9** by comparison of its vpc retention time, melting point, mass spectrum, and nmr spectrum with those of an authentic sample. The compound of shorter retention time of run 5 was identified similarly as *anti*-**9**-*d*.[13] The longer retention time compounds of runs 3 and 5 were **10** and **10**-*d*, respectively. Although the mass spectra of **10** and **10**-*d* are nearly identical with those of **9** and *anti*-**9**-*d*, their infrared spectra and vpc retention times are distinctly different. The high-field portions of the nmr spectra are characteristic of a 2-substituted bicyclo[3.2.0]heptane skeleton.

The couplings of the low-field 2-proton resonances serve to determine the stereochemistry of **10**. (The arguments for the chlorides apply to the alcohols as well.) Molecular models of *endo* and *exo* 2-substituted bicyclo[3.2.0]heptanes show that the 1-bridgehead proton is geometrically disposed to couple very strongly with an *exo* 2 proton but very weakly with an *endo* 3 proton. Owing to ring puckering an *exo* 3 proton couples weakly with both *exo* and *endo* 2 protons and an *endo* 3 proton couples strongly with both *exo* and *endo* 2 protons. Therefore, an *endo* 2 proton (substituent



endo

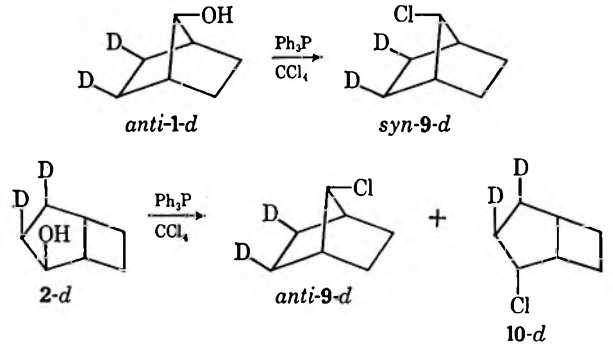
exo) should exhibit an AX, and an *exo* 2 proton (substituent *endo*) should exhibit an ABX pattern, where it is assumed that the weak couplings are much less than the major couplings (first-order analysis). Consistent

(15) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **33**, 1288 (1968).

with this interpretation, doublets are observed for the 2 protons of **2** and **2**-*d*, whereas rough quartets are observed for the comparable protons of **10** and **10**-*d*.

Discussion

Reaction of neither **1** nor **2** with triphenylphosphine and carbon tetrachloride exhibit SN1 characteristics. Solvolyses products of *anti*-**3**-*d* are formed with 80–90% *retention* of configuration;[3,4] solvolysis products of **4** are predominantly rearranged (7-norbornyl), presumably with substituent *syn* to C-3–C-4 of **4**, but the unrearranged portion is of retained configuration exclusively.[5] In contrast, we find that *anti*-**1**-*d* is converted into *syn*-**9**-*d* exclusively and **2**-*d* yields *anti*-**9**-*d* and inverted unrearranged **10**-*d*.



Nonsolvolytic displacement reactions at the 7 position of norbornanes are difficult and to our knowledge the only other such reaction where the stereochemistry has been determined[16] also proceeds with inversion.

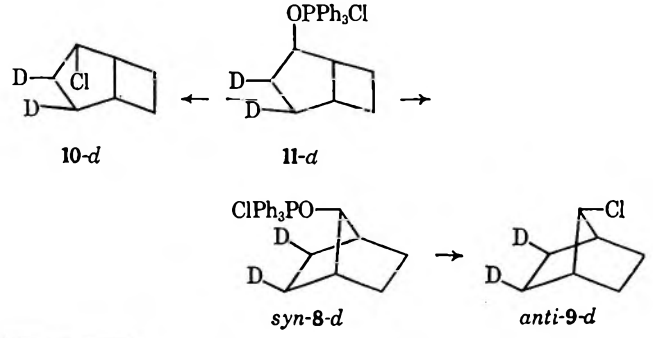
As has been shown by Downie, Lee, and Matough[17] and by Ried and Appel,[18] phosphines attack carbon tetrachloride at chlorine, forming a chlorophosphonium trichloromethide salt, **12**, which reacts with alcohols as shown below.

$$R_3P: + Cl{-}CCl_3 \rightarrow \underset{\mathbf{12}}{R_3PCl^+CCl_3^-} \quad (1)$$

$$R_3PCl^+CCl_3^- + R'OH \rightarrow R_3PCl^+OR'^- + HCCl_3 \quad (2)$$

$$R_3PCl^+OR' \rightarrow R_3POR'^+Cl^- \rightarrow R_3P{=}O + R'Cl \quad (3)$$

That [3.2.0] and [2.2.1] products are obtained from **2**-*d* indicates that **11**-*d* decomposes by two pathways. The easiest way for us to explain the formation of *anti*-**9**-*d* is by internal return to *syn*-**8**-*d* followed by its decomposition to *anti*-**9**-*d*. The energy of activation for internal return must be comparable with that for formation of **10**-*d* since both products are formed in similar amounts.



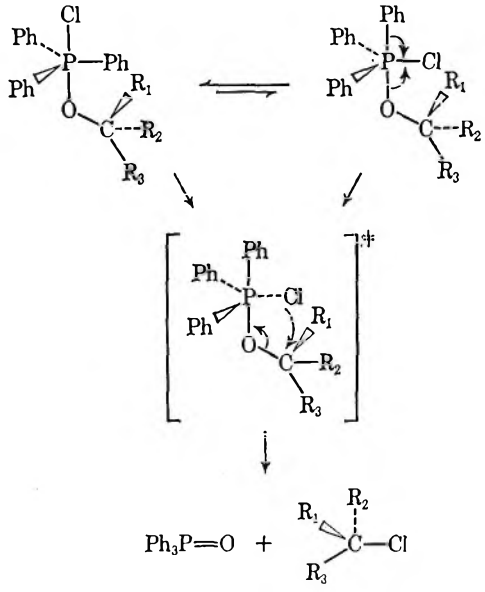
But the existence of a cationoid intermediate poses the dilemma that it should collapse by front-side attack, in analogy to the work of Miles[3] and Gassman,[4] whereas the experimental results show that under 10% of the chloride is formed by this route. This means that either the ion pair formed, $R^+OPPh_3Cl^-$, is so "tight" that it does not react with external nucleophile or that nucleophilic species are absent. Since added external nucleophile (cyanide) does not compete with chlorine in the homogeneous decomposition of the 2-phenylethoxyphosphorane,[19] there is some evidence supporting the former contention. Similarly pyrolysis of an admixture of **8** and sodium cyanide affords only chloride.

The observed propensity for inversion accords with a modified SN2 reaction (eq 3). However, it must be recognized that under reaction conditions (pyrolysis for **1** and **2**, carbon tetrachloride solution for other alcohols) chloride ion, if present, must be part of a quite tight ion pair, $ROPPh_3^+ Cl^-$. (Note the distinction between this ion pair and that, discussed above, resulting from C–O heterolysis.) That external nucleophiles do not compete with chloride in decomposition of the oxyphosphoranes such as **8**, and that (admittedly rough) kinetic data point to a first-order decomposition of oxyphosphorane, requires product formation either *via* a tight ion pair or an intramolecular covalent decomposition. On this basis we suggest that a reasonable reaction mechanism involves intramolecular, reasonably concerted decomposition of the oxyphosphoranes **8** and **11**. An activated complex in which P–Cl and C–O bond cleavage are concerted with C–Cl and P=O bond formation affords the high energy of the latter bond as an effective driving force which is probably responsible for the relative facility with which reaction occurs.

The observed inversion places some rigid requirements on the reaction profile. If in nonpolar media we are dealing with pentacovalent phosphorus as a trigonal bipyramid, then the most stable arrangement is one where both oxygen and chlorine are apical.[20] Product can not be formed directly from this conformer by a unimolecular decomposition unless ionic chloride wanders around the periphery in a tight ion pair, in which case one deals with a tetrahedral phosphorus as a cation. The operational distinction between a trigonal bipyramidal oxyphosphorane and a tight ion pair with tetrahedral phosphorous may even vanish. Alternatively, either apical oxygen or chlorine may be converted into the equatorial conformer by pseudorotation.[21] The feasibility of product formation from the latter conformer is suggested by inspection of models, which indicate that chlorine is some 2.0–2.5 Å from the carbon being substituted. If one requires that chlorine attack colinearly with oxygen to effect *inversion*, spatial requirements become too severe for reaction to occur directly from a trigonal bipyramid.

(16) J. T. Lumb and G. H. Whitham, *Chem. Commun.*, 400 (1966). We thank a referee for calling this to our attention.
(17) I. M. Downie, J. B. Lee, and M. F. S. Matough, *ibid.*, 1350 (1968).
(18) W. Ried and H. Appel, *Justus Liebigs Ann. Chem.*, **679**, 51 (1964).
(19) R. G. Weiss and E. I. Snyder, submitted for publication.
(20) E. Muetterties and R. Schunn, *Quart. Rev.* (London), **20**, 245 (1966). The more electronegative substituents on a trigonal bipyramidal phosphorus atom assume the apical positions at equilibrium.
(21) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

It seems reasonable that P–Cl bond cleavage precedes somewhat C–O bond cleavage in a very tight ion pair.



This rationale is not without its difficulties. In particular, we fail to understand why a concerted, four-center decomposition with *retention* of configuration fails to occur. Models suggest that the latter is sterically less severe than an inversion process, and analogs of this process are known.[22] Nor do we understand the reluctance toward sufficient C–O bond cleavage to give a cation which behaves as do more typical cations. Thus neopentyl alcohol affords no rearranged products, and the neopentyl chloride is formed with inversion.[19] Even cyclopropyl alcohol reacts to give, in part, unrearranged cyclopropyl chloride.[19] It must be recognized explicitly that the mechanistic hypothesis presented has not yet been subjected to rigorous mechanistic tests and remains speculative at present.

Experimental Section

Boiling and melting points (sealed capillary) are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were recorded on a Varian Associates A-60 spectrometer using an NMR Specialties HD-50A decoupler when appropriate. Vpc analyses were performed on a Wilkens Aerograph chromatograph using the following columns (0.25 in. o.d.): column A, 15-ft 20% Ucon HB5100 on 40/60 Chromosorb W; column B, 10-ft 10% DC550 on 80/100 Chromosorb W, HMDS; column C, 10-ft 10% *p*-cresyl phosphate on 80/100 Chromosorb W, HMDS. Triphenylphosphine (Carlisle Chemical Co.) was recrystallized from cyclohexane–isopropyl alcohol and melted in a dry atmosphere prior to use. Carbon tetrachloride was stored over phosphorus pentoxide.

anti-**7-Hydroxybicyclo[2.2.1]heptene** (*anti*-**13**).—The method of Tanida and Tsuji[23] was used to prepare 7-benzoyloxybicyclo-[2.2.1]heptadiene. Reduction with lithium aluminum hydride in ether[24] yielded *anti*-**13** containing 11% benzyl alcohol as determined by vpc analysis (A, 130°).

exo,exo-**2,3-Dideuterio-*anti*-7-hydroxybicyclo[2.2.1]heptane** (*anti*-**1-*d***).—A solution of 2.3 g of crude *anti*-**13**, 0.25 g of Pd–C, and 50 ml of absolute methanol was shaken for 1 hr in a Paar bottle under 30 psi of deuterium gas.[16] The mixture was filtered through diatomaceous earth and the solvent was distilled. The residue was sublimed at 85° (1 mm) to yield 2.0 g of *anti*-**1-*d***, mp 154–156.5°.

Anal.[25] Calcd for $C_7H_{10}D_2O$: 16.66 atom % excess. Found: 16.60 atom % excess or 1.99 D per molecule.

syn-**7-Hydroxybicyclo[2.4.1]heptene** (*syn*-**13**), mp 80–86°, was prepared according to Baird.[26]

7-Hydroxybicyclo[2.2.1]heptane (**1**).—Reduction of *syn*-**13** over 10% Pd–C (0.58 mol %) at 20 psi of hydrogen afforded **1**, mp 146–150° (lit.[27] mp 152–153°), after recrystallization from pentane and sublimation at 90° (1 atm).

exo,exo-**2,3-Dideuterio-*anti*-7-chlorobicyclo[2.2.1]heptane** (*anti*-**9-*d***).—*anti*-7-Chlorobicyclo[2.2.1]heptane was prepared from *anti*-**13** by the method of Tanida and Hata.[28] A 6.7-g (0.105 mol) portion of acetic acid-d_4 (Stohler, 99.5% D) in 5 ml of methyl alcohol-*d* was slowly dripped into an ice-cooled, mechanically stirred mixture of the above olefin (2.06 g, 0.016 mol) and potassium azodicarboxylate[29] (9.3 g, 0.048 mol) in 20 ml of methanol-*d*. Stirring was continued overnight at room temperature. The mixture was diluted with water and extracted with pentane (three 25-ml portions). The combined organic phases were washed with water, dried ($MgSO_4$), and distilled, bp 40°. The residue, 1.4 g (66%), was sublimed five times at 35–60° (1 atm) to yield *anti*-9-*d*,[30] mp 46–47°.

Anal. Calcd for $C_7H_9D_2Cl$: 18.18 atom % excess. Found: 17.05 atom % excess or 1.87 D per molecule.

An undeuterated sample, **9**, was prepared in an analogous fashion. Analyses by vpc (column A, 120°) of purified samples of **9** and *anti*-9-*d* showed no impurity.

exo,exo-**2,3-Dideuterio-*syn*-7-chlorobicyclo[2.2.1]heptane** (*syn*-**9-*d***).—*syn,exo*-2,7-Dichlorobicyclo[2.2.1]heptane (14.3 g, 0.0867 mol), prepared according to Roberts, Johnson, and Carboni,[31] was stirred in a closed flask for 3.5 days with potassium *t*-butoxide (14.3 g, 0.13 mol) in 50 ml of dry dimethyl sulfoxide. The solution was diluted with water and extracted with pentane (four 75-ml portions). The combined pentane extracts were washed with water, dried ($MgSO_4$), and distilled. By nmr and vpc (column B, 105°) analyses, the cut with a boiling point of 50° (16 mm) [lit. bp 45° (16 mm)], yield 10.7 g (96%), was >99% *syn*-7-chlorobicyclo[2.2.1]heptane. Reduction with potassium azodicarboxylate as described above yielded, after sublimations at 75° (77 mm) and 75° (1 atm), *syn*-9-*d* (61%).

Anal. Calcd for $C_7H_9D_2Cl$: 18.18 atom % excess. Found: 16.20 atom % excess or 1.78 D per molecule.

exo,exo-**3,4-Dideuterio-*exo*-2-hydroxybicyclo[3.2.0]heptane** (**2-*d***).—*exo*-2-Hydroxybicyclo[3.2.0]hept-3-ene, prepared by the method of Winstein and Stafford,[32] was reduced in absolute methanol using 5% Pd–C (0.13 mol %) under 20 psig of deuterium gas. The product, **2-*d***, was a viscous liquid.

Anal. Calcd for $C_7H_{10}D_2O$: 16.66 atom % excess. Found: 14.60 atom % excess or 1.75 D per molecule.

An undeuterated sample of **2** was prepared in an analogous manner. By nmr and vpc (column C, 100°) analyses, the only noted impurity in **2** and **2-*d*** was unreduced *exo*-2-hydroxybicyclo[3.2.0]-hept-3-ene (≤5%). In our hands, the purity of **2** and **2-*d*** was not improved by repeated distillation, sublimation, and recrystallization.

Reactions of Triphenylphosphine, Carbon Tetrachloride, and Alcohols. A. With *anti*-1-*d*.—A solution of *anti*-**1-*d*** (1.14 g, 0.01 mol) and triphenylphosphine (2.88 g, 0.011 mol) in 6 ml of carbon tetrachloride was stirred in a closed flask for 24 hr at room temperature. Solvent was distilled at ≤35° (30 mm) in a dry atmosphere. The residue was heated slowly at 16 mm pressure to 175°. The distillate collected in a Dry Ice trap (1.15 g) was sublimed and eluted on a 1.5-g Florisil column first with pentane and then with methanol. Pentane was carefully distilled and the residue obtained was sublimed at 55–70° to give *syn*-**9-*d*** mp 43–45.

Anal. Calcd for $C_7H_9D_2Cl$: 18.18 atom % excess. Found: 17.90 atom % excess or 1.97 D per molecule. Distillation of the methanolic fraction left a solid whose nmr spectrum was that of *anti*-**1-*d***.

(22) E. S. Lewis and W. C. Herndon, *J. Amer. Chem. Soc.*, **83**, 1955 (1961).
(23) H. Tanida and T. Tsuji, *J. Org. Chem.*, **29**, 849 (1964).
(24) B. Franzus and E. I. Snyder, *J. Amer. Chem. Soc.*, **87**, 3423 (1965).
(25) Analyses conducted by Mr. Josef Nemeth, Urbana, Ill.
(26) W. Baird, Jr., *J. Org. Chem.*, **31**, 2411 (1966).
(27) P. R. Story, *ibid.*, **26**, 287 (1961).
(28) H. Tanida and Y. Hata, *ibid.*, **30**, 977 (1965).
(29) We acknowledge the gift of potassium azodicarboxylate from Dr. J. W. Hamersma; J. W. Hamersma and E. I. Snyder, *ibid.*, **30**, 3985 (1965).
(30) W. Baird, Jr., B. Franzus, and J. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).
(31) J. D. Roberts, F. Johnson, and R. Carboni, *ibid.*, **76**, 5692 (1954).
(32) S. Winstein and E. T. Stafford, *ibid.*, **79**, 505 (1957).

In a similar fashion, **1** was allowed to react to yield **9** (53%), mp 41–44°.

When the dried phosphonium salt **8** was heated in chloroform at 60° for 45 hr, no chloride **9** resulted.

B. With 2-*d*.—A solution of **2-*d*** (1.14 g, 0.01 mol) and triphenylphosphine (2.88 g, 0.011 mol) in 6 ml of carbon tetrachloride was stirred in a dry atmosphere at 60–65° for 3.5 hr. The solvent was removed at 1 mm. By vpc analysis (column C, 100°), the distillate collected by slowly heating the residue to 180° (1 mm) contained a 13.3:86 ratio of **10-*d*** to ***anti*-9-*d***. Pure samples of ***anti*-9-*d*** and **10-*d*** were collected by vpc (column C, 65°).

Similar reactions of **2** were conducted. Ratios of **10** to **9** varied from 3:97 for residue pyrolyzed at 160° (30 min) to 1.18: for pyrolysis at 60° (6 hr in carbon tetrachloride). The maximum yield for purified **9** and **10** in any run was 19% (30% crude).

Isomerization Experiment of 10 and 9.—A solution of 0.1 g of **9** and **10**, 0.1 g of triphenylphosphine, and 0.1 g of triphenylphosphine oxide in 0.2 ml of chloroform was heated to 150° during 5 min. The ratios of **10** to **9** measured by vpc (column C, 100°) before and after heating were 1.0:3.0 and 1.0:3.1, respectively.

Kinetically Followed Decomposition of 8.—Crude **8** was prepared by stirring a solution of **1** (0.85 g, 7.6 mmol) and triphenylphosphine (2.15 g, 8.2 mmol) in 7 ml of carbon tetrachloride at 65° for 3.5 hr. Solvent was removed *in vacuo* and the residue was twice shaken up in chloroform and precipitated with anhydrous ether. After being dried *in vacuo* over phosphorus pentoxide, **8** was dissolved in deuteriochloroform (1% TMS) and sealed in two nmr tubes. The tubes were heated at 120 ± 3° and the decomposition of **8** and appearance of **9** were monitored periodically by recording the nmr spectrum and integrating the signals of the 7 proton of **8** (4.82 ppm) and of **9** (3.94 ppm). Experimental plots of log [**8**] *vs.* time and log ($[9]_\infty - [9]$) *vs.* time were constructed. Both gave roughly straight-line slopes: for decomposition of **8**, $k \cong 7.7 \times 10^{-6}$ sec^{-1}; for formation of **9**, $k \cong 8.2 \times 10^{-6}$ sec^{-1}.

Registry No.—Triphenylphosphine, 603-35-0; carbon tetrachloride, 56-23-5; ***anti*-1-*d***, 23667-07-4; **2-*d***, 23667-08-5; **9**, 765-80-0; ***anti*-9-*d***, 23667-10-9; ***syn*-9-*d***, 23754-34-9; **13**, 13118-70-2.

Acknowledgment.—This work was made possible through support from the National Science Foundation and Petroleum Research Fund. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support.

Vinylogous Imides. II. Ultraviolet Spectra and the Application of Woodward's Rules[1,2]

DARYL L. OSTERCAMP[3]

Department of Chemistry, Concordia College, Moorehead, Minnesota 56560

Received July 7, 1969

The ultraviolet spectra of a variety of β-amino α,β-unsaturated carbonyl compounds and their N-alkyl and N-acyl derivatives were examined with due regard for chromophore stereochemistry. Included in this study were 37 vinylogous amides, –NC=CC(O)–; 26 vinylogous imides, –(O)CNC=CC(O)–; 13 vinylogous urethans, –NC=CCOOR; and 2 vinylogous ureas, –NC=CC(O)N–. Analysis of the relative locations of the $\pi \rightarrow \pi^*$ transitions gave substituent increments of +75 mμ for *cis*-β-amino, +65 mμ for *trans*-β-amino, +10 mμ for β-N-alkyl, −10 mμ for β-N-acetyl, and +6 mμ for β-N-benzoyl. These substituent constants can be used to distinguish between *cis*- and *trans*-vinylogous imides, and also to reinforce stereochemical assignments for vinylogous amides and urethans based upon their molar extinction coefficients.

Empirical rules for correlating the structure of an α,β-unsaturated ketone with the ultraviolet (uv) absorption maximum of its $\pi \rightarrow \pi^*$ transition were first enunciated by Woodward[4] in 1941. Subsequently these rules were expanded to include the corresponding aldehydes,[5] acids, and esters,[6] and the effect of ring size on band positions for α,β-unsaturated carbonyl compounds in general.[7] Considerable study has also been devoted to the bathochromic effects of various substituents. In 1959 Fieser and Fieser[8] modified slightly the solvent corrections initially applied by Woodward.[4] As spectral information accumulated, the results, including substituent shifts, have been published[8,9] periodically in tabular form to facilitate their application.

The availability of vinylogous amides, β-amino α,β-unsaturated ketones, –NC=CC(O)–, and imides, β-amido α,β-unsaturated ketones, –(O)CN=CC(O)–, of known structure and stereochemistry from a previous project[1] prompted us to investigate their uv spectral properties. Although a substituent increment of +95 mμ for a β-dialkylamino group (–NR_2) of a vinylogous amide was reported[10] in 1946, the compounds included in this study were limited in both number and scope. In addition the relationship of stereochemistry to substituent shift has not been thoroughly investigated for this system. Planar structures I–IV[11] allow maximum resonance stabilization. In the case of form II intramolecular hydrogen bonding of –NH to carbonyl oxygen is also possible.

Examination of the literature revealed the existence of spectral data for related compounds such as vinylo-

(1) Part I: D. L. Ostercamp, *J. Org. Chem.*, **30**, 1169 (1965).

(2) Presented in part at the 3rd Great Lakes Regional Meeting of the American Chemical Society, DeKalb, Ill., June 1969.

(3) Address for the 1969–1970 academic year: School of Chemical Sciences, University of East Anglia, Norwich, England.

(4) R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1941).

(5) L. K. Evans and A. E. Gilliam, *J. Chem. Soc.*, 565 (1943).

(6) A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957).

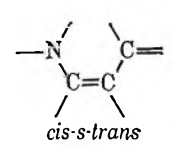
(7) W. M. Schubert and W. A. Sweeney, *J. Amer. Chem. Soc.*, **77**, 2297 (1955).

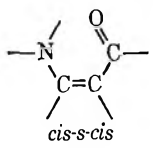
(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 15–21.

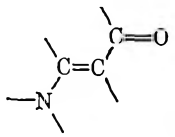
(9) (a) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1949, pp 184–198; (b) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 58; (c) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1962, Chapter 10; (d) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, pp 11–15; (e) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1969, p 96.

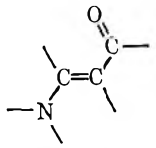
(10) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(11) Stereochemical labels throughout this paper refer to the chromophoric system and not to any specific compound.


cis-s-trans
I


cis-s-cis
II


trans-s-trans
III


trans-s-cis
IV

gous urethans, -NC=CCOOR,[10,12-18] N-acyl derivatives,[16] and vinylogous ureas, -NC=CC(O)N-,[15,19] and the results are included in the present paper.

Experimental Section[20]

Materials.—Acetyl chloride, benzoyl chloride, and pyridine were all freshly distilled (pyridine from BaO) under a dry atmosphere prior to use. Analytical reagent grade acetic anhydride was used without further purification.

Spectra.—Ultraviolet spectra were measured using a Cary Model 14 recording spectrophotometer (Spectrograde solvents) with cells of 1.00-cm path length. The wavelengths were good to ±1 mμ, the extinction to ±2%. Nmr data were obtained on a Varian A-60 spectrometer with tetramethylsilane as the internal reference.

Preparation of Compounds.—The existence of suitable ultraviolet absorption data in the literature obviated the synthesis of many compounds. In addition, the preparation or source of a number of compounds utilized in the present work has been described previously by the author.[1] Samples of 4-methylamino-3-penten-2-one (**18**)[21] and 4-benzylamino-3-penten-2-one (**19**)[22] were readily obtained from the appropriate amine and 2,4-pentanedione.

1-Acetyl-2-aminocyclohexene (1).—A solution of 14.4 g (0.103 mol) of freshly distilled 2-acetylcyclohexanone, bp 104–106° (16 mm), in 100 ml of absolute methanol was saturated for 2.5 hr with ammonia. Development of a light yellow color was accompanied by slight warming of the solution as the reaction proceeded. After standing at room temperature for 2 hr, the solution was saturated for 2.5 hr again with ammonia. A third and a fourth treatment with ammonia (2 hr each time) on succeeding days resulted in complete conversion into **1** and **5** (tlc).[20] Subsequent removal of solvent gave a slightly wet, yellow solid, which was then dissolved in CH_2Cl_2. After the organic solution had been washed with 100 ml of 5% NaOH and then water, it was dried (Na_2SO_4) and freed of solvent. The resulting yellow mixture of crystalline **1** and **5** (12.2 g, 85.1%), mp 63–93°, was recrystallized once from cyclohexane and then twice from methanol–water to yield 5.57 g (38.9%) of white **1**, mp 99–104°. Removal of solvent from each mother liquor and subsequent chromatography of the individual solid residues gave an additional 2.34 g (16.3%) of **1** (eluted first with ether), mp 103–104°, and 1.40 g (9.8%) of **5** (eluted with ethyl acetate), mp 112–114°.

Material isolated by chromatography was recrystallized twice from cyclohexane and then vacuum sublimed at 95° (1 mm) to afford an analytically pure sample of **1**: mp 104.5–105.4°; nmr ($CDDl_3$) δ 7.3 (br s, 2, NH_2), 2.38 (m, 4, 2 CH_2C=C), 2.07 (s, 3, CH_3CO), and 1.62 ppm (m, 4).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.13; H, 9.49; N, 10.27.

2-(1-Aminoethylidene)cyclohexanone (5).—This compound was a coproduct with **1**. Two recrystallizations from cyclohexane followed by vacuum sublimation at 108° (0.5 mm) gave pure **5**, mp 112.8–113.5°.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.11; H, 9.54; N, 10.27.

2-(1-Acetylaminoethylidene)cyclohexanone (6).—A suspension of 1.00 g (0.00718 mol) of **5** and 5.0 ml of acetic anhydride was heated to reflux under a dry atmosphere, with formation of a yellow color accompanying solution of starting material. After refluxing for 5 min, the solution was allowed to stand overnight. Alcoholysis of excess anhydride by adding 20 ml of methanol and refluxing the resulting solution for 15 min was followed by removal of solvent to give a light yellow, semicrystalline oil. Chromatography (ether) of the crude material yielded 1.10 g (84.5%) of a viscous, colorless oil which crystallized completely in the refrigerator. Two recrystallizations of the product from hexane in a cold room afforded an analytical sample of **6**, mp 35–36°.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.20; H, 8.56; N, 7.88.

2-(1-Benzoylaminoethylidene)cyclohexanone (7).—A solution of 1.00 g (0.00719 mol) of benzoyl chloride in 15 ml of dry ether was added dropwise under a dry atmosphere to a stirred suspension of 1.00 g (0.0718 mol) of **5** in 25 ml of dry ether and 0.790 g (0.0100 mol) of pyridine. The expected precipitate of pyridine hydrochloride appeared almost immediately. After stirring overnight, the reaction mixture was transferred to a separatory funnel and washed with two 25-ml portions of 5% HCl, one 25-ml portion of 5% $NaHCO_3$, and finally with water. The organic layer was separated, dried (Na_2SO_4), and freed of solvent to yield 1.60 g of light yellow crystals. After chromatography (ether) of the crude product and subsequent recrystallization from hexane, there remained 1.46 g (83.5%) of white, crystalline product. Vacuum sublimation at 64° (0.5 mm) for 4 days yielded pure **7**, mp 66.0–66.5°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 73.79; H, 7.00; N, 5.86.

The syntheses of **2** and **3** essentially paralleled that of **7**, except that larger amounts of reagents were used.

1-Acetyl-2-acetylaminocyclohexene (2).—From 6.00 g (0.0432 mol) of **1** and 3.38 g (0.0432 mol) of acetyl chloride there resulted 5.90 g of light yellow, liquid product. Fractional distillation of this material under reduced pressure gave 4.55 g (58.3%) of **2**, bp 116–118° (0.9 mm). A second distillation afforded an analytical sample of **2**, bp 119–121° (1.2 mm).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.99; H, 8.19; N, 7.49.

1-Acetyl-2-benzoylaminocyclohexene (3).—From 4.00 g (0.0287 mol) of **1** and 3.87 g (0.0276 mol) of benzoyl chloride there was obtained 5.28 g of light yellow, solid product. The crude product was recrystallized from methanol–water; a total of 4.47 g (64.1%) of light yellow **3**, mp 73–76°, was obtained when all crops were combined. Chromatography (benzene) of this material removed most of the color, and subsequent vacuum sublimation at 75° (1.0 mm) for 5 days gave an analytical sample of essentially white **3**, mp 76.5–77.0°.

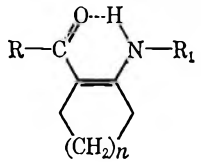
Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 73.77; H, 6.91; N, 5.82.

Ethyl 4-(1-Aminoethylidene)-5-oxohexanoate (21).—The synthetic procedure outlined previously for compounds **1** and **5** was used to prepare **21** from 8.00 g (0.0400 mol) of ethyl 4-acetyl-5-oxohexanoate.[23] Recrystallization of the crude product (4.58 g) from cyclohexane–ethyl acetate yielded 3.43 g (43.2%) of off-white **21**, mp 85–87°. Chromatography (ethyl acetate) of this material followed by one recrystallization from water–ethanol and two from cyclohexane–ethyl acetate produced white platelets. The analytical sample of **21** was then obtained by vacuum sublimation at 83° (0.5 mm): mp 87.0–88.0°; ir

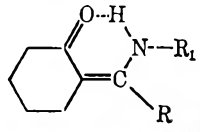
(12) F. C. Pennington and W. D. Kehret, *J. Org. Chem.*, **32**, 2034 (1967).
(13) C. M. Hofmann and S. F. Safir, *ibid.*, **27**, 3565 (1962).
(14) J. C. Powers, *ibid.*, **30**, 2534 (1965).
(15) P. M. Quan and L. D. Quin, *ibid.*, **31**, 2487 (1966).
(16) C. A. Grob, *Helv. Chim. Acta*, **33**, 1787 (1950).
(17) H. P. Schad, *ibid.*, **38**, 1117 (1955).
(18) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
(19) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Teroshima, *J. Org. Chem.*, **33**, 747 (1968).
(20) Melting points and boiling points are uncorrected. Reaction progress and product purity were monitored by thin layer chromatography (Eastman chromogram sheet type K301R silica gel with fluorescent indicator) in the appropriate solvent or solvent pair. All spots on chromatograms were detected by uv light. Preparative chromatography was carried out on columns dry packed with Florisil. Solvents were evaporated under reduced pressure on a rotary evaporator with a bath of suitable temperature. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(21) H. F. Holtzclaw, Jr., J. P. Collman, and R. M. Alire, *J. Amer. Chem. Soc.*, **80**, 1100 (1958).
(22) L. Rugheimer and G. Ritter, *Chem. Ber.*, **45**, 1332 (1912).
(23) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).

TABLE I

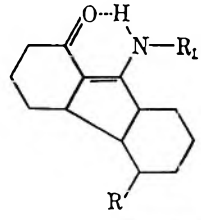
ULTRAVIOLET ABSORPTION DATA FOR ISOCYCLIC AND ACYCLIC *cis-s-cis* COMPOUNDS



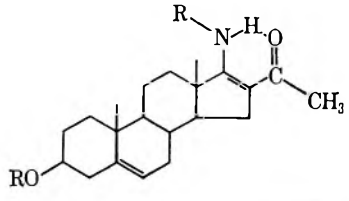
Compd	R	R_1	n	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
1	CH_3	H	2	M	312	317	−5	14,100	
2	CH_3	CH_3CO	2	M	302	303	−1	13,100	
3	CH_3	C_6H_5CO	2	M	318	321	−3	13,300	
						285[c]		7630	
						239		11,000	
4	CH_3O	$CH_3CH_2CH_2$	1	95% A	307	297	10	15,800	*d*



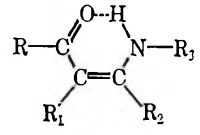
Compd	R	R_1	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
5	CH_3	H	M	317	320	−3	15,700	
6	CH_3	CH_3CO	M	307	313	−6	14,000	
7	CH_3	C_6H_5CO	M	323	331	−8	14,400	
					242		9900	
8	H	$C_6H_5CH_2$	A	315	328	−13	26,200	*e*
9	H	C_6H_5	A		357		15,500	*e*
					295		2080	*e*
					235		5360	*e*



Compd	R	R_1	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
10	O=	H	95% A	322	310	12	11,000	*f*
11	HO	H	95% A	322	320	2	13,200	*f*
12	O=	CH_3CO	95% A	312	301	11	9400	*f*
13	CH_3CO_2	CH_3CO	95% A	312	312	0	10,000	*f*



Compd	R	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
14	H	95% A	317	314	3	16,500	*g*
15	CH_3CO	95% A	307	310	−3	12,600	*g*



Compd	R	R_1	R_2	R_3	Solvent[a]	Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
16	CH_3	H	H	H	A	290	290	0	...	*h*
17	CH_3	H	CH_3	H	M	302	299	3	15,500	
17	CH_3	H	CH_3	H	A		299		...	*h*
17	CH_3	H	CH_3	H	C		286		13,500	
17	CH_3	H	CH_3	H	H		285		6120	*i*
18	CH_3	H	CH_3	CH_3	M	312	309	3	18,100	
18	CH_3	H	CH_3	CH_3	C		302		15,400	
19	CH_3	H	CH_3	$C_6H_5CH_2$	M	312	311	1	21,300	

TABLE I
(*Continued*)

Compd	R	R_1	R_2	R_3	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
19	CH_3	H	CH_3	$C_6H_5CH_2$	C		302		17,300	
20	CH_3	CH_3	CH_3	H	M	312	316	−4	15,000	
21	CH_3	$C_2H_5O_2CCH_2CH_2$	CH_3	H	M	312	313	−1	14,800	
22	C_6H_5	H	H	H	A	323[i]	324	−1	19,000	*k*
							242		11,000	*k*
23	C_6H_5	H	CH_3	H	M	331[l]	329	2	19,400	
							240		8670	
							328		19,700	*m*
							240		8,670	*m*
24	CH_3	H	CH_3	CH_3CO	M	292	293	−1	17,000	
25	CH_3	H	CH_3	$ClCH_2CO$	M	292	292	0	16,300	
25	CH_3	H	CH_3	$ClCH_2CO$	C		290		16,500	
26	CH_3	H	CH_3	C_6H_5CO	M	308	310	−2	15,900	
							286[c]		10,200	
							239		11,000	
27	CH_3	H	CH_3	*p*-ClC_6H_4CO	M	308	311	−3	16,200	
							286[c]		10,100	
							247		15,200	
28	CH_3	CH_3	CH_3	CH_3CO	M	302	303	−1	12,400	
28	CH_3	CH_3	CH_3	CH_3CO	C		307		14,800	
29	CH_3	CH_3	CH_3	C_6H_5CO	M	318	322	−4	13,000	
							285[c]		5190	
							239		10,300	
29	CH_3	CH_3	CH_3	C_6H_5CO	E		322		14,200	
							285[c]		5790	
							238		10,800	
29	CH_3	CH_3	CH_3	C_6H_5CO	C		232		14,000	
							286[c]		5350	
							240		10,200	
30	C_6H_5	H	CH_3	CH_3CO	M	321[l]	318	3	22,200	
							260		6490	
31	C_6H_5	H	CH_3	C_6H_5CO	M	337[l]	332	5	23,200	
							249		12,600	
32	CH_3O	H	H	c-C_6H_{11}	MC	281	281	0	19,000	*n*
33	C_2H_5O	H	CH_3	H	95% A	282	275	7	18,200	*o*
34	C_2H_5O	H	CH_3	$-CH_2-$[p]	M	292	293	−1	32,100	*q*
							280		31,100	*q*
35	C_2H_5O	H	CH_3	$C_6H_5CH_2$	95% A	292	287	5	~23,400	*r*
36	C_2H_5O	H	CH_3	CH_3CO	95% A	272	271	1	18,600	*o*

[a] A = ethanol, C = cyclohexane, E = ether, H = heptane, M = methanol, MC = methylene chloride. [b] Calculated − observed. [c] Shoulder. [d] See ref 12. [e] C. A. Grob and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 725 (1967). [f] E. Wenkert, R. L. Johnson, and L. L. Smith, *J. Org. Chem.*, **32**, 3224 (1967). [g] J. Romo and A. Romo de Vivar, *J. Amer. Chem. Soc.*, **81**, 3446 (1959). [h] P. J. Brignel, U. Eisner, and P. G. Farrell, *J. Chem. Soc., B*, 1083 (1966). [i] N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411, (1949). [j] Based upon a λ_{max} of 248 mμ for the parent compound, phenyl vinyl ketone; see ref 10. [k] See ref 10. [l] Based upon a λ_{max} of 256 mμ for the parent compound, 1-phenyl-2-buten-1-one: G. W. Cannon, A. A. Santilli, and P. Shenian, *J. Amer. Chem. Soc.*, **81**, 1660 (1959). [m] M. M. Robison, W. G. Pierson, L. Dorfman, B. F. Lambert, and R. A. Lucas, *J. Org. Chem.*, **31**, 3206 (1966). [n] See ref 18. [o] See ref 16. [p] Two identical chromophore units are connected by an ethylene bridge. [q] See ref 13. [r] See ref 17.

($CHCl_3$) 3480 (NH), 1715 (ester C=O), 1600 (C=O), and 1570 cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.46; H, 8.80; N, 7.15.

5,5-Dimethyl-3-amino-2-cyclohexen-1-one (45).—This compound was prepared from 5,5-dimethyl-1,3-cyclohexanedione and ammonia according to the procedure of Zymalkowski and Rimek.[24] Yields as high as 90% of pure **45** were obtained, mp 165–166.5° (lit.[24] mp 162–164°).

5,5-Dimethyl-3-methylamino-2-cyclohexen-1-one (46).—Substitution of methylamine for ammonia in the above synthesis resulted in an 88% yield of the colorless **46**. A sample was recrystallized from acetonitrile for spectral purposes, mp 153–154.5 (lit.[25] mp 156°).

3-Acetylamino-2-cyclohexen-1-one (49).—A suspension of 2.50 g (0.0225 mol) of light yellow 3-amino-2-cyclohexen-1-one, mp 120–129° (lit.[24] mp 128–131°), in 15 ml of acetic anhydride and 4 drops of pyridine was heated just to reflux under a dry atmosphere. When the resulting orange solution was allowed to stand at room temperature for 5 hr, 1.47 g of **49**, mp 164–166°, was deposited. Concentration of the mother liquor followed by recrystallization of the solid residue from benzene–methanol afforded an additional 1.00 g of product, mp 162–165°. After the crude product (2.47 g, 71.7%) had been chromatographed (1:2 ethyl acetate–cyclohexane) and then recrystallized from acetonitrile, a sample of **49** was submitted for analysis: mp 166.5–167.5°; nmr ($CDCl_3$) δ 8.7 (broad s, 1, NH), 6.82 (s, 1, CH=C), 2.37 (m, 6), and 2.16 ppm (s, 3, CH_3CO).

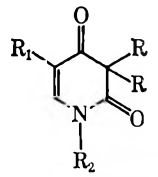
Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.15. Found: C, 63.00; H, 7.23; N, 9.21.

5,5-Dimethyl-3-acetylamino-2-cyclohexen-1-one (50).—A suspension of 12.93 g (0.0928 mol) of **45** in 60 ml of acetic anhydride and 2.0 ml of pyridine was heated slowly until starting material dissolved, and then refluxed under a dry atmosphere for 1 hr. A semicrystalline residue resulted when the reaction solution was concentrated. Use of acetone as a recrystallizing solvent gave 14.18 g (84.3%) of colorless **50**, mp 153–157°, in two crops. Two additional recrystallizations from acetone provided white cubelets of **50**: mp 156.3–157.8°; nmr ($CDCl_3$) δ 9.15 (s, 1, NH),

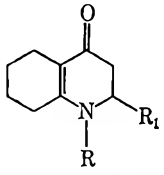
(24) F. Zymalkowski and H. Rimek, *Arch. Pharm.* (Weinheim), **294**, 759 (1961); *Chem. Abstr.*, **57**, 7228*h* (1962).

(25) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, 2209 (1964).

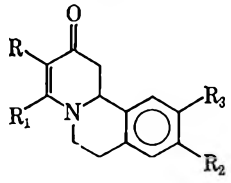
TABLE II
ULTRAVIOLET ABSORPTION DATA FOR HETEROCYCLIC *cis-s-trans* COMPOUNDS



Compd	R	R_1	R_2	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
37	C_2H_5	H	H	M	280	303	+23	8240	
38	C_2H_5	H	CH_3	M	290	313	−23	8190	
38	C_2H_5	H	CH_3	C		303		7700	
39	CH_3	C_2H_5	$(CH_3)_2CH$	M	300	(321)[c]	(−21)[c]		
				C		311		9300	*d*



Compd	R	R_1	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
40	CH_3	H	A	332	336	−4	14,350	*e*
41	$-(CH_2)_4-$		A	332	336	−4	14,000	*e*



Compd	R	R_1	R_2	R_3	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
42	H	CH_3	H	H	95% A	322	319	3	17,200	*f*
43	$-(CH_2)_4-$		H	H	95% A	332	333	−1	14,300	*f*
43	$-(CH_2)_4-$		H	H	A	332	336	−4	12,900	*g*
43	$-(CH_2)_4-$		H	H	C		312		11,200	*g*
44	CH_3	CH_3	CH_3O	CH_3O	95% A	332	335	−3	15,700	*f*

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] Includes solvent shift measured for compound **38**. [d] J. C. Martin, K. C. Brannock, and R. H. Meen, *J. Org. Chem.*, **31**, 2966 (1966). [e] A. I. Meyers, A. H. Reine, J. C. Sicar, K. B. Rao, S. Singh, W. Weidmann, and M. Fitzpatrick, *J. Heterocycl. Chem.*, **5**, 151 (1968). [f] M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1966). [g] See W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sicar, and A. I. Meyers, *ibid.*, **30**, 3667 (1965).

6.88 (s, 1, CH=C), 2.42 (s, 2, CH_2C=C), 2.25 (s, 2, CH_2CO), 2.17 (s, 3, CH_3CO), and 1.10 ppm (s, 6).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.25; N, 8.56; N, 7.96.

5,5-Dimethyl-3-benzoylamino-2-cyclohexen-1-one (51).—A stirred suspension of 4.00 g (0.0287 mol) of **45** in 125 ml of dry[26] 1,2-dimethoxyethane and 2.27 g (0.0287 mol) of pyridine was heated until solution was effected. Heating was discontinued and a solution of 4.03 g (0.0287 mol) of benzoyl chloride in 25 ml of dry[26] 1,2-dimethoxyethane was added dropwise. The addition of the acid chloride was accompanied by the formation of light brown oil droplets. After being stirred overnight at room temperature, the reaction mixture now consisted of a viscous deep red-brown lower layer and a much larger light orange upper layer. Because the lower layer contained no product (tlc)[20] and was essentially water soluble, it was discarded after decantation of the light orange solution. Removal of solvent from the upper layer gave an orange syrup which partially crystallized upon standing. Recrystallization of this material from ethyl acetate gave 1.19 g of yellow crystals, mp 142–146°. A satisfactory second crop could not be obtained; so the mother liquor was diluted with 40 ml of ethyl acetate prior to being washed with 60 ml of 5% HCl. An ethyl acetate (50 ml) extract of the acid wash was combined with the original solution. When the resulting solution was dried (Na_2SO_4) and freed of solvent, 2.14 g of a yellow solid was obtained. This material was reduced to a powder and then triturated with 5% $NaHCO_3$. Recrystallization of the solid residue from acetonitrile gave an additional 0.86 g of yellow **51**, mp 146–148°, in several crops. Total yield of product was 2.05 g (29.4%). Chromatography (ethyl acetate) of the yellow product followed by vacuum sublimation at 145° (1 mm) for 2 days yielded colorless material. An analytical sample of **51** was prepared by recrystallization from ethyl acetate: mp 148.5–149°; nmr ($CDCl_3$) δ 8.98 (s, 1, NH), 7.85 (m, 2), 7.46 (m, 3), 6.92 (s, 1, CH=C), 2.57 (s, 2, CH_2C=C), 2.15 (s, 3, CH_3CO), and 1.06 ppm (s, 6).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.28; H, 7.14; N, 5.92.

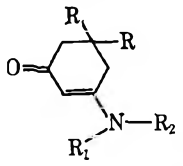
(26) The solvent was distilled directly from lithium aluminum hydride into the reaction vessel and dropping funnel.

Results and Discussion

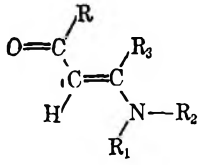
Spectral data, including a comparison of calculated and observed values for λ_{max}, is included in Tables I–IV. Arrangement of the various compounds is governed by the stereochemistry of the conjugated system[11] and location of the nitrogen atom, although later discussion will focus on functionality.

Designation of the absorption bands as $\pi \rightarrow \pi^*$ transitions is supported both by the locations and intensities of the various maxima. The π–p conjugate interaction of the parent α,β-unsaturated carbonyl system with the β nitrogen's unshared electron pair

TABLE III
ULTRAVIOLET ABSORPTION DATA FOR ISOCYCLIC AND ACYCLIC *trans-s-trans* COMPOUNDS



Compd	R	R_1	R_2	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
45	CH_3	H	H	M	292	287	5	28,000	
45	CH_3	H	H	E		270		23,400	
46	CH_3	H	CH_3	M	302	288	14	30,000	
47	CH_3	H	c-C_6H_{11}	A	302	293	9	32,000	c
48	CH_3	CH_3	c-C_6H_{11}	A	312	303	9	32,500	c
49	H	H	CH_3CO	M	282	278	4	19,300	
50	CH_3	H	CH_3CO	M	282	280	2	18,400	
51	CH_3	H	C_6H_5CO	M	298	291	7	21,200	
						233		8140	
51	CH_3	H	C_6H_5CO	E		279		19,500	
						231		9440	



Compd	R	R_1	R_2	R_3	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
52	$CH_3CH_2CH_2$	C_2H_5	C_2H_5	H	A	300	307	−7	28,000	d
53	$CH_3CH_2CH_2$	$-(CH_2)_5-$		H	A	300	308	−8	28,000	e
54	CH_3	$-(CH_2)_4-$		CH_3	A	312	312	0	32,000	c
55	C_6H_5	CH_3	$HOCH_2CH_2$	H	A	333[f]	344	−11	23,300	g
							243		11,300	g
56	C_6H_5	C_2H_5	C_2H_5	H	A	333[f]	343	−10	26,000	d
							243		12,000	d
57	CH_3O	H	c-C_6H_{11}	H	MC	271	270	1	23,400	h
58	CH_3O	$-(CH_2)_4-$		H	A	282	283	−1	30,200	h
							228		1990	h
59	CH_3O	$-(CH_2)_5-$		H	A	282	282	0	32,200	h
59	CH_3O	$-(CH_2)_5-$			E		273		26,500	i
60	CH_3O	$(CH_3)_2CH$	$(CH_3)_2CH$	H	A	282	283	−1	30,200	h
61	C_2H_5O	H	$C_6H_5CH_2$	CH_3	95% A	282	276	6	≈28,800	j
62	C_2H_5O	C_2H_5	C_2H_5	CH_3	A	292	288	4	31,000	d
63	C_2H_5O	H	CH_3CO	CH_3	95% A	262	265	−3	18,600	k

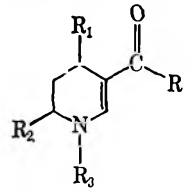
[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965). [d] See ref 10. [e] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946). [f] See footnote *j*, Table I. [g] G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962). [h] See ref 18. [i] E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966). [j] See ref 17. [k] See ref 16.

would be expected[9c,10,27] to produce the bathochromic and hyperchromic effects which are observed. Measurement of solvent effects also provides additional confirmatory evidence, although considerable variation in the relationship between absorption maxima and solvent polarity exists in the present work. A solvent *correction, relative to ethanol or methanol*, of +11 mμ has been proposed[8] for the $\pi \rightarrow \pi^*$ bands of α,β-unsaturated ketones in hexane solution. This compares with extreme values in cyclohexane of +24 mμ for the *cis-s-trans*-vinylogous amide, 1,2,3,4,7,11b-hexahydro-6H-dibenzo[*a,f*]quinolizin-13(12H)-one (**43**),[23] and −4 mμ for the chelated *cis-s-cis* vinylogous imide, 4-acetylamino-3-methyl-3-penten-2-one (**28**). Comments on this apparent discrepancy will be postponed until specific compound categories are examined.

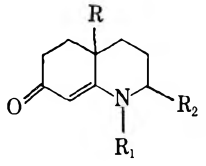
Many of the compounds chosen as examples for the present study exist as stable stereoisomers, owing to partial or complete incorporation of the conjugated system into a cyclic ring. In the case of acyclic representatives, stereochemical classification was based largely on nmr and infrared studies in chloroform and/or less polar solvents.[29] However, solvent-dependent interconversions of *cis* and *trans* isomers[11] have recently been observed for acyclic vinylogous amides [-NHC=CC(O)-][30,31] and vinylogous urethans (-NHC=CCOOR)[16,17,30-33] derived from primary amines. Relative isomer stability in solution would depend upon several factors, including steric effects, intramolecular or intermolecular hydrogen bonding of solute molecules, and solute–solvent interactions. Unless there is sufficient steric resistence to formation of the six-membered chelate ring, the intramolecularly hydrogen-bonded

(27) W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **29**, 385 (1964).
(28) See Table II., footnote *g*.
(29) For details, see the appropriate references for specific compounds.
(30) G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, **85**, 2697 (1963).
(31) C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc., B*, 1217 (1966).
(32) K. Herbig, R. Huisgen, and H. Huber, *Chem. Ber.*, **99**, 2546 (1966).
(33) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

TABLE IV
ULTRAVIOLET ABSORPTION DATA FOR HETEROCYCLIC *trans-s-trans* COMPOUNDS



Compd	R	R_1	R_2	R_3	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
64	CH_3	H	H	H	A	300	301	−1	21,150	*c*
65	$C_2H_5O_2CCH_2CH_2$	H	H	H	95% A	300	302	−2	26,000	*d*
66	CH_3	H	H	CH_3	A	310	315	−5	31,300	*e*
67	CH_3	H	H	$HOCH_2CH_2$	A	310	311	−1	29,000	*e*
68	CH_3	N≡C	H	CH_3	A	310	298	12	30,000	*f*
69	C_6H_5	C_6H_5	H	H	M	333[g]	305	28	24,000	*h*
							227		10,400	*h*
70	CH_3	H	O=	$C_6H_5CH_2$	A	290	294	−4	16,600	*i*
71	C_2H_5O	H	H	H	95% A	282	286	−4	21,000	*d*
72	CH_3O	H	H	CH_3	A	292	295	−3	23,600	*f*
73	NH_2	H	H	H	95% A	282	287	−5	19,500	*d*
74	NH_2	H	H	CH_3	A	292	297	−5	27,600	*e*
75[j]	NH_2	H	H	CH_3CO	M	272	271	1	19,400	



Compd	R	R_1	R_2	Solvent[a]	λ_{max}, mμ Calcd	λ_{max}, mμ Obsd	$\Delta\lambda_{max}$[b]	ε	Ref
76	H	H	H	A	302[k]	298	4	30,800	*l*
77	H	C_2H_5	H	A	312[k]	304	8	31,600	*l*
78	H	H	O=	M	282[k]	278	4	30,200	
79	H	CH_3	O=	M	292[k]	279	13	27,400	
79	H	CH_3	O=	E		272		30,500	
79	H	CH_3	O=	C		271		29,600	
80	C_6H_5	H	O=	M	282[k]	280	2	27,300	
81	C_6H_5	CH_3	O=	M	292[k]	281	11	27,200	

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] M. Freifelder, *J. Org. Chem.*, **29**, 2895 (1964). [d] See ref 15. [e] See ref 19. [f] See ref 14. [g] See footnote *j*, Table I. [h] See R. E. Lyle and D. A. Nelson, *J. Org. Chem.*, **28**, 169 (1963). [i] A. G. Anderson, Jr., and G. Berkelhammer, *J. Amer. Chem. Soc.*, **80**, 992 (1958). [j] This compound was kindly supplied by Professor L. D. Quin of Duke University; see ref 15. [k] No allowance is made for the location of the carbon–carbon double bond. [l] See footnote *e*, Table I.

cis-s-cis structure II is distinctly,[32,33] and in many cases completely,[17,30,34] favored in dilute solution in nonpolar solvents such as C_6H_6 and CCl_4. Increase in solution concentration and/or use of polar solvents, particularly those which form strong hydrogen bonds, should enhance intermolecular bonding and so displace the equilibrium in favor of the extended *trans* isomer III or IV. This conclusion has been amply verified in the literature.[17,30,31,35]

The above statements regarding isomer stability can also be applied to other classes of acyclic compounds in this paper. Strengthening of the intramolecular hydrogen bond *via* N-acylation should enhance the relative stability of the *cis-s-cis* structure II, and our results for chelatable vinylogous imides, –(O)CNHC=CC(O)–, support this prediction. Conversely, acyclic compounds derived from secondary amines (see Table III) can not undergo chelation, and here the *trans* isomer III or IV should be favored, unless opposing steric effects exist.

Assignment of substituent constants to β-amino, β-N-alkylamino, and β-N-acylamino groups of various α,β-unsaturated carbonyl derivatives is a main objective of the present investigation. To facilitate understanding of Tables I–IV by the reader, these values are presented in Table V, along with essential ones from the literature. Their justification will become explicit as particular classes of compounds are now discussed.

Vinylogous Amides.—It is generally agreed that the absorption intensities of the $\pi \rightarrow \pi^*$ transitions of *trans* isomers are greater than those for the *cis* isomers of a conjugated system.[36] Consistent agreement with this guideline exists for fixed *cis* compounds **1**, **10**, **11**, **14**, and **40–44**, and fixed *trans* compounds **45–48**, **64–69**, **76**, and **77**. Molar extinction coefficients (in methanol or ethanol) range in value from 11,000 (**10**) to 17,200 (**42**) for *cis* isomers and from 21,150 (**64**) to 32,500 (**48**)

(34) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961); **84**, 2692 (1962).

(35) For example, Schad[17] found that in CCl_4 at 20° the *trans* isomer (**61**) of ethyl 3-benzylaminocrotonate completely isomerizes to the *cis* form (**35**) within 30 min. In ethanol at 20° an equilibrium ratio of the two isomers (**35** to **61**) of *ca.* 3 is attained in 70 hr. It should be noted that whenever comparisons are possible, *i.e.*, identical concentrations in the same solvent and analogous structures, the chelated *cis-s-cis* form II of a vinylogous amide is more stable relative to the *trans* form than is the case with the corresponding urethan and its weaker intramolecular hydrogen bond.[30,31,34]

(36) Reference 9d, p 20.

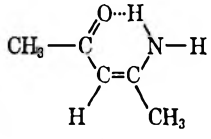
TABLE V
CONSTANTS FOR CALCULATION OF ABSORPTION MAXIMA OF α,β-UNSATURATED CARBONYL DERIVATIVES IN ETHANOL

Parent system[a]	Ketone, 215 mμ	Ester, 197 mμ
α-Alkyl[a]	+10	+10
β-Alkyl[a]	+12	+10
Exocyclic double bond[a]	+5	+5
Endocyclic double bond[a] (five-membered ring)	+5	+5
cis-β-Amino	+75	+75
trans-β-Amino	+65	+65
β-N-Alkyl[b]	+10	+10
β-N-Acetyl[b]	−10	−10
β-N-Benzoyl[b]	+6	...

[a] Literature values from ref 9c, pp 218, 219. [b] To be added to constants for *cis*- or *trans*-β-amino.

for the *trans* forms. Extension of this criterion to acyclic examples provides confirmatory evidence for previous stereochemical assignments resulting from nmr and infrared studies,[29] and also substantiates provisional judgments based upon structural analogy.

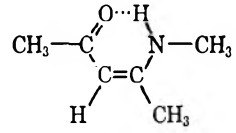
An initial value of the substituent constant for the chelated *cis*-β-amino group (–NH_2) can be derived from the observed λ_{max} of 4-amino-3-penten-2-one (**17**) in methanol solution. Dudek and Holm[34] have deter-



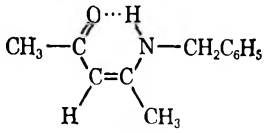
17

mined the nmr spectrum of **17** in deuteriochloroform and were able to detect only the chelated *cis-s-cis*-structure. The relative stability of this form could only increase in very dilute cyclohexane solution. Therefore, the close correlation of the molar extinction coefficients[37] of **17** in methanol (ε 15,500) and cyclohexane (ε 13,500) indicates that no substantial change in stereochemistry has occurred in the polar, strongly hydrogen-bonding solvent methanol.[38] Subtraction of constant values of 215 and 12 mμ for parent enone and β-alkyl, respectively, from the observed λ_{max} of 299 mμ for **17** yields a provisional value of +72 mμ for the chelated *cis*-β-amino group.

Compounds **5**, **20**, and **21** also possess the indicated stereochemistry in view of the close similarity in structure and absorption intensity between them and **17**. Cross conjugation of a phenyl group with the vinylogous amide chromophore, as in 3-amino-1-phenyl-2-propen-1-one (**22**) and 3-amino-1-phenyl-2-buten-1-one (**23**), results in a hyperchromic effect of sufficient magnitude so as to blur the distinction between *cis* and *trans* isomers. Consequently, assignment of a chelated structure to **22** and **23** is not absolute.[39] N-Alkylation, as in the cases of **8** and **19**, is also accompanied by a hyperchromic effect, particularly when the alkyl group is benzyl.[40] However, both **19** and its N-methyl analog



18



19

18 yield nmr data[34] (deuteriochloroform as solvent) consistent only with the chelated form. Even in a solvent as polar as pyridine or acetone, **19** retains its stereochemical integrity.[34] Comparison of the observed λ_{max} values of **17** and **18** in methanol permits a direct calculation of the bathochromic effect of N-alkylation, *i.e.*, +10 mμ.

A final substituent constant of +75 mμ for the chelated *cis*-β-amino group is obtained when calculated λ_{max} values are adjusted to agree within ±5 mμ of the observed values for 12 of the 14 model compounds in Table I. The small differences for **22** and **23** are probably fortuitous in view of the large deviation between calculated and observed λ_{max} values for similar *trans* compounds **55** and **56** (*vide infra*). Significant deviations exist for compounds **8**–**10**. Apparently, the conjugation extends to the aromatic ring in both **8** and **9**. An explanation for the low band position observed for **10** is not readily apparent, since **10** is structurally quite similar to the "normal" compound **11**.

Application of substituent constants calculated for chelated *cis* vinylogous amides to *cis-s-trans* compounds **40**–**44** (Table II) is quite successful. Evidently, the absence of intramolecular hydrogen bonding in these compounds does not result in the expected hypsochromic shift,[41] and the nomenclature in Table V reflects this observation.

As noted earlier in this section, molar extinction coefficients are relatively large for *trans* vinylogous amides, and an ϵ_{max} of 30,000 or more is not unusual for the examples shown in Tables III and IV. For many of these compounds stereochemical mobility, particularly *s-cis* ⇄ *s-trans*, cannot be arbitrarily excluded. In most of the cases, however, β hydrogen is *cis* to the carbonyl group and the stable conformations of compounds **52**, **53**, and **64**–**67** are presumably *s-trans*, the arrangement generally favored with α,β-unsaturated ketones.[42] The steric properties of the β-methyl group[42] in **54** and of the 1-phenyl group[43] in **55** and **56** would result in an *s-cis* conformation for these molecules if chromophore planarity is retained. Substitution at the 4 position of the ring in **68** and **69** produces a hypsochromic effect, which can be examined more fruitfully as substituent constants are now discussed.

The relatively close agreement between calculated and observed values for *cis* vinylogous amides unfortunately does not extend to the λ_{max} values of the *trans* isomers. An increment of +10 mμ is retained for a β-N-alkyl substituent, although its apparent batho-

(37) Although the position of λ_{max} for $\pi \rightarrow \pi^*$ transitions is usually affected by solvent polarity, it is not accompanied by a marked change in absorption intensity.[9c]

(38) If significant isomerization of *cis*-**17** to the *trans* form had taken place in methanol solution, one should observe an ϵ_{max} much closer to the measured value of 28,000 for 5,5-dimethyl-3-amino-2-cyclohexen-1-one (**45**), a cyclic *trans-s-trans* compound which duplicates the skeletal features of **17**. A more subtle change in stereochemistry to the nonchelated *cis-s-trans* conformer owing to substantial solvation of carbonyl and amino groups by methanol would result in an increase in nonbonded interactions, as exemplified in studies of 1-acetylcyclohexene and 2-methyl-1-acetylcyclohexene: R. L. Erskine and F. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(39) Two isomers were isolated in the synthesis of **22**, and the spectral values in Table I represent a compromise.[10]

(40) This may be due to homoconjugation of the aromatic ring with the vinylogous amide chromophore: E. Santos, J. Padilla, and P. Crabbé, *Can. J. Chem.*, **45**, 2275 (1967).

(41) L. K. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1963, p 528.

(42) Reference 9c, p 421.

(43) S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967).

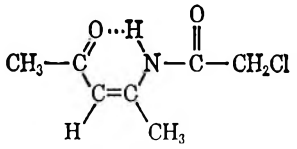
chromic effect varies from +1 (**46** *vs.* **45**) to +14 mμ (**66** *vs.* **64**). Assignment of a substituent constant of +65 mμ to *trans*-β-amino appears to give a reasonable correspondence both in the frequency and absolute magnitudes of positive and negative deviations from the calculated λ_{max} values.

Inspection of Tables III and IV indicates that values of $\Delta\lambda_{max}$ are acceptable for those *trans* vinylogous amides where steric hindrance to conjugation is minimal, *i.e.*, for compounds **45**, **64**–**67**, and **76**. In contrast, $\Delta\lambda_{max}$ for N,N-dialkyl compounds **48** and **52**–**56** varies from +9 (**48**) to −11 mμ (**55**). Qualitative examination of their molecular models does indicate that an increase in nonbonded interactions between an N-alkyl group and the *cis* α hydrogen accompanies rehybridization of the nitrogen atom from sp^3 to sp^2. However, the anticipated hypochromic effect owing to loss of chromophore planarity does not materialize. Because of the large variation observed in $\Delta\lambda_{max}$, extreme caution must be exercised when assignment of a *trans* configuration to a vinylogous amide is based solely upon the location of the absorption band. The comparatively low-wavelength absorptions of both 3-acetyl-4-cyano-1-methyl-1,4,5,6-tetrahydropyridine (**68**)[14] and 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (**69**)[44] are in accord with the studies of Hofmann, Kosower, and Wallenfels[45] concerning the "methyl effect" in the uv spectra of the 1,4-dihydropyridines.

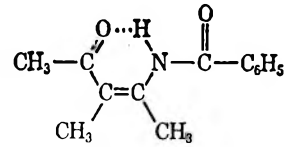
The existence of a pronounced solvent effect for nonchelated *cis* and *trans* vinylogous amides has been noted in the literature,[28] and the large shift of −17 mμ relative to methanol in λ_{max} for the *trans-s-trans* compound **45** in ether[46] is as expected. In contrast, the chelated *cis-s-cis* vinylogous amides **17**–**19** in cyclohexane show "normal"[8] shifts of −13, −7, and −9 mμ, respectively, again relative to methanol. Evidently, chelation provides important stabilization of the excited state in a nonpolar solvent.

Given the magnitude of substituent constants for the *cis*-β-amino and *trans*-β-amino groups, it would appear that the vinylogous amide chromophore can be successfully detected by the uv spectroscopy relative to alternative arrangements of the nitrogen atom and the two multiple bonds. Assignment of stereochemistry can then be made on the basis of the molar extinction coefficients in alcohol solution, if conjugation involving an aromatic ring is absent. For vinylogous amides lacking the benzoyl group and/or an N-benzyl substituent, values of ϵ_{max} range from 11,000 (**10**) to 18,100 (**18**) for *cis* and from 21,150 (**64**) to 32,500 (**48**) for *trans* isomers. Use of substituent constants to confirm these results would be possible for *cis* compounds, and, with care, for *trans* compounds as well.

Vinylogous Imides.—Previous arguments regarding the stereochemical integrity of vinylogous amides are also applicable in the present context. In the case of acyclic vinylogous imides the spectral consequences of solvent variation are of considerable importance. No significant dependence of either λ_{max} or ϵ_{max} upon solvent polarity was observed for three model compounds, 4-chloroacetylamino-3-penten-2-one (**25**), 4-acetylamino-3-methyl-3-penten-2-one (**28**), and 4-benzoylamino-3-methyl-3-penten-2-one (**29**). Evidently, the chelated



25



29

cis isomer enjoys unique stability in solution owing to strong intramolecular hydrogen bonding.[47] The absence of a solvent-induced shift in band position indicates that chelation also provides substantial stabilization of ground and excited states in a polar (methanol) as well as a nonpolar (cyclohexane) solvent.

The introduction of an electron-withdrawing acyl group at the nitrogen atom of a vinylogous amide should give a compound absorbing at shorter wavelength and with reduced intensity. However, no consistent pattern emerges when reduced intensity. However, no consistent pattern emerges when one examines the molar extinction coefficients of model vinylogous imides in Tables I–IV. A small hypochromic effect accompanies N-acylation in most cases, and *trans* isomers generally show higher absorption intensities than *cis* ones.

Comparison of observed λ_{max} values demonstrates that N-acetylation of a vinylogous amide results in a hypsochromic shift in band position. Numerical values for this effect range from −4 (**15** *vs.* **14**) to −14 mμ (**2** *vs.* **1**). If previously calculated substituent constants for β-amino (*cis* or *trans*) and β-N-alkyl are retained and a substituent increment of −10 mμ is assigned to β-N-acetyl, then $\Delta\lambda_{max}$ for 11 model N-acetyl compounds exceeds ±4 mμ in only two examples, chelated *cis-s-cis* compounds **6** and **12**. However, comparison on an individual basis of **6** with **5** and of **12** with **10** yields constants of −7 and −9 mμ respectively, for β-N-acetyl.

Additional support is provided by spectral data for heterocyclic *trans-s-trans* vinylogous imides **70** and **78**–**81**. Each of these compounds can be envisioned as resulting from the replacement of a methylene group ($-CH_2-$) in the vinylogous amide by a carbonyl group (C=O). Based upon substituent constants of +10 mμ for β-N-alkyl and −10 mμ for β-N-acetyl, a hypsochromic shift of −20 mμ should manifest itself in the observed λ_{max}. Experimentally, the results are as follows: **69** *vs.* **66**, −21; **78** *vs.* **76**, −20; **79** *vs.* **77**, −25; **80** *vs.* **76**, −18; **81** *vs.* **77**, −23 mμ. Calculated values of λ_{max} for the N-methyl compounds **79** and **81** are quite high, and presumably are due to steric interaction of the methyl group with the α vinylic hydrogen, a phenomenon discussed earlier for related *trans* vinylogous amides.

Three heterocyclic *cis-s-cis* vinylogous imides, **37**–**39**, were investigated, and the data contrast strongly with the results presented above. There appears to be a normal spectral response to alkyl substitution and solvent polarity. Explanation of the observed band intensities and positions requires additional information, and these compounds must be regarded as exceptional for the time being.

A moderate bathochromic shift in the observed λ_{max}, ranging from +3 (**31** *vs.* **23**) to +11 mμ (**26** *vs.* **17**),

(44) See Table IV, footnote *h*.

(45) D. Hofmann, E. Kosower, and K. Wallenfels, *J. Amer. Chem. Soc.*, **83**, 3314 (1961).

(46) Compound **45** and related ones are essentially insoluble in cyclohexane.

(47) This conclusion is supported by nmr data.[1]

accompanies N-benzoylation and indicates that the aromatic ring is not completely insulated from the original vinylogous amide chromophore. The final substituent constant of +6 mμ for β-N-benzoyl is obtained in the manner outlined previously for β-N-acetyl.

Use of substituent increments to distinguish between *cis* or *trans* vinylogous imides appears quite feasible. For 15 out of the 18 *cis* compounds studied, $\Delta\lambda_{max} \leqq 0$ mμ. Only one exception, compound **12**, remains if the two examples with 1-phenyl substituents (**30** and **31**) are excluded. The relative insensitivity of the band position of a chelated *cis-s-cis* compound to solvent polarity further characterizes this isomer. A total of eight *trans-s-trans* compounds were examined, and the calculated λ_{max} exceeds the observed value for all compounds except 1-benzyl-5-acetyl-3,4-dihydro-2-pyridone (**70**). The (theoretical) assignment of a *cis* configuration to **70** would yield a $\Delta\lambda_{max}$ of +6 mμ, clearly an unacceptable value. Comparison of the molar absorptivity of a new vinylogous imide with those of structural analogs in Tables I–IV would likely provide additional proof of configuration.

Vinylogous Urethans.—Although our primary goal was the investigation of vinylogous amides and imides, we were naturally interested in applying the results to other related systems. The preparation of a number of β-amino α,β-unsaturated esters (vinylogous urethans), together with uv data, was recently reported by Huisgen, Herbig, Siegl, and Huber,[18] and the stereochemistry of these compounds was firmly established through nmr and infrared measurements. Inclusion of several isolated examples from the literature provided a total of five *cis* and eight *trans* model compounds.

It appears that stereochemical assignments can be given to vinylogous urethans on the same basis previously advanced for the corresponding amides. Omitting N-benzyl compounds **35** and **61**, molar extinction coefficients vary from 15,800 (**4**) to 19,000 (**32**) for *cis-s-cis* structures and from 21,000 (**71**) to 32,500 (**59**) for *trans* compounds in polar solvents. An ϵ_{max} of 32,100 for diethyl 3,3′-(ethyldiimino)dicrotonate (**34**) reflects the presence of two identical vinylogous urethan chromophore units in the same molecule.

Apparently, the newly obtained substituent constants for β-amino and β-N-alkyl can effectively supplement intensity measurements for *trans* vinylogous urethans.[48] Only in the case of ethyl 3-benzylaminocrotonate (**61**) does $\Delta\lambda_{max}$ for *trans* isomer exceed the limits of ±4 mμ. Similar calculations for the *cis-s-cis* compounds **4** and **32–35**, found in Table I, show no correspondingly ueful trend.

Grob[16] reinvestigated the acetylation of ethyl 3-aminocrotonate and isolated both geometric isomers (**36** and **63**) of ethyl 3-acetylaminocrotonate, an N-acyl vinylogous urethan. Although their ϵ_{max} values are identical, band positions are as expected for **36** and **63**.

Vinylogous Ureas.—A parent value for the $\pi \rightarrow \pi^*$ band position of an α,β-unsaturated amide apparently has not been reported in the literature. The λ_{max} values calculated for 1,4,5,6-tetrahydronicotinamide (**73**)[14] and its N-methyl and N-acetyl derivatives **74**[19] and **75**,[14] respectively, are based upon a constant of 197 mμ for the related α,β-unsaturated ester chromophore. Before the apparent consistency in $\Delta\lambda_{max}$ found here can be confirmed, additional spectral data for other vinylogous ureas (and parent α,β-unsaturated amides) is obviously needed.

Registry No.—**1**, 23645-69-4; **2**, 23645-70-7; **3**, 23674-49-9; **4**, 10472-19-2; **5**, 23652-78-0; **6**, 23652-79-1; **7**, 23652-80-4; **8**, 23652-81-5; **9**, 23652-82-6; **10**, 13369-48-7; **11**, 13369-51-2; **12**, 13369-50-1; **13**, 13369-52-3; **14**, 5297-31-4; **15**, 5088-57-3; **16**, 2802-09-7; **17**, 23652-84-8; **18**, 23652-85-9; **19**, 23652-86-0; **20**, 23652-87-1; **21**, 23652-88-2; **22**, 23652-89-3; **23**, 23652-90-6; **24**, 23652-91-7; **25**, 23754-49-6; **26**, 23112-27-8; **27**, 23112-29-0; **28**, 23652-94-0; **29**, 23652-95-1; **30**, 23652-96-2; **31**, 23652-52-0; **32**, 7542-81-6; **33**, 626-34-6; **34**, 23652-55-3; **35**, 21759-74-0; **36**, 23652-56-4; **37**, 77-04-3; **38**, 1130-18-3; **39**, 13382-19-9; **40**, 1127-58-8; **41**, 14099-74-2; **42**, 5114-60-3; **43**, 4155-70-8; **44**, 5114-65-8; **45**, 873-95-0; **46**, 701-58-6; **47**, 1500-76-1; **48**, 23645-82-1; **49**, 23674-56-8; **50**, 23645-83-2; **51**, 23674-57-9; **52**, 23652-57-5; **53**, 23652-58-6; **54**, 23652-59-7; **55**, 23652-60-0; **56**, 23674-58-0; **57**, 7542-80-5; **58**, 7542-90-7; **59**, 7542-91-8; **60**, 5229-31-2; **61**, 21731-13-5; **62**, 21731-16-8; **63**, 23652-67-7; **64**, 7032-12-4; **65**, 7032-09-9; **66**, 14996-96-4; **67**, 14996-94-2; **68**, 3284-34-2; **69**, 3335-03-3; **70**, 23645-88-7; **71**, 3335-05-5; **72**, 3284-32-0; **73**, 7032-11-3; **74**, 14996-98-6; **75**, 7032-13-5; **76**, 1971-15-9; **77**, 16236-60-5; **78**, 1128-75-2; **79**, 1130-77-4; **80**, 1216-47-3; **81**, 1149-82-2.

(48) Bowden, Braude, and Jones[10] have proposed a substituent increment of +81 mμ for a β-dialkylamino group (–NR_2). Only one model compound of unknown configuration, ethyl 3-diethylaminocrotonate (**62**), was involved. Our assignment of a *trans* structure to **62** is based upon analogy to later work[18] and its relatively large molar absorptivity.

Photochemical Reactions of N-Alkylanilines[1]

YOSHIRO OGATA AND KATSUHIKO TAKAGI

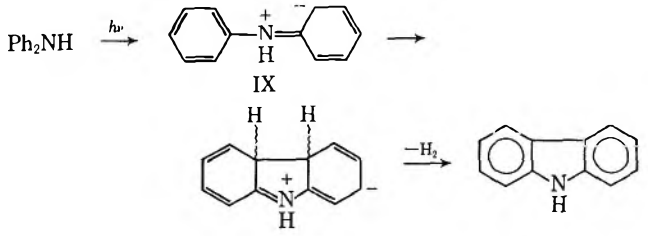
Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

Received June 19, 1969

Ultraviolet irradiation of N-phenylbenzylamine (Ia) and N-α-phenethylaniline (Ib) in various solvents gave *ortho*- and *para*-alkylated anilines in yields of 5.5–42.5% together with aniline and coupling products of alkyl radicals (V). The *ortho*/*para* ratio is 2–8, and it rises to *ca.* 20 in the presence of radical scavenger, hydroquinone. No rearrangement of *ortho* to *para* occurs. The irradiation of a mixture of N-phenylbenzylamine (Ia) and N-(*o*-tolyl)-α-phenethylamine (Id) gave no cross-bred products at N and *ortho* positions. With optically active N-α-phenethylaniline (VI), appreciable optical activity was retained in recovered VI and in both *ortho* (VII) and *para* isomers (VIII). On the other hand, addition of hydroquinone to the reaction system results in a *ca.* twofold increase of the optical activity of VIII. The reaction mechanism is discussed on the basis of these data.

Thermal rearrangement of N-monoalkylaniline hydrochlorides in a sealed tube to give ring-alkylated anilines has long been known as the Hofmann–Martius rearrangement,[2,3] while the photochemical secondary processes of aromatic amines have little been investigated, and no report is thus far available on the photorearrangement of N-alkylanilines.

N,N-Dimethylaniline itself is quite stable under ultraviolet (uv) light.[4] The N,N-dimethylaniline hydrochloride can be photolyzed,[4] but the rearrangement to ring-alkylated aniline has not been observed. Diphenylamines have been reported to be photolyzed to carbazoles through an intramolecular charge-separated species (IX) followed by the ring formation at *ortho* positions.[5]

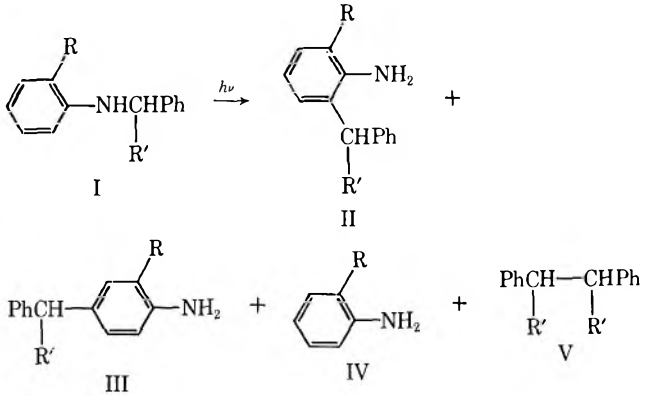


The present paper describes a novel rearrangement of N-monoalkylanilines involving an alkyl–N bond fission to ring-alkylated anilines by uv irradiation, *i.e.*, photochemical Hofmann–Martius rearrangement of N-phenylbenzylamine (Ia) and N-α-phenethylaniline (Ib).

Results and Discussion

The Photolysis of N-Alkylaniline.—The uv irradiation of 0.1 *M* solution of 1:1 isopropyl alcohol–*t*-butyl alcohol containing N-phenylbenzylamine (Ia) under nitrogen atmosphere by a high press Hg lamp (Halos, 300 W) for 20 hr gave *o*- (IIa) and *p*-aminodiphenylmethanes (IIIa) in yields of 28.9 and 13.6%, respectively, together with decomposition products, aniline (5.8%) and bibenzyl (3.0%). The quantum yield of disappearance of Ia was *ca.* 0.48. This photorearrangement occurs also in other solvents, *e.g.*, benzene and *t*-butyl alcohol (Table I).

In a similar manner, irradiation of N-α-phenethylaniline (Ib) also gave *o*-α-phenethylaniline (IIb, 26.1%) and *p*-α-phenethylaniline (IIIb, 8.1%), aniline (IV, 8.4%), and 2,3-diphenylbutane (Vb, 1.9%). The rearranged products (IIa and IIIa) isolated by means of chromatography on a 15 × 300 mm column, slurry packed with 100 mesh silica gel (Mallinckrodt) in benzene, were identified with corresponding authentic samples by means of glpc, melting point, and ir and uv spectra. Further, all of these products were estimated by glpc. The *para* isomer is not formed by the rearrangement of the *ortho* isomer as confirmed in our hands, and hence the *ortho*/*para* ratio was approximately constant in a range of 2.4–3.7 during irradiation time of 6–20 hr.



In the photolysis of Ia and Ib, the main product is their *ortho* isomer, *i.e.*, the *ortho*/*para* ratio is *ca.* 2–3, indicating that these reactions may go through an intramolecular pathway.

Photolysis of a mixture Ia and Id gave Ia, IIa, IIIa, Id, IId, and IIId as products, but no cross-bred product such as Ib, Ic, or IIc was detected. N cross-bred products (Ib and Ic) and an *ortho* cross-bred product (IIc) were not formed at all. Their identity was established by comparison of their retention times by glpc of the photo cross-bred products with those of authentic samples and/or photolysates of Ib, Ic, and Id. IIb,

(1) Contribution No. 135.

(2) (a) A. W. Hofmann and C. A. Martius, *Ber.*, **4**, 742 (1871); A. W. Hofmann, *ibid.*, **5**, 704 (1872); **7**, 526 (1874). (b) H. Hart and J. R. Kosak, *J. Org. Chem.*, **27**, 116 (1962). (c) Y. Ogata, H. Tabuchi, and K. Yoshida, *Tetrahedron*, **20**, 2717 (1964).

(3) W. J. Hickinbottom, *J. Chem. Soc.*, 404, 1119 (1937).

(4) C. Pac and H. Sakurai, *Tetrahedron Lett.*, 1865 (1968); *Kogyo Kagaku Zasshi*, **72**, 230 (1969).

(5) (a) K.-H. Grellmann, G. M. Sherman, and H. Linshitz, *J. Amer. Chem. Soc.*, **85**, 1881 (1963); (b) H. Linshitz and K.-H. Grellmann, *ibid.*, **86**, 303 (1964).

TABLE I

YIELDS[a] OF PHOTOPRODUCTS FROM N-PHENYLBENZYLAMINE (Ia) AND N-α-PHENETHYLANILINE (Ib)

Reactant[b]	Solvent	Additive	% Conversion	% *ortho* product II	% *para* product III	% Aniline (IV)	% Dialkyl V	*ortho*/*para*
Ia	Mixed solvent[c]		55.4	28.9	13.6	5.8	3.0	2.1
	t-Butyl alcohol		54.2	11.6	1.5	6.9	0.9	7.7
	Benzene		53.8	4.8	0.7	4.8	1.3	7.3
	Mixed solvent[c]	Oxygen	47.0	10.6	1.6	5.1	0.4	6.5[d]
	t-Butyl alcohol	Oxygen	59.2	11.0	1.2	12.8		7.3[e]
	t-Butyl alcohol	Naphthalene	52.2	11.5	1.6	1.6		8.6
	Mixed solvent[c]	Hydroquinone	74.5	18.9	0.9	9.8	0.1	20.7
Ib	Mixed solvent[c]		57.2	26.0	8.1	8.4	1.9	3.2

[a] Yields based on the consumed substrates. [b] Irradiation for 20 hr with a 300-W high press Hg lamp. [c] Isopropyl alcohol–*t*-butyl alcohol 1:1 (v/v). [d] Benzylideneaniline (1.1%) was formed as a by-product. [e] Benzylideneaniline, 6.0%.

TABLE II

YIELDS[a] OF PHOTOPRODUCTS FROM OPTICALLY ACTIVE N-α-PHENETHYLANILINE (VI)

Reactant	Solvent	Additive	% Conversion	% *ortho* product VII	% *para* product VIII	*ortho*/*para*
VI	Mixed solvent[b]		71.4	27.1	19.0	1.4
	Mixed solvent[b]		63.6	24.5	13.6	1.8
	Mixed solvent[b]	Hydroquinone	81.7	20.6	12.9	1.6

[a] Based on isolated products by means of column chromatography. [b] Isopropyl alcohol–*t*-butyl alcohol 1:1 (v/v).

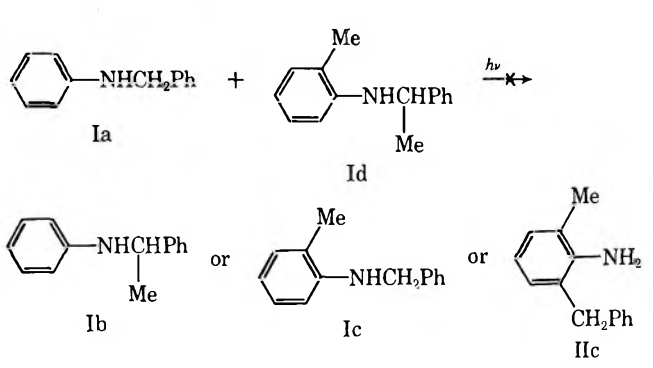
TABLE III

PHOTOREARRANGEMENT OF OPTICALLY ACTIVE N-α-PHENETHYLANILINE (VI)

Additive	Rotation[a] of recovered VI, degree	Rotation[a] of rearranged products, degree: *ortho* product VII	Rotation[a] of rearranged products, degree: *para* product VIII
	−18.4 ± 0.6[b]	+4.7 + 0.5[c]	−3.7 ± 0.6[d]
	−22.3 ± 2.1[e]	+3.9 = 1.5[f]	−0.9 ± 1.8[g]
Hydroquinone	−19.8 ± 1.0[h]	+1.6 ± 0.6[i]	−0.6 ± 1.3[j]

[a] The values of $[\alpha]^{25}D$ were measured in ethyl alcohol. The figures following ± mean mechanical errors caused by ORD recorder. [b] *c* 1.74, *l* 0.2. [c] *c* 1.18, *l* 0.2. [d] *c* 0.80, *l* 0.2. [e] *c* 2.42, *l* 0.1. [f] *c* 1.02, *l* 0.1. [g] *c* 0.57, *l* 0.1. [h] *c* 1.01, *l* 0.1. [i] *c* 1.01, *l* 0.5. [j] *c* 0.63, *l* 0.5.

IIIb, and IIIc were not detectable by glpc on account of the overlap of glpc peaks of IIb to Ia, IIIb to IIIa, and IIIc to IIId.



The photolysis of Ia in the presence of equimolar hydroquinone gave *ca.* 20 times as much *ortho* isomer as *para* isomer, which is probably caused by trapping the intermediary alkyl radical and hence the suppression of *para*-isomer formation. This indicates that the *para* isomer may be formed by two processes, *i.e.*, intra- and intermolecular processes, and the *para* isomer is more favorably produced by the latter process than the *ortho* isomer.

The Photolysis of Optically Active N-α-Phenethylaniline (VI).—Optically active N-α-phenethylaniline (VI) (*l* form) was separated from Ib (*dl* form) as a salt of camphor-β-sulfonic acid. The salt, after being recrystallized from benzene, contains *ca.* 80% optically pure *l* form, $[\alpha]^{25}D$ + 83.9° ± 1.0° (10% solution in absolute ethyl alcohol) {lit.[6] $[\alpha]^{20}D$ + 104° 68′ (10% solution in absolute ethyl alcohol)}. Optically active N-α-phenethylaniline (VI, *l* form), $[\alpha]^{25}D$ −26.1° ± 0.9° (2.1% solution in absolute ethyl alcohol), was obtained by its treatment with aqueous barium hydroxide. A solution of 1:1 isopropyl alcohol/*t*-butyl alcohol containing 0.66 g of VI was irradiated for 30 hr. The reaction mixture, after condensation *in vacuo*, was separated by chromatography on silica gel, where benzene–3% acetone eluted the following products in the following order: 242.1 mg of the recovered N-α-phenethylaniline (VI), 102.4 mg (24.5%) of *o*-α-phenethylaniline (VII), 56.8 mg (13.6%) of *p*-α-phenethylaniline (VIII), and aniline (IV) (Table II). Each fraction was identified by uv, ir, and glpc. Optical rotations of the photoproducts in ethyl alcohol follow: VI, $[\alpha]^{25}D$ −22.3° ± 2.1°; VII, +3.9° ± 1.5°; VIII, −0.9° ± 1.8° (Table III).

These facts show that recovered N-α-phenethylaniline (VI) and both the *ortho*-rearranged product VII and the *para* isomer VIII retain some optical activity. In conclusion, the photorearrangement of VI to VII and VIII is, partially at least, intramolecular. Hart, *et al.*,[2b] have reported that the thermal rearrangement of optically active VI with hydrochloric acid or zinc chloride gave essentially racemic VII (13%) and VIII (75%). Furthermore, the intermolecularity of the rearrangement was proposed in view of the predominant

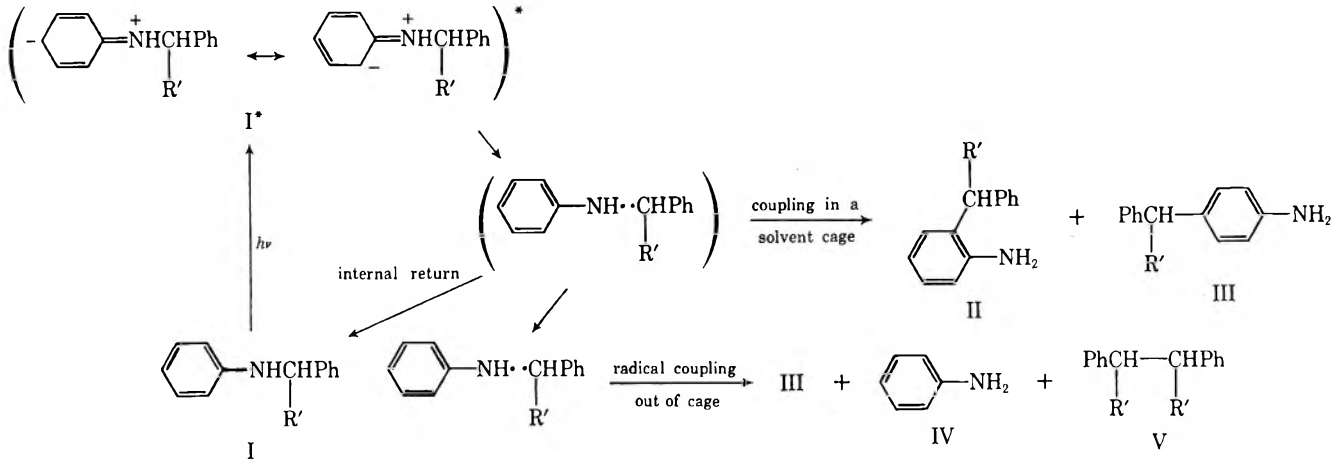
(6) R. Descamps, *Bull. Soc. Chim. Belg.*, **33**, 269 (1924); *Chem. Abstr.*, **18**, 2879 (1924).

para rearrangement (*ortho/para* ratio of 1:2–1:6), which is in contrast to the ratio of *ca.* 2 in this photorearrangement. On the contrary, thermal rearrangement of optically active α-phenethyl phenyl ether gives *o*- and *p*-α-phenethylphenols (in an *ortho/para* ratio of 85:15), both of which are also optically active.[7]

Irradiation of optically active VI in the presence of a radical scavenger, hydroquinone, gave optically active *ortho*- and *para*-rearranged products; *i.e.*, similarly, column chromatography of the reaction mixture gave 100.5 mg of recovered N-α-phenethylaniline (VI), $[\alpha]^{25}D$ −19.8° ± 1.0°, 101.0 mg of *ortho* isomer, $[\alpha]^{25}D$ +1.6° ± 0.6°, and 63.0 mg of *para* isomer, $[\alpha]^{25}D$ −6.0° ± 1.3°.

As shown in Table III, the *para*-rearranged product retained some optical activity, more than that in the reaction without hydroquinone, whereas recovered N-α-phenethylaniline was always optically pure, when compared with the original N-α-phenethylaniline (VI), within experimental error; this is in accordance with the absence of N cross-bred products. *o*-α-Phenethylaniline was a little less optically pure in the presence of hydroquinone than without it, probably because of contamination of some other materials. Essentially, both of N-α-phenethylaniline and the *ortho* isomer may be unaffected by the presence of hydroquinone.

These results suggest the following reaction scheme for the photorearrangement.



Generally, N-alkylanilines absorb uv light at 243–248 mμ (ε ~12,000) and 291–296 (~2000); the former is attributable to the transition of $^1B_{1u} \leftarrow {}^1A_{1g}$ (probably the transition to intramolecular charge-separated species) and the latter to $^1B_{2u} \leftarrow {}^1A_{1g}$. On irradiation of *ca.* 250-mμ light, N-alkylanilines (I) are subject to cleavage into anilino and alkyl radicals *via* the above intramolecular charge-separated species (I*), whose N–alkyl bond is liable to scission on account of a decrease of electron density at the nitrogen position. The radicals then couple with the anilino radical at the position with high density of odd electron to form I, II, and III.

Shizuka[8] studied the secondary processes of the photochemical rearrangement of *para*-substituted acetanilides to *o*-acetylaniline, and estimated the very high recombination quantum yields (*ca.* 0.9 in cyclohexane) of anilino and acetyl radicals. This effect is attributable to a solvent cage effect. It is conceivable that photorearrangement of I occurs mostly in a solvent cage and only partially out of the cage, because a solvent (isopropyl alcohol–*t*-butyl alcohol) more viscous than cyclohexane is used in our reaction. Furthermore, the liberated anilino radical, which causes hydrogen bonding with surrounding hydroxy compounds, migrates out of the solvent cage with difficulty; the subsequent internal return of the two radicals gives the starting material without loss of stereochemical configuration. In addition, it is less probable that the alkyl radical has a chance to couple with another alkyl radical out of the solvent cage.

The hydroxylic solvents seem to favor the rearrangement (Table I). This solvent effect is not due to the viscosity effect, since there is no correlation of the yields with solvent viscosities. Therefore, the pronounced solvent effect on the yield of *ortho* and *para* isomers may be explained as follows. (i) Solvent hydrogen bonded to the nitrogen atom of N-alkylaniline may accelerate the C–N bond scission and the effect of hydroxylic solvent on quinoid form, formed in the subsequent step, also facilitate the rearrangement. This speculation is not inconsistent with the observed orientation of other photochemical rearrangements. It has been reported that the formation of *ortho* and *para* isomers in photochemical Fries rearrangement of aryl esters is more favorable in polar solvents than in nonpolar.[9] Similar solvent effect has been observed in the photochemical rearrangements of aryl ethers[10] and benzyl methyl ketone.[11] (ii) The hydrogen atom donating ability of the solvent is also important. This effect may be interpreted tentatively in terms of hydrogen abstraction of the resulting alkyl radical. The migrating alkyl radical should interact more with hydrogen-donating solvents as the radical is more apart from the anilino radical; hence the ratio of *ortho/para* decreases with increasing hydrogen-donating ability of the solvent.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were obtained by the method of liquid film on a Perkin-Elmer grating infrared spectrophotometer, Model 337, ultraviolet spectra on a Shimazu auto ultraviolet spectrophotometer, Model SV-50A, and optical rotation on a Jasco optical

(7) H. Hart and H. S. Eleuterio, *J. Amer. Chem. Soc.*, **76**, 519 (1954).
(8) H. Shizuka, *Bull. Chem. Soc. Jap.*, **42**, 57 (1969).
(9) R. A. Finnegan and D. Knutson, *Tetrahedron Lett.*, 3429 (1968).
(10) Y. Ogata, K. Takagi, and I. Ishino, *Tetrahedron*, in press.
(11) Y. Ogata, K. Takagi, and Y. Izawa, *Tetrahedron*, **24**, 1617 (1968).

rotatory dispersion spectrophotometer, Model ORD/UV-5. Quantitative analysis of photolysates was done by a Yanagimoto gas chromatography with a flame ionization detector, Model GCG-550F, employing a 1.7 m × 2.5 m column packed with PEG 20M (2.5 wt %) on Chamelite CS of 80–100 mesh using N_2 as a carrier gas at 160 to 250°.

Materials.—N-Phenylbenzylamine (Ia) was prepared by heating (at 90–95°) aniline with benzyl chloride in aqueous sodium bicarbonate: bp 158–163° (5 mm) [lit.[12] bp 178–180° (12 mm)]; mp 36.5–37° (lit.[12] mp 36°); λ_{max}^{MeOH} 247 mμ (log ε 4.08) and 296 (3.25); ν_{max} (Nujol) 3410 (–NH), 1320 (C–N), and 1270 cm^{-1} (C–N). Other N-alkylanilines (Ib, Ic, and Id) were prepared similarly: N-α-phenethylaniline (Ib), bp 129° (3 mm) [lit.[2a] bp 132–134° (1 mm)], λ_{max}^{MeOH} 247 mμ (log ε 4.10) and 296 (3.23), from aniline and α-chloroethylbenzene; N-(*o*-tolyl)benzylamine (Ic), bp 138–145° (4 mm), mp 59.0–60.3°, λ_{max}^{MeOH} 244.5 mμ (log ε 4.09) and 293 (3.33), from *o*-toluidine and benzyl chloride; and N-(*o*-tolyl)-α-phenethylamine (Id), bp 137–139° (4 mm), λ_{max}^{MeOH} 243.5 mμ (log ε 4.11) and 291 (3.37), from *o*-toluidine and α-chloroethylbenzene. *o*-Aminodiphenylmethane (IIa) was prepared by reduction of *o*-nitrodiphenylmethane obtained from the Friedel–Crafts reaction of *o*-nitrobenzyl chloride with benzene: bp 153–155° (2 mm) [lit.[13] 172–173° (12 mm)], λ_{max}^{MeOH} 234 mμ (log ε 3.87) and 288 (3.29). *p*-Aminodiphenylmethane (IIIa) was prepared by tin reduction of *p*-nitrodiphenylmethane: bp 142–144° (1 mm), mp 33–4.5° (lit.[3] mp 34–35°), λ_{max}^{MeOH} 240 mμ (log ε 4.03) and 292 (2.93). *o*- and *p*-α-phenethylanilines (IIb and IIIb) were prepared by the rearrangement of *N*-α-phenethylaniline hydrochloride.[2] The mixture of *o*- and *p*-α-phenethylanilines, bp 135–136° (5 mm), was chromatographed on a 15 × 300 mm column packed with 100 mesh silica gel in benzene to separate *o*- and *p*-α-phenethylanilines (IIb and IIIb). The former on recrystallization from benzene, gave white crystalls (IIb): mp 57.5–58.5° (lit.[2a] mp 58.5–59°); λ_{max}^{MeOH} 234 mμ (log ε 3.87) and 288 (3.29); ν_{max} 3440, 3350 (–NH_2) and 750 cm^{-1} (4 H). The latter was eluted as an oil (IIIb): λ_{max}^{MeOH} 240 mμ (log ε 4.12) and 289 (3.12); ν_{max} 3430, 3340, 3200 (–NH_2), and 830 cm^{-1} (2 H). Bibenzyl (Va), mp 51.3–51.8° (lit.[14] mp 51–52°), was prepared by the Friedel–Crafts reaction of benzene with 1,2-dichloroethane,[14] and 2,3-diphenylbutane (Vb), mp 123–124° (lit.[15] mp 125–126°), by the Grignard reaction of α-bromoethylbenzene.[15]

Optically Active N-α-Phenethylaniline (VI).—Freshly distilled *dl*-N-α-phenethylaniline (14 g, 0.07 mol) was heated at 80° with camphor-β-sulfonic acid (15 g, 0.1 mol) to give a dark solution, from which the salt of *l*-amine was precipitated. The precipitate, on recrystallization, yielded 8.5 g of the salt of *l*-amine, $[\alpha]^{25}D$ +83.9° ± 1.0° (*c* 1.00 g/10 cc, ethyl alcohol, *l* 0.1 dm) {lit.[6] $[\alpha]^{20}D$ +104° 68′ (10% ethyl alcohol solution)}, which, on treatment with excess barium hydroxide, gave free amine (3.5 g) which after recrystallization showed mp 47.5–48.1° (lit. mp 49.2° for *l*-form,[6] mp 26.4° for *dl* form[2a]), $[\alpha]^{25}D$ −26.1° ± 0.9° (*c* 0.215 g/10 cc, ethyl alcohol, *l* 0.1 dm).

General Procedure.—All experiments were carried out in a cylindrical quartz vessel (20 × 150 mm) under a nitrogen atmosphere, except for preparative experiments. A Halos high press 300-W Hg lamp with a water-cooling quartz jacket was used as a light source.

A solution (0.1 *M*) of *ca.* 0.6 g of N-alkylaniline (I) in 1:1 isopropyl alcohol–*t*-butyl alcohol (30 ml) were placed in the quartz vessel, which together with the lamp was immersed in running water at 15–25° for 20 hr. A reaction mixture was evaporated under reduced pressure either to determine the yield by means of glpc or to isolate products.

A Typical Procedure for the Photolysis of N-Phenylbenzylamine (Ia).—A solution of isopropyl alcohol-*t*-butyl alcohol (300 ml) containing Ia (3.83 g) was irradiated under nitrogen gas for 30 hr. The concentrated reaction mixture was chromatographed on a 15 × 300 mm column, slurry packed in benzene–3% acetone with 100 mesh silica gel (Mallinckrodt), using benzene–3% acetone as a eluent. Fractions 2–6 (each 5 ml), were Ia: λ_{max}^{MeOH} 248 and 295 mμ. Fractions 10–12 were IIa: λ_{max}^{MeOH} 234 and 285 mμ; ν_{max} 3430, 3370 (–NH_2), 1630, 1280 (C–N), and 750 cm^{-1} (4 H). Fractions were IIIa: λ_{max}^{MeOH} 240 and 288 mμ; ν_{max} 3430, 3360 (–NH_2), 1630, 1280 (C–N), and 830 cm^{-1} (2 H).

Effect of Oxygen or Hydroquinone on Photolysates of N-Phenylbenzylamine (Ia).—A *t*-butyl alcohol solution (30 ml) containing 0.601 g of Ia was irradiated under an oxygen atmosphere. The reaction product contained benzylideneaniline (6.0%), IIa, IIIa, IV, and Va. A mixture of 0.624 g (3.41 mmol) of Ia and 0.331 g (3.04 mmol) of hydroquinone in 1:1 isopropyl alcohol–*t*-butyl alcohol was irradiated for 20 hr. Gas chromatography of the products shows that conversion of Ia was 74.3% and the yields of IIa, IIIa, IV, and Va were 18.9, 0.9, 9.8, and 0.1%, respectively.

Photolysis of N-α-Phenethylaniline (Ib).—The irradiation of Ib (0.661 g) in 1:1 isopropyl alcohol–*t*-butyl alcohol for 20 hr yielded IIb (26.0%), IIIb (8.1%), IV (9.8%), and Vb (1.9%).

Photolysis of a Mixture of N-Phenylbenzylamine (Ia) and N-(*o*-Tolyl)-α-phenethylamine (Id).—A mixture of Ia (0.308 g, 1.68 mmol) and Id (0.350 g, 1.66 mmol) in 1:1 isopropyl alcohol–*t*-butyl alcohol was irradiated for 20 hr. The reaction mixture was condensed by evaporation and analyzed by glpc. The products were identified by comparison of their retention times with corresponding authentic samples (Ib, Ic, IIa, IIb, IIIa, and IIIb) and photolysates of Ic and Id (IIc, IId, IIIc, and IIId). In all possible cross-bred products, Ib, Ic, and IIc were not observed.

Photolysis of Optically Active N-α-Phenethylaniline (VI).—The photolysis was carried out with a solution of optically active N-α-phenethylaniline (VI, 0.600 g, 3.04 mmol) in 30 ml of 1:1 isopropyl alcohol–*t*-butyl alcohol for 30 hr. After removal of the solvent *in vacuo*, the residual oil was fractionated by chromatography with a 15 × 300 mm column, packed with 100 mesh silica (Mallinckrodt) in benzene; 500-g fractions were collected. Fractions 1–2 were crude Vb (26.9 mg). Fractions 4–12 were N-α-phenethylaniline (VI, 242.1 mg): λ_{max}^{MeOH} 247 mμ (log ε 4.09) and 296 (3.29); ν_{max} 3420 (–NH), 1315, and 1250 cm^{-1} (C–N). Fractions 18–36 were *o*-α-phenethylaniline (VII, 102.4 mg, 24.5%): mp 57.1–57.5° (lit.[2a] mp 58.5–9.0°); λ_{max}^{MeOH} 234 mμ (log ε 3.96) and 287 (3.40); ν_{max} 3450, 3360 (–NH_2), and 745 cm^{-1} (4 H). Fractions 41–61 were *p*-α-phenethylaniline (VIII, 56.8 mg, 13.6 %): λ_{max}^{MeOH} 240 mμ (log ε 4.64) and 289 (3.31); ν_{max} 3450, 3350 (–NH_2) and 825 cm^{-1} (2 H). Fractions 73–78 were oil (40 mg), containing aniline. The purity of products was checked by glpc.

Optical rotatory densities of these isolated products (VI, VII, and VIII) were measured in ethyl alcohol: for N-α-phenethylaniline (VI), $[\alpha]^{25}D$ −22.3° ± 2.1° (*c* 0.242 g/10 cc, *l* 0.1 dm); for *o*-α-phenethylaniline (VII), $[\alpha]^{25}D$ +3.9° ± 1.5° (*c* 0.102 g/10 cc, *l* 0.1 dm); for *p*-α-phenethylaniline (VIII), $[\alpha]^{25}D$ −0.9° ± 1.8° (*c* 0.057 g/10 cc, *l* 0.1 dm).

Photolysis of Optically Active N-α-Phenethylaniline (VI) in the Presence of Hydroquinone.—The photolysis was carried out with a mixture of 0.600 g (3.04 mmol) of optically active N-α-phenethylaniline (VI) and 0.29 g (2.61 mmol) of hydroquinone in 30 ml of 1:1 isopropyl alcohol–*t*-butyl alcohol at room temperature for 30 hr. After similar work-up, the reaction mixture was chromatographed on a 15 × 300 mm column, packed with 100 mesh silica gel (Mallinckrodt) in benzene; 400-g fractions were collected. Fractions 6–12 were recovered N-α-phenethylaniline (VI, 100.5 mg): λ_{max}^{MeOH} 247 mμ (log ε 4.07) and 2.96 (3.29); ν_{max} 3450 (–NH) and 1320 cm^{-1} (C–N). Fractions 20–37 were *o*-α-phenethylaniline (VII, 101.0 mg): λ_{max}^{MeOH} 234 mμ (log ε 3.95) and 287 (3.36); ν_{max} 3460, 3360 (–NH_2), and 745 cm^{-1} (4 H). Fractions 41–61 were *p*-α-phenethylaniline (VIII, 63.05 mg): λ_{max}^{MeOH} 240 mμ (log ε 4.45) and 289 (3.31); ν_{max} 3440, 3360 (–NH_2), and 825 cm^{-1} (2 H).

Optical rotatory densities were measured in ethanol: N-α-phenethylaniline (VI), $[\alpha]^{25}D$ −19.8° ± 1.0° (*c* 0.101 g/10 cc, *l* 0.1 dm); *o*-α-phenethylaniline (VII), $[\alpha]^{25}D$ +1.6° ± 0.6° (*c* 0.101 g/10 cc, *l* 0.5 dm); *p*-α-phenethylaniline (VIII), $[\alpha]^{25}D$ −6.0° ± 1.3° (*c* 0.063 g/10 cc, *l* 0.5 dm).

Registry No.—Ia, 103-32-2; Ib, 23652-68-8; VI, 21232-37-1.

Acknowledgment.—The authors wish to thank Professor K. Yamazaki for his aid in the measurement of optical rotatory densities and Mitsubishi Chemical Industries Co. for their gift of materials.

(12) F. G. Willson and T. S. Wheeler, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1956, p 102.

(13) P. Carré, *Compt. Rend.*, **148**, 102 (1909); *Chem. Abstr.*, **3**, 1162 (1909).

(14) S. Yura, K. Sato, T. Koizumi, and R. Oda, *Kogyo Kagaku Zasshi*, **44**, 722 (1941).

(15) J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **50**, 551 (1928).

Stereochemistry of Selenium Dioxide Oxidation of Cyclohexenyl Systems[1]

EDWARD N. TRACHTENBERG AND JANE RUMFORD CARVER[2]

Department of Chemistry, Clark University, Worcester, Massachusetts 01610

Received September 4, 1969

The allylic oxidation of a series of alkylated cyclohexenes by selenium dioxide in wet dioxane at high olefin to selenium dioxide ratios has been found to proceed stereoselectively. The conversions of 1,4-dimethylcyclohexene into 2,5-dimethylcyclohex-2-en-1-ol and of *cis*-3,5-dimethylcyclohexene into 1,5-dimethylcyclohex-2-en-1-ol both favor the axial alcohol by 70–75%, whereas the conversion of limonene into carveol and *trans*-Δ^2-octalin into *trans*-Δ^2-octalol-1 show slightly lower steric preference for the axial product. The oxidation of 3,3,5-trimethylcyclohexene to 4,4,6-trimethylcyclohex-2-en-1-ol shows the highest stereospecificity with the axial alcohol favored by over 90%. By contrast, oxidation of *cis*-3,5-dimethylcyclohexene to *cis*-4,6-dimethylcyclohex-2-en-1-ol and of 3-methylcyclohexene to 4-methylcyclohex-2-en-1-ol shows very little stereoselectivity and, indeed, in the latter case slightly favors equatorial product. It has also been found from studies of limonene, 3-methylcyclohexene, and *cis*-3,5-dimethylcyclohexene that attack at tertiary allylic sites may be preferred over that at methylene, in contrast to previous literature reports. These results bear on the mechanism of selenium dioxide oxidation of olefins.

Although most of the synthetically useful applications of selenium dioxide oxidation of organic compounds lead to the introduction of carbonyl groups or other unsaturation[3] and, therefore, do not ordinarily introduce new asymmetric centers, the oxidation of olefins to allylic alcohols, or their derivatives, may involve the creation of a new asymmetric center. The stereochemistry of this process has received inadequate attention although there are a few interesting results in the literature. Thus, Fieser has shown that methyl Δ^3-cholenate gives approximately equal yields of the methyl 3α- and 3β-Δ^4-cholenates along with some of the expected methyl $\Delta^{3,5}$-choladienate.[4] By contrast, he also found that Δ^7-cholestanyl acetate gives only the 7α-acetoxy-Δ^{8-14}-cholestanyl acetate.[5] In both of these cases, the products are allylically rearranged. Sakuda also observed some stereoselectivity in the oxidation of a number of monoterpenes. The tertiary carbinols found among the products of selenium dioxide oxidation of dihydrocarveol,[6] isopulegol,[7] and β-terpineol[8] all are formed stereoselectively. However, in each case the product has that stereochemistry which permits the molecule to assume the most stable conformation. Because the products are tertiary allylic alcohols capable of ready ionization and stereochemical equilibration, the result is of limited significance.

The first indication that the reaction proceeds stereoselectively is to be found in the work of Zacharewicz on 3-*p*-menthene.[9] Unfortunately, he did not elucidate the stereochemistry of the 3-*p*-menthen-5-ol which he obtained and characterized as a phthalate. Later workers, however, obtained the same material by other methods and demonstrated that it has *trans* stereochemistry.[10] More recently, Suga has shown that the oxidation of 3-*p*-menthene with selenium dioxide in acetic acid–acetic anhydride gives a mixture of the *trans*-3-*p*-menthen-5-ol and its acetate along with a lesser yield of 3-*p*-menthen-5-one,[11] and Wiberg in a similar oxidation of 1-*p*-menthene obtained *trans*- and *cis*-carvotanacetol acetate in a 3:2 ratio.[12] Schaefer has reported that selenium dioxide oxidation of a mixture of 3- and 4-methylcyclohexene gives a complex mixture of ketones, alcohols, and *n*-butyl ethers.[13] Reduction of the ethers revealed that the 2-, 3-, and 4-methylcyclohexyl *n*-butyl ethers are formed stereoselectively with the *cis*-2, *trans*-3, and *cis*-4 products predominating by about 4:1. Finally, oxidation of the sesquiterpene, β-cyclodihydrocostunolide, has been shown to yield the 3α-hydroxy product.[14]

The stereochemical results involving the formation of secondary carbinols are more significant than those of Sakuda resulting in the formation of tertiary alcohols for two reasons. First, the former products in many cases are the presumably less stable pseudoaxial allylic alcohols, although it should be recognized that the pattern of greater stability for equatorial over axial groups, so well established in cyclohexane chemistry,[15] cannot blindly be extended to cyclohexene systems.[16] Second, there is more likelihood that the former products represent the stereochemistry of the reaction rather than just reflect the result of some post-reaction equilibration process. However, the few cases studied involve a variety of conditions with respect to both solvent and temperature, and, in one case, study of a mixture rather than of a pure olefin.

We wish here to report on the systematic study of the selenium dioxide oxidation of a variety of alkylated cyclohexene systems in refluxing wet dioxane at high (4:1 or 8:1) olefin/oxidant ratios. Under these conditions, one obtains mostly allylic alcohols although

(1) Supported by Grant 489-A from the Petroleum Research Fund of the American Chemical Society.

(2) Extracted in part from the Ph.D. dissertation submitted by J. R. C. to Clark University in 1969.

(3) (a) E. N. Trachtenberg in "Oxidation," Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969, pp 119–187; (b) N. Rabjohn, *Org. React.*, **5**, 331 (1949); (c) G. R. Waitkins and C. W. Clark, *Chem. Rev.*, **36**, 235 (1945).

(4) C. H. Issidorides, M. Fieser, and L. F. Fieser, *J. Amer. Chem. Soc.*, **82**, 2002 (1960).

(5) L. F. Fieser and G. Ourisson, *ibid.*, **75**, 4404 (1953).

(6) Y. Sakuda, *Bull. Chem. Soc. Jap.*, **34**, 514 (1961).

(7) Y. Sakuda, *J. Sci. Hiroshima Univ., Ser. A-11*, **25**, 207 (1961).

(8) Y. Sakuda, *Nippon Kagaku Zasshi*, **82**, 117 (1961); *Chem. Abstr.*, **56**, 8752c (1962).

(9) W. Zacharewicz, *Rocz. Chem.*, **22**, 68 (1948); *Chem. Abstr.*, **43**, 2976b, (1949).

(10) (a) J. P. Bain and R. L. Webb, U. S. Patent 3,014,080 (1961); *Chem. Abstr.*, **56**, 10198 (1962); (b) A. K. Macbeth, B. Milligan, and J. S. Shannon, *J. Chem. Soc.*, 2574 (1953); (c) W. Treibs, G. Lucius, H. Kegler, and H. Breslauer, *Ann.*, **581**, 59 (1953); (d) G. Ohloff and G. Uhde, *Helv. Chim. Acta*, **48**, 10 (1965).

(11) T. Suga, M. Sugimoto, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **36**, 1363 (1963).

(12) K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

(13) J. P. Schaefer, B. Horvath, and H. P. Klein, *ibid.*, **33**, 2647 (1968).

(14) S. P. Pathak and G. H. Kulkarni, *Chem. Ind.* (London), 1566 (1968).

(15) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1967, pp 36–127.

(16) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

α,β-unsaturated carbonyl compounds are also produced in some cases. We were concerned mostly with the stereochemistry of the process, but our studies also produced new evidence on the order of preference for attack at secondary and tertiary allylic positions. Guillemonat, in a classic study of selenium dioxide oxidation of olefins, established the rule that methylene is attacked more readily than methine in systems in which the two positions are equivalent with respect to other rules regarding site of attack.[17] However, this work antedated modern techniques of gas chromatographic separation, and his conclusion is questionable.

The compounds chosen for study were 1,4-dimethylcyclohexene (**1**), limonene (**2**), 3-methylcyclohexene (**3**), *cis*-3,5-dimethylcyclohexene (**4**), 3,3,5-trimethylcyclohexene (**5**), and *trans*-Δ^2-octalin (**6**). Compound **1** was readily prepared by the acid-catalyzed dehydration of commercially available 2,5-dimethylcyclohexanol. Compound **2** is commercially available. Compound **3** could be obtained by purification of commercially available material and **4** more tediously by the acid-catalyzed dehydration of a commercial mixture of *trans,trans*-3,5-dimethylcyclohexanol and *cis,cis*-3,5-dimethylcyclohexanol. Some double-bond migration occurs during the dehydration, but the resultant products which contain a trisubstituted double bond can be selectively removed by oxidation with selenium dioxide. It has long been known that trisubstituted double bonds are more readily oxidized than disubstituted ones.[17,18] Compound **5** was made by the acid-catalyzed dehydration of commercially available 3,3,5-trimethylcyclohexanol, and compound **6** was prepared by a three-step synthesis reported by Johnson starting with butadiene and *p*-benzoquinone.[19]

Initial separation of the products of the selenium dioxide oxidation of these olefins was effected by vacuum fractionation to yield a highly volatile fraction consisting of unreacted olefin, dioxane, and water, a less volatile fraction consisting of allylic alcohols, α,β-unsaturated carbonyl compounds (and, in the case of relatively involatile substrates, unreacted olefin), and a residue consisting of organoselenium compounds and metallic selenium. The relative yields of oxidation products were determined by glpc analysis of both the crude and fractionated products; the values agreed within experimental error indicating lack of isomerization during distillation.

Identification of the oxidation products was achieved by a combination of elemental analysis, infrared (ir) and nuclear magnetic resonance (nmr) spectroscopy, and chemical conversion into known compounds or into newly synthesized reference compounds of assured structure and stereochemistry. Particular use was made of the fact that, in an epimeric pair of 2-cyclohexenols, a dilute solution in carbon tetrachloride of the compound with a pseudoequatorial hydroxyl shows more intense ir absorption at the intermolecularly hydrogen-bonded O–H stretching frequency around 3350 cm^{-1}. Identification of this stretching mode is possible not only from its frequency but also from its concentration dependence. It should be noted that, whereas cyclohexanols with frozen conformation can be clearly identified as axial or equatorial on the basis of their respective C–O stretch at 996–1036 and 1037–1044 cm^{-1},[20] the spectra of cyclohexanols capable of chair–chair interconversion are frequently more complex in that bands may either be shifted or else new bands may appear.[21] Even then, the equatorial alcohols usually show C–O stretch at higher frequencies than their epimers. However, this generalization does not hold up in the case of 2-cyclohexenols such as those of most concern in the present study.[22]

The fact that the nmr signal for axial protons in cyclohexanes is found at higher field than that for the corresponding equatorial hydrogen[23] is not found to be generally true for the pseudoaxial and pseudoequatorial protons of 2-cyclohexenols. The chemical-shift difference is smaller and inversions in order are found. A much more reliable method for assigning configuration of epimeric carbinol (H–C–OH) protons depends on differences in their coupling behavior, the identification of the signal due to the proton in question being easily made because of the downfield shift caused by the hydroxyl. Because of its more favorable geometry, a pseudoequatorial allylic proton is more strongly coupled to an adjacent vinyl proton, the increased complexity of the signal due to the latter being clearly evident in a comparison of the spectra of two epimeric 2-cyclohexenols. On the other hand, a pseudoaxial allylic proton, because of its more favorable geometry, is much more strongly coupled to an axial homoallylic proton, leading to a broader and more complex pattern for both. Although the signal for the homoallylic protons is usually obscured by the presence of other proton absorptions in the same region, the increased complexity of the pseudoaxial allylic proton signal is clearly defined. It is interesting to note that the center of the vinylic proton multiplet in a 2-cyclohexenol bearing a pseudoaxial hydroxyl is consistently at lower field than that of its epimer. This may be due to greater ionicity of the pseudoaxial carbinol and concomitantly greater deshielding of the vinylic proton in that case.

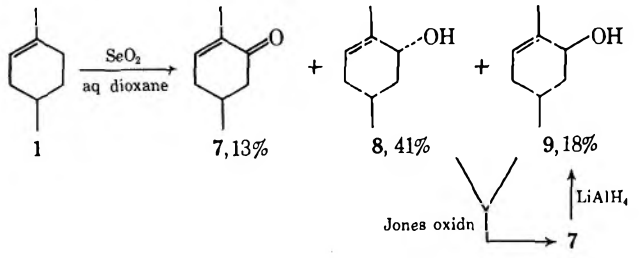
In addition to these spectroscopic methods, great use was made of the fact that lithium aluminum hydride reduction of cyclohexanones is stereoselective and gives an overwhelming preponderance of equatorial alcohol. There are some exceptions to this as in the case of 3,3,5-trimethylcyclohexanone which yields slightly more of the *trans*- than of the *cis*-3,3,5-trimethylcyclohexanol.[24] Nevertheless, the generalization that most cyclohexanones and 2-cyclohexenones give the thermodynamically more stable equatorial product on reduction with lithium aluminum hydride is usually valid[25] and has proved useful in this study in establishing the configuration of the 2-cyclohexenols and their catalytic reduction products.

(17) A. Guillemonat, *Ann. Chim.* (Paris), **11**, 143 (1939).
(18) R. K. Callow and O. Rosenheim, *J. Chem. Soc.*, 387 (1933).
(19) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Drager, and W. N. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961).
(20) A. R. H. Cole, R. N. Jones, and K. Dobriner, *ibid.*, **74**, 5571 (1952).
(21) W. Hückel and Y. Riad, *Ann.*, **637**, 33 (1960).
(22) B. M. Mitzner, V. J. Mancini, S. Lemberg, and E. T. Theimer, *Appl. Spectrosc.*, **22**, 34 (1968).
(23) E. L. Eliel, M. H. Gianni, and Th. H. Williams, *Tetrahedron Lett.*, 741 (1962).
(24) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).
(25) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

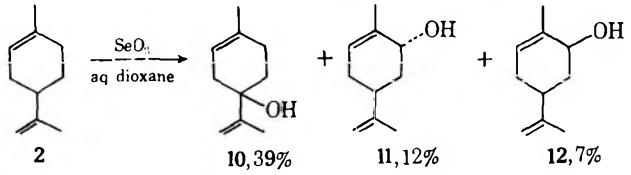
Results and Conclusions

The results of the selenium dioxide oxidation of compounds **1**–**6** are shown in Schemes I–VI, respectively. The yields given are based on olefin consumed. Also included in each scheme are those chemical conversions which were performed to establish the structure and stereochemistry of the products. In each case, this involved conversion either into compounds of already proven structure or into compounds whose structures could be deduced from their method of synthesis and their ir and nmr spectra. In some cases, minor products formed in the selenium dioxide oxidation in yields of less than 1% were not characterized and are, therefore, not included in Schemes I–VI. They are, however, included in the Experimental Section.

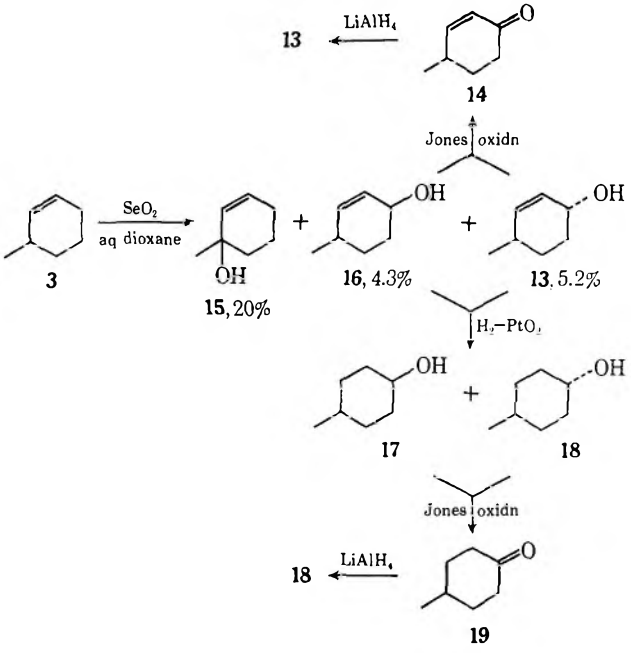
SCHEME I



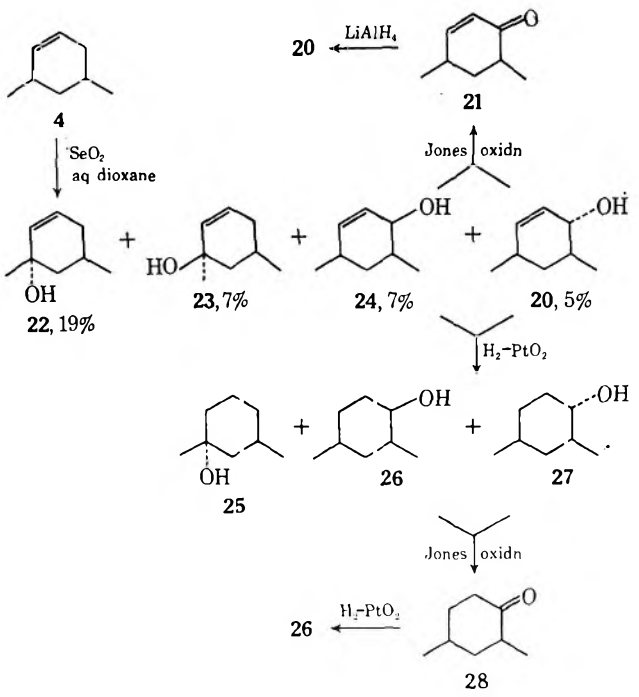
SCHEME II



SCHEME III



SCHEME IV

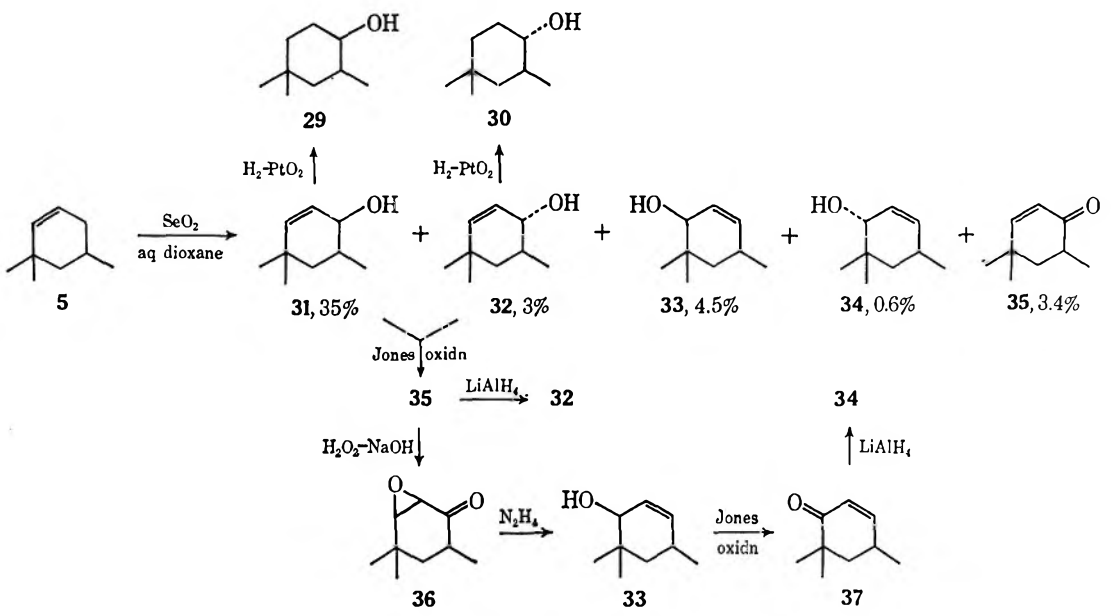


The first interesting result is that the reactivity sequence[17] for attack by selenium dioxide of $CH_2 > CH_3 > CH$ is not generally valid. Thus, in the case of both **3** and **4**, where there is a choice between endocyclic secondary and tertiary positions, attack at the latter is preferred by about twofold. Even more striking are the results with limonene (**2**). Here there are two double bonds susceptible to attack. It is well established that trisubstituted double bonds are more readily attacked than are disubstituted double bonds with the oxidation occurring at an allylic site on the disubstituted side;[17] yet here oxidation occurs by a threefold preference at the tertiary site allylic to the disubstituted double bond. The oxidation which occurs at the other double bond follows the rules established by Guillemonat[17] in that the endocyclic secondary position is preferred over the exocyclic primary carbon. Further study might indeed confirm that the order of preference should be $CH > CH_2 > CH_3$ and that the previously established order is incorrect. Thus, we have observed that tertiary allylic carbinols occurring in a mixture with secondary allylic alcohols are selectively converted into involatile products by further treatment with selenium dioxide. Since all of the work which led to establishment of the earlier sequence involved lower olefin/selenium dioxide ratios and since it antedated glpc so that separation of products had to be effected by distillation, it is easy to see why such an error could have been made. For mechanistic reasons,[26] the newly proposed reactivity sequence is more understandable. It should be noted that, although α-cyclodihydrocostunolide has also recently been shown to form a tertiary carbinol instead of a primary carbinol,[27] this result would have been predicted anyway on grounds that endocyclic positions are favored over exocyclic in cyclohexenyl systems.[17] More significant is the recent observation of Büchi that carvone (**43**) gives almost eight times as much **45** and **46** as **44** indicating a strong preference for attack at

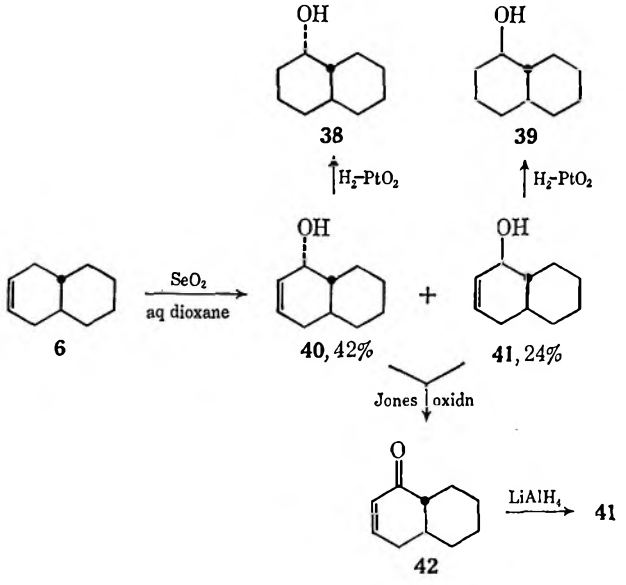
(26) E. N. Trachtenberg, C. H. Nelson, and J. R. Carver, *J. Org. Chem.*, **35**, 1653 (1970).

(27) S. P. Pathak and G. H. Kulkarni, *Chem. Ind.* (London), 913 (1968).

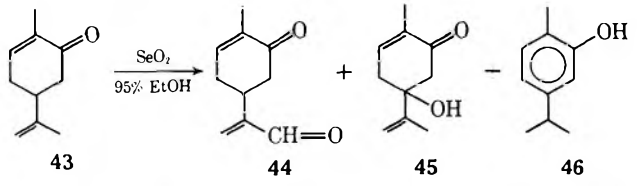
SCHEME V



SCHEME VI



CH > CH_3.[28] Our results further indicate that the preference for attack at CH also exceeds that for reaction at CH_2.



The second interesting observation, that the reaction shows stereospecificity, is clearly seen in Schemes I–VI. Although the pseudoaxial product is generally formed preferentially, this is not true in the case of **3**. This latter result differs from Schaefer's claim that a mixture of the 3- and 4-methylcyclohexenes gives 80% axial *n*-butyl ethers on oxidation with selenium dioxide in butanol followed by catalytic reduction.[13]

(28) G. Büchi and H. Wüest, *J. Org. Chem.* **34**, 857 (1969).

It should be emphasized that the stereospecificity observed in these oxidations is a function of the reaction and is not merely due to some post-reaction equilibration. This follows most clearly from our results with D-(+)-1-*p*-menthene which gives optically active *cis*- and *trans*-carvotanacetols.[26] Since the only reasonable pathway for epimerizing these alcohols under the reaction conditions involves ionization to an allylic cation followed by recombination and since such ionization produces a delocalized cation having a plane of symmetry **47**, it follows that equilibration would necessarily also lead to complete racemization.

A mechanism which accounts for these stereochemical results, including the highly enhanced stereospecificity in the case of **5**, is presented in the accompanying paper.[26]

Experimental Section

Infrared spectra were obtained on thin liquid films with a Perkin-Elmer Infracord. Those in dilute solution (5 mg/100 μl of carbon tetrachloride) were obtained on a Perkin-Elmer Model 337 grating spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian HA-60 or a Jeolco JNM C-60H on samples dissolved in carbon tetrachloride or deuteriochloroform containing tetramethylsilane (TMS) as internal standard. Optical rotations were determined on benzene solutions (unless otherwise noted) with a Rudolph Model 80 CSPI photoelectric polarimeter, and refractive indices were measured on a Bausch and Lomb Abbe 3L refractometer. Melting points were determined in soft glass capillaries on a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by the Alfred Bernhardt Microanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany, or by M–H–W Laboratories, Garden City, Mich.

Gas chromatographic analyses and separations were performed on a Wilkens–Varian Model A-700 Autoprep packed with the Wilkens–Varian materials specified below and equipped with a thermal conductivity detector with helium gas as carrier. Peak areas were determined by cutting out the peaks and weighing them or, in the case of sharp symmetrical peaks, by measuring peak height. Calibration curves for each compound in dioxane solution were prepared to determine the proportionality between peak area and concentration in the concentration range encountered in these experiments. One preparative column was used: column A, $^3/_8$ in. by 10 ft stainless steel containing 20% FFAP (free fatty acid phase of Carbowax) on 60–80 mesh Chromosorb W, acid washed and treated with DMCS (dimethyldichlorosilane). Two analytical columns were used: column B, $^1/_4$ in. by 10 ft stainless steel containing 3% UCON HB 5100 (Union Carbide polyethylene glycol, polar) on 60–80 mesh Chromosorb G; column C, $^1/_4$ in. by 10 ft aluminum containing 15% FFAP on 60–80 mesh Chromosorb W.

1,4-Dimethylcyclohexene (1).—Aldrich 2,5-dimethylcyclohexanol was dehydrated over *p*-toluenesulfonic acid according to the method of Slomp.[29] Analysis of the crude olefin by glpc (column A) revealed the presence of two minor contaminants (shorter R_t), which were removed when the mixture was distilled over sodium through a 3-ft Podbielniak column. Pure **1** was also obtained by preparative glpc (column A), bp 128–129° (lit.[30] bp 127–128°), n^{20}D 1.4457 (lit.[31] n^{20}D 1.4458).

D-(+)-Limonene (2).—Eastman highest purity **2**, glpc unipeak (column C), n^{20}D 1.4721 (lit.[32] n^{20}D 1.4724), $[\alpha]$D +116.1° (*c* 8) (lit.[32] $[\alpha]$D +122.4°), was used without further purification.

3-Methylcyclohexene (3).—Aldrich **3** was redistilled, bp 101°, n^{20}D 1.4438 (lit.[33] n^{20}D 1.4435). Its ir was identical with that of authentic **3**.[34] It exhibited one spot on a silica gel tlc plate with benzene as the solvent and sulfuric acid, followed by charring at 110°, as the indicator.

***cis*-3,5-Dimethylcyclohexene (4).**—Aldrich 3,5-dimethylcyclohexanol, which was shown by preparative glpc (column A) to contain mostly *trans,trans*-3,5-dimethylcyclohexanol, n^{20}D 1.4512 (lit.[35] n^{20}D 1.4513), and *cis,cis*-3,5-dimethylcyclohexanol, n^{20}D 1.4548 (lit.[35] n^{20}D 1.4550), was dehydrated over *p*-toluenesulfonic acid according to the method of Slomp.[29] The crude olefin was refluxed from sodium for 6 hr and distilled through a 200-mm Vigreux column to afford **4**, bp 119.5–120°, which glpc (column C) showed to contain *ca.* 5% trisubstituted olefin (longer R_t). All of the contaminant was selectively removed by oxidizing the mixture with a limited amount of selenium dioxide in the usual way (*vide infra*) with an olefin/oxidant ratio of 10:1. It was then distilled from sodium to afford a dioxane solution of pure **4**, some of which was glpc (column A) collected: n^{20}D 1.4410; ir 3040 (m, CH=CH) and 678 cm^{-1} (s, CH=CH); nmr δ 5.55 (AB quartet, 2, CH=CH), 1.17–2.50 (m, 6, CH, CH_2), and 0.96 (2d, 6, $CHCH_3$).

Anal. Calcd for C_8H_{14} (110.19): C, 87.19; H, 12.81. Found: C, 87.46; H, 12.57.

3,3,5-Trimethylcyclohexene (5).—Aldrich 3,3,5-trimethylcyclohexanol was dehydrated over *p*-toluenesulfonic acid according to the method of Slomp.[29] It was purified by distillation from sodium on a Nester–Faust 300-plate spinning-band column (reflux ratio of 50:1) to afford **5**, bp 131.5° (lit.[29] bp 131.33°), n^{20}D 1.4388 (lit.[29] n^{20}D 1.4386). Its ir showed no absorption at 714 cm^{-1} characteristic of the isomeric 3,5,5-trimethylcyclohexene.[36]

***trans*-Δ^2-Octalin (6).**—The following modification of the method of Henbest[37] was used to make *cis*-5,8,9,10-tetrahydro-1,4-naphthoquinone (**48**). A solution of 100 g (0.93 mol) of Eastman *p*-benzoquinone in 75 g (1.39 mol) of Matheson butadiene and 1000 ml of benzene was kept at room temperature for 2 weeks. The solution was then filtered and rotary evaporated, and the residue was recrystallized once from petroleum ether to give 102 g (68%) of **48**, mp 52–56° (lit.[37] mp 57°).

The general procedure of Johnson[19] was employed to convert **48** into a mixture which was shown by glpc (column A) to consist of *trans*-Δ^2-octalin and *cis*-Δ^2-octalin in the ratio of 72:28 (lit.[38] 70:30). Pure **6** was obtained by vacuum fractionation of the mixture on a 3-ft Podbielniak column at a rate of 2 drops/min, bp 60° (5 mm), n^{20}D 1.4812 (lit.[38] n^{20}D 1.4815).

Standard Procedure for Selenium Dioxide Oxidation of Olefins.—A solution of selenious acid made by warming Fairmount Co. selenium dioxide in aqueous dioxane was added dropwise to a magnetically stirred, refluxing solution of olefin in dioxane. It was determined that Fairmount selenium dioxide could be used without further purification since it gave the same results as did resublimed material. The dioxane used was Fisher histological grade and showed only one peak on glpc (column C). The solution rapidly yellowed, and the color intensified to orange and then red as selenium precipitated during the addition and the subsequent 12–20-hr period of refluxing. Glpc analysis was performed on the crude product so as to determine relative yields.

Separation and identification of the products was performed by vacuum fractionation through a 10-cm Claisen column which was connected in series to a tared trap maintained at room temperature followed by two traps cooled with Dry Ice. The low boiling fraction (fraction 1 which collected in the latter two traps) was found to contain water, dioxane, and volatile, unreacted olefin although in some cases, which are noted, the olefin was sufficiently involatile as to be captured by the room temperature trap. The volatile oxidation products were in fraction 2 which collected in the room temperature trap. The contents of the traps were weighed and collected and those in fraction 2 were analyzed by glpc (column B unless otherwise noted) and then separated by preparative glpc (column A unless otherwise specified). It was necessary to do the preparative glpc on distilled material to avoid contamination of the glpc column by noneluting organoselenium by-products. The glpc peak ratios on both crude and distilled product agreed.

Standard Procedure for Jones Oxidation of Alcohols.—In a typical experiment, Jones reagent[39] was added dropwise to a stirred solution of 0.4 g of alcohol in 4 ml of reagent grade acetone until a permanent orange color persisted. The mixture was diluted with 12 ml of water and extracted with two 4-ml portions of chloroform. The combined chloroform extracts were washed with two 5-ml portions of water and rotary evaporated to afford the crude ketone which was purified by preparative glpc (column A).

Standard Procedure for Lithium Aluminum Hydride Reduction of Ketones.—In a typical manner, to a solution of 200 mg (5.2 mmol) of lithium aluminum hydride[40] in 10 ml of anhydrous ether, which had been stirring for 1 hr to effect solution, was added dropwise by means of a Hamilton syringe 200 μl of a ketone. After the mixture stirred for 1–2 hr, water was cautiously added to destroy excess hydride. The mixture was then filtered and the filtrate was rotary evaporated and analyzed by glpc (column C) and ir.

Standard Procedure for Hydrogenation of Allylic Alcohols.—In a typical experiment, approximately 0.1 g of Adams catalyst[41] was added to a solution of 0.2 ml of the desired alcohol in 5 ml of methanol in a Parr bomb at an initial hydrogen pressure of 50 psi. The mixture was shaken at room temperature until uptake of hydrogen ceased. After the catalyst had been filtered off, the filtrate was rotary evaporated to an oil which was purified by preparative glpc (column A).

Selenium Dioxide Oxidation of 1,4-Dimethylcyclohexene (1).—A solution of selenium dioxide (0.101 g, 0.9 mmol) in 0.2 ml of water and 1.0 ml of dioxane was added dropwise over a 4-hr period to a solution of 0.806 g (7.3 mmol) of **1** in 1.0 ml of dioxane by the standard procedure. Glpc analysis (column B, *t* 72°) of the crude product showed 81.2% of recovered **1** in addition to four oxidation products (*t* 95°), peak 1 (2.4%, R_t 8.7 min), peak 2 (7.8%, R_t 10.2 min), peak 3 (3.4% R_t 12.0 min), and peak 4 (4.2%, R_t 20.4 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 74–77° (3 mm).

(29) G. Slomp, Jr., M. Inatome, J. M. Derfer, K. W. Greenlee, and C. E. Boord, *J. Org. Chem.*, **25**, 514 (1960).

(30) O. Wallach, *Ann.*, **396**, 264 (1913).

(31) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **72**, 6090 (1960).

(32) G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).

(33) W. Hückel and A. Hubele, *ibid.*, **613**, 27 (1958).

(34) S. Pinchas, J. Shabtai, and E. Gil-Av, *Anal. Chem.*, **30**, 1863 (1958); API Spectrum No. 898.

(35) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(36) A. Arai, C. C. Yao, and I. Ichikizaki, *Bull. Chem. Soc. Jap.*, **36**, 1432 (1963).

(37) H. B. Henbest, M. Smith, and A. Thomas, *J. Chem. Soc.*, 3293 (1958).

(38) W. Hückel and H. Waiblinger, *Ann.*, **666**, 17 (1963).

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

(40) Ventron.

(41) Engelhard Industries.

Peak 1 was 2,5-dimethylcyclohex-2-en-1-one (**7**): uv max (cyclohexane) 232 mμ; ir 1672 cm^{-1} (s, C=CC=O). Its 2,4-dinitrophenylhydrazone melted at 189–190°.

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.30): C, 55.25; H, 5.30. Found: C, 55.34; H, 5.37.

Its semicarbazone (EtOH) melted at 196–197°.

Anal. Calcd for $C_9H_{15}N_3O$ (181.23): C, 59.64; H, 8.34. Found: C, 59.31; H, 8.22.

Peak 2 was *trans*-2,5-dimethylcyclohex-2-en-1-ol (**8**): ir (CCl_4) 3630 (s, free OH) and 3370 cm^{-1} (s, b, bonded OH); nmr δ 5.38 (broad d, 1, CH=C), 3.78 (broad s, 1, CHOH), 2.67 (s, 1, OH), 1.25–2.40 (m, 5, CH, CH_2), 1.67 (s, 3, C=CCH_3), and 0.93 (d, 3, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 75.99; H, 11.49.

Peak 3 was *cis*-2,5-dimethylcyclohex-2-en-1-ol (**9**): ir (CCl_4) 3623, 3650 (s, free OH), and 3370 cm^{-1} (s, b, bonded OH); nmr δ 5.30 (broad s, 1, CH=C), 4.00 (broad m, 1, CHOH), 2.75 (s, 1, OH), 1.25–2.40 (m, 5, CH, CH_2), 1.61 (s, 3, C=C-CH_3), and 0.93 (d, 3, $CHCH_3$). Its ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of **8**.

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 76.44; H, 11.52.

Peak 4 was not identified.

Jones oxidation of fraction 2 afforded **7** which was reduced by lithium aluminum hydride to a mixture which was predominantly **9**. When **1** was oxidized at an olefin/selenium dioxide ratio of 1.45:1, the 19% of oxidation product which was obtained was mostly **7** with some **8** but no **9**. The derivatives of **7** described above were prepared from this ketone-rich product.

Selenium Dioxide Oxidation of D-(+)-Limonene (2).—A solution of 0.859 g (7.7 mmol) of selenium dioxide in 2.0 ml of water and 10.0 ml of dioxane was added dropwise over a 3-hr period to a solution of 8.426 g (61.9 mmol) of **2** in 10.0 ml of dioxane by the standard procedure. Glpc analysis of the crude product (column B, *t* 78°) showed 84.8 ± 1.2% of recovered **2** in addition to five oxidation products (*t* 112°), peak 1 (5.8%, R_t 3.6 min), peak 2 (1.8%, R_t 6.6 min), peak 3 (1.0%, R_t 7.5 min), peak 4 (1.0%, R_t 8.7 min), and peak 5 (2.6%, R_t 13.8 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 41–76° (1 mm). Unreacted olefin was found to be present in both fractions.

Peak 1 was 1,8(9)-*p*-menthadien-4-ol (**10**): $n^{20}D$ 1.4957 (lit.[42] $n^{20}D$ 1.4961); $[\alpha]D$ +13.6° (neat). Its ir was superimposable on that of an authentic sample of **10** obtained from Dragoco Co., Holzminden, Germany. Its phenylurethan had mp 126–127° which was not depressed upon admixture with that prepared from an authentic sample of **10**.

Anal. Calcd for $C_{10}H_{16}O$ (152.23): C, 78.89; H, 10.59. Found: C, 78.88; H, 10.55.

Peak 2 was *trans*-carveol (**11**). It was identified by ir comparison[22] and by peak enrichment with authentic **11** (column B), prepared by the method of Klein and Ohloff.[43]

Peak 3 was *cis*-carveol (**12**). It was identified by ir comparison[22] and by peak enrichment with authentic **12** (column B), prepared by the method of Schroeter.[44]

Peaks 4 and 5 were not identified.

When this reaction was run at lower olefin/selenium dioxide ratios, the yield of **10** was much lower. This was due to decomposition of **10** by the selenium dioxide as shown by the following control experiment. A solution of selenious acid prepared by warming 72 mg (0.65 mmol) of selenium dioxide in 40 μl of water and 200 μl of dioxane was added to a solution of 199 mg (1.3 mmol) of **10** in 200 μl of dioxane. The solution was heated on a water bath for only 10 min, during which time black selenium precipitated out. Glpc analysis (column B) of the crude product revealed that half of the starting material **10** had been consumed. Under these analytical conditions, no other peaks appeared. After addition of another 72 mg (0.65 mmol) of selenium dioxide in 40 μl of water and 200 μl of dioxane, all of **10** had been consumed.

Selenium Dioxide Oxidation of 3-Methylcyclohexene (3).—A solution of 0.468 g (4.2 mmol) of selenium dioxide in 0.4 ml of water and 2.0 ml of dioxane was added over a 5-hr period to a solution of 1.635 g (17 mmol) of 3-methylcyclohexene (**3**) in 2.0 ml of dioxane according to the standard procedure. Glpc analysis of the crude product (column B, *t* 45°) showed 56% of recovered **3** in addition to three oxidation products (*t* 73°), peak 1 (8.8%, R_t 3.9 min), peak 2 (2.4%, R_t 7.5 min), and peak 3 (2.3%, R_t 8.7 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 48–49° (2 mm).

Peak 1 was pure 1-methylcyclohex-2-en-1-ol (**15**): ir 3375 (s, OH), 1100 (s), 1125 (s), and 1180 cm^{-1} (s) (tertiary unsaturated alcohol); nmr δ 5.55 (overlapping AB quartet, 2, CH=CH), 2.25 (s, 1, OH), 1.50–2.10 (m, 6, CH_2), and 1.24 (s, 3, CH_3).

Anal. Calcd for $C_7H_{12}O$ (112.16): C, 74.95; H, 10.78. Found: C, 75.24; H, 10.71.

Peak 2 was a *ca.* 4:1 mixture of *cis*-4-methylcyclohex-2-en-1-ol (**16**) [nmr δ 5.71 (overlapping AB quartet, 2, CH=CH), 4.13 (m, 1, CHOH), 1.18–2.05 (m, 7, CH, CH_2, OH), and 1.02 (d, 3, CH_3)] and *trans*-6-methylcyclohex-2-en-1-ol, although this latter product which was only formed in overall yield of *ca.* 0.5% was not isolated.

Anal. of peak 2. Calcd for $C_7H_{12}O$ (112.16): C, 74.95; H, 10.78. Found: C, 75.03; H, 10.89.

Peak 3 was pure *trans*-4-methylcyclohex-2-en-1-ol (**13**): nmr δ 5.61 (overlapping AB quartet, 2, CH=CH), 4.02 (m, 1, CH-OH), 2.65 (s, 1, OH), 1.17–2.50 (m, 6, CH, CH_2), and 1.00 (d, 3, CH_3).

Anal. Calcd for $C_7H_{12}O$ (112.16): C, 74.95; H, 10.78. Found: C, 74.85; H, 10.83.

Hydrogenation of the entire fraction 2 over Adams catalyst in methanol produced a mixture of methylcyclohexanols of which the major secondary carbinol is *trans*-4-methylcyclohexanol (**18**). Its ir and R_t are identical with those of authentic **18**.[45] Further confirmation comes from the fact that **18** is the major product of lithium aluminum hydride reduction of 4-methylcyclohexanone (**19**) which in turn had been made by Jones oxidation of Aldrich *cis*-4-methylcyclohexanol (**17**). The minor secondary carbinol obtained in the catalytic reduction of fraction 2 is **17**. Its ir and R_t are identical with those of Aldrich **17**, $n^{20}D$ 1.4617 (lit.[46] $n^{20}D$ 1.4614). Jones oxidation of fraction 2 yields mostly 4-methylcyclohex-2-en-1-one (**14**)[47] which was collected by preparative glpc (column A) and was lithium aluminum hydride reduced to a mixture of **16** and **13** with the latter predominating.

The minor alcohol in peak 2 was shown to be *trans*-6-methylcyclohex-2-en-1-ol from its broad upfield carbinol (H–C–OH) nmr signal detectable in the nmr of peak 2 and from glpc (column C) identity of R_t of the product of its catalytic hydrogenation with that of *trans*-2-methylcyclohexanol from the lithium aluminum hydride reduction of Aldrich 2-methylcyclohexanone.

The determination of the relative amounts of *trans*-6-methylcyclohex-2-en-1-ol and **16** in peak 2 was made by cutting out and weighing the H–C–OH nmr signals at δ 3.77 and 4.13, respectively, in a 2*x* scan and is therefore only approximate. The difference between the two signals is in agreement with the upfield shift reported by Eliel for the effect of a vicinal *trans*-equatorial methyl on a cyclohexanol H–C–OH signal.[23]

Selenium Dioxide Oxidation of *cis*-3,5-Dimethylcyclohexene (4).—A solution of 1.428 g (12.8 mmol) of selenium dioxide in 3.0 ml of water and 10.0 ml of dioxane was added dropwise over a 3–5 hr period to a solution of 5.615 g (51 mmol) of **4** in 18.7 ml of dioxane by the standard procedure. Glpc analysis (column B, *t* 58°) of the crude product showed 62.9 ± 1% of recovered **4** in addition to four oxidation products (*t* 80°), peak 1 (7.2%, R_t 3.6 min), peak 2 (2.7%, R_t 4.8 min), peak 3 (2.6%, R_t 5.4 min), and peak 4 (2.8%, R_t 7.5 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 76–78° (4 mm).

Peak 1 was *cis*-1,5-dimethylcyclohex-2-en-1-ol (**22**): ir (CCl_4) 3630 (s, free OH) and 3485 cm^{-1} (s, b, bonded OH); nmr δ 5.53 (overlapping AB quartet, 2, CH=CH), 2.00 (s, 1, OH), 1.25–2.33 (m, 5, CH, CH_2), 1.17 [s, 3, C(OH)CH_3], and 0.97 (d, 3, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 75.99; H, 11.31.

Peak 2 was *trans*-1,5-dimethylcyclohex-2-en-1-ol (**23**): ir (CCl_4) 3625 (s, free OH) and 3475 cm^{-1} (s, b, bonded OH); nmr δ 5.49 (overlapping AB quartet, 2, CH=CH), 1.65 (s, 1, OH), 1.25–2.33 (m, 5, CH, CH_2), 1.18 [s, 3, C(OH)CH_3], and

(42) E. Klein and W. Rojahn, *Tetrahedron*, **21**, 2173 (1965).
(43) E. Klein and G. Ohloff, *ibid.*, **19**, 1091 (1963).
(44) S. Schroeter, *Ann.*, **674**, 118 (1964).
(45) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).
(46) L. M. Jackson, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 1717 (1949).
(47) W. G. Dauben, G W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).

0.97 (d, 3, $CHCH_3$). Its concentration-dependent ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of peak 1.

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 75.98; H, 11.04.

Peak 3 was *cis,cis*-4,6-dimethylcyclohex-2-en-1-ol (**24**): ir (CCl_4) 3625 (s, free OH) and 3485 cm^{-1} (s, b, bonded OH); nmr δ 5.40–5.95 (m, 2, CH=CH), 3.80 (m, 1, CHOH), 2.15 (broad singlet, 1, OH), 1.25–2.40 (m, 4, CH, CH_2), and 2.00 (2d, 6, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 75.62; H, 10.89.

Peak 4 was *trans,trans*-4,6-dimethylcyclohex-2-en-1-ol (**20**): ir (CCl_4) 3640 (s, free OH) and 3500 cm^{-1} (s, b, bonded OH); nmr δ 5.41–5.62 (m, 2, CH=CH), 3.48–4.00 (m, 1, CHOH), 2.48 (s, 1, OH), 1.25–2.40 (m, 4, CH, CH_2), and 1.98 (m, 6, $CHCH_3$). Its concentration-dependent ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of peak 3.

Anal. Calcd for $C_8H_{14}O$ (126.19): C, 76.14; H, 11.18. Found: C, 76.05; H, 11.26.

Peak 4 also contained some other isomer which is evident by its carbinol (H–C–OH) signal at δ 3.93 in the nmr. Area integration of the two carbinol proton signals indicated that the other isomer was present to the extent of *ca.* 33%, so that the actual amount of **20** in peak 4 in the crude selenium dioxide oxidation product was 1.9%. The structure of the contaminant present in overall yield of less than 1% was not determined.

Hydrogenation of fraction 2 over Adams catalyst in methanol produced, as the major product, *cis*-1,3-dimethylcyclohexanol (**25**), $n^{20}D$ 1.4526 (lit.[48] $n^{20}D$ 1.4527). Its ir agreed with reported values.[49] The secondary alcohol, *cis,cis*-2,4-dimethylcyclohexanol (**26**) was also isolated, the R_t and ir of which were identical with those of authentic **26** whose synthesis is described below. Similarly, the secondary carbinol, *trans,trans*-2,4-dimethylcyclohexanol (**27**) was isolated; its ir and R_t were identical with those of authentic **27** whose synthesis is described below.

The Jones oxidation of fraction 2 produced one ketonic product, **21**,[50] which was glpc collected (column A) and subsequently reduced with lithium aluminum hydride to a mixture which was predominantly **20** as evidenced by R_t and ir.

When this reaction was repeated with an olefin/selenium dioxide ratio of 2:1, only 31.3 ± 1.3% of **4** was recovered and only 14.5 ± 0.4% of oxidation product was formed.

Preparation of *cis,cis*-2,4-Dimethylcyclohexanol (26) and *trans,trans*-2,4-Dimethylcyclohexanol (27).—2,4-Dimethylcyclohexanol (K & K Laboratories) was shown by glpc (column C) to contain four alcohols, **26** (21%), **27** (61%), and two unidentified alcohols (18%, not completely separated) in order of increasing R_t. From the Jones oxidation of this mixture was isolated as the major oxidation product (83%) *cis*-2,4-dimethylcyclohexanone (**28**), $n^{20}D$ 1.4454 (lit.[51] $n^{20}D$ 1.4442), whose ir spectrum was identical with that reported for an authentic sample.[52] Ketone **28** was hydrogenated over Adams catalyst in methanol to a mixture of alcohols, **26** (79%) [$n^{20}D$ 1.4578, ir axial C–OH stretch at 983 cm^{-1},[21] nmr (CCl_4) δ 3.70 (calcd 3.74)[23] ($W_{1/2}$ = 7 Hz)] and **27** (21%) [$n^{20}D$ 1.4563 (lit.[53] $n^{20}D$ 1.4560), ir equatorial O–H stretch at 1048 cm^{-1},[21] nmr (CCl_4) δ 2.99 (calcd 3.00)[23] ($W_{1/2}$ = 18 Hz, H–C–OH), α-naphthylurethan mp 150–151° (lit.[54] mp 152.5–153.5°)].

Selenium Dioxide Oxidation of 3,3,5-Trimethylcyclohexene (5).—A solution of 2.243 g (20.2 mmol) of selenium dioxide in 2.4 ml of water and 8.0 ml of dioxane was added over a 3-hr period to a solution of 4.971 g (40.0 mmol) of **5** in 8.0 ml of dioxane by the standard procedure. Glpc analysis of the crude product (column B, *t* 55°) showed 34.5 ± 1.2% of recovered **5** in addition to two oxidation products (*t* 90°), peak 1 (27.8%, R_t 4.8 min) and peak 2 (2.4%, R_t 5.7 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 76–78° (2 mm).

Peak 1 was mostly *cis*-4,4,6-trimethylcyclohex-2-en-1-ol (**31**): ir (CCl_4) 3635 (s, free OH) and 3495 cm^{-1} (s, b, bonded OH); nmr δ 5.60 (AB quartet, 2, CH=CH), 3.72 (m, 1, CHOH), 2.00 (s, 1, OH), 1.16–2.40 (m, 3, CH, CH_2), and 0.98 (overlapping d and 2s, 9, CH_3). It was hydrogenated over Adams catalyst in methanol to *cis*-2,4,4-trimethylcyclohexanol (**29**), $n^{23}D$ 1.4602 (lit.[54] $n^{24}D$ 1.4605). Its ir agreed with that of an authentic sample.[55]

Anal. Calcd for $C_9H_{16}O$ (140.22): C, 77.09; H, 11.50. Found: C, 76.85; H, 11.59.

Peak 2 was mostly *trans*-4,4,6-trimethylcyclohex-2-en-1-ol (**32**): ir (CCl_4) 3640 and 3615 (s, free OH) and 3429 cm^{-1} (very broad, s, bonded OH); nmr δ 5.40 (overlapping AB quartet, 2, CH=CH), 3.60 (d, 1, CHOH), 3.40 (s, 1, OH), 1.16–2.33 (m, 3, CH, CH_2), and 0.98 (overlapping d and 2s, 9, CH_3). Its concentration-dependent ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of peak 1. Peak 2 was hydrogenated over Adams catalyst in methanol to *trans*-2,4,4-trimethylcyclohexanol (**30**), whose ir agreed with that of an authentic sample.[55]

Anal. Calcd for $C_9H_{16}O$ (140.22): C, 77.09; H. 11.50. Found: C, 77.25; H, 11.42.

Jones oxidation of fraction 2 afforded 4,4,6-trimethylcyclohex-2-en-1-one (**35**), whose ir and nmr agreed with published spectra.[47] It was reduced by lithium aluminum hydride to a mixture of **31** and **32** in a ratio of 4:96. Fraction 2 also contained a small amount of ketone **35**, whose R_t was identical with that of **31**. When fraction 2 was treated with lithium aluminum hydride under nonepimerizing conditions, the ratio of peak 1 to peak 2 changed from 92:8 to 84:16 which indicated that peak 1 contained 8% **35**. It was also found by measuring the areas under the two carbinol (H–C–OH) proton nmr signals at δ 3.72 and 3.38 that peak 1 additionally contains *ca.* 10% *cis*-4,6,6-trimethylcyclohex-2-en-1-ol (**33**) so that the actual amount of **31** in peak 1 of the crude selenium dioxide oxidation product of **5** was only 22.7%. These two signals at δ 3.72 and 3.38 are assignable to compounds **31** and **33**, respectively. Similarly, by area integration of the carbinol (H–C–OH) signals at δ 3.60 and 3.80, it was determined that peak 2 also contained *ca.* 18% *trans*-4,6,6-trimethylcyclohex-2-en-1-ol (**34**) so that the actual amount of **32** in peak 2 of the crude selenium dioxide oxidation product of **5** was only 2.0%. The δ 3.60 and 3.80 signals are assignable to **32** and **34**, respectively. The structures **33** and **34** were established by comparison with authentic samples whose syntheses are described below.

Preparation of *cis*- (33) and *trans*-4,6,6-Trimethylcyclohex-2-en-1-ol (34).—By the general procedure for the Wharton reaction described by Klein and Ohloff,[43] **35** was converted in 24% overall yield into **33**: ir (CCl_4) 3635 (s, free OH) and 3490 cm^{-1} (s, b, bonded OH); nmr δ 5.63 (overlapping AB quartet, 2, CH=CH), 3.38 (d, 1, CHOH), 1.25–2.40 (m, 3, CH, CH_2), 1.20 (s, 1, OH), and 0.96 (overlapping 2s and d, 9, CH_3). The Wharton reaction is known to be highly stereospecific and to give predominantly the axial alcohol.[43]

Jones oxidation of **33** produced ketone **37** which was reduced by lithium aluminum hydride to a mixture rich in **34**: nmr δ 5.38 (m, 2, CH=CH), 3.80 (d, 1, CHOH), 1.75 (s, 1, OH), 1.25–2.40 (m, 3, CH, CH_2), and 0.96 (overlapping d and 2s, 9, CH_3). Its concentration-dependent ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of **33**.

Selenium Dioxide Oxidation of Δ^2-*trans*-Octalin (6).—A solution of 0.522 g (4.7 mmol) of selenium dioxide in 1.0 ml of water and 5.0 ml of dioxane was added over a 4-hr period to a solution of 2.541 g (18.7 mmol) of **6** in 5.0 ml of dioxane by the standard procedure. Glpc analysis of the crude product (column B, *t* 88°) showed 82.0 ± 1.4% of recovered **6** in addition to three oxidation products (*t* 130°), peak 1 (7.8%, R_t 4.8 min), peak 2 (4.4%, R_t 6.0 min), and peak 3 (2.5%, R_t 6.6 min). Vacuum fractionation gave fraction 1, bp <25° (1–2 mm), and fraction 2, bp 33–72° (1 mm).

(48) M. I. Batuev, A. A. Akhrem, A. V. Kamernitskii, and A. D. Matveeva, *Izv. Akad. Nauk SSSR. Otd. Khim Nauk* 1668 (1959); *Chem. Abstr.*, **54**, 9797*h* (1960).

(49) G. Chiurdoglu, A. Cardon, and W. Masschelein, *Bull. Soc. Chim. Belges*, **68**, 388 (1959).

(50) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(51) R. C. Lawes, *J. Amer. Chem. Soc.*, **84**, 239 (1962).

(52) E. C. Kornfeld, R. J. Jones, and T. V. Parke, *ibid.*, **71**, 150 (1949).

(53) H. E. Ungnade and A. D. McLaren, *ibid.*, **66**, 118 (1944).

(54) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

(55) D. J. Pasto and F. M. Klein, *ibid.*, **33**, 1468 (1968), reported the compound and the spectrum was obtained by private communication.

Peak 1 was *trans,syn*-Δ^2-octalol-1 (**40**): ir (CCl_4) 3633 (s, free OH) and 3500 cm^{-1} (m, b, bonded OH); nmr δ 5.88 (m, 2, CH=CH), 3.88 (broad singlet, 1, CHOH), 1.33 (s, 1, OH), and 0.50–2.40 (broad band, 13, all other protons). It was hydrogenated over Adams catalyst in methanol to *trans,syn*-1-decalol (**38**) whose ir was identical with that of authentic **38**.[21]

Anal. Calcd for $C_{10}H_{16}O$ (152.23): C, 78.89; H, 10.59. Found: C, 78.62; H, 10.49.

Peak 2 was *trans,anti*-Δ^2-octalol-1 (**41**): ir (CCl_4) 3625 and 3650 (s, free OH), and 3500 cm^{-1} (s, b, bonded OH); nmr δ 5.60 (m, 2, CH=CH), 3.80 (broad singlet, 1, CHOH), 1.67 (s, 1, OH), and 0.50–2.40 (broad band, 13, all other protons). Its ir absorption in dilute carbon tetrachloride solution in the intermolecular O–H stretching region was more intense than in the corresponding spectrum of **40**. It was hydrogenated over Adams catalyst in methanol to *trans,anti*-1-decalol (**39**) whose ir was identical with that of authentic **39**.[21] Jones oxidation of fraction 2 produced the enone **42** which was collected by preparative glpc (column A) and subsequently reduced by lithium aluminum hydride to a mixture which contained *ca.* 95% **41**.

Anal. Calcd for $C_{10}H_{16}O$ (152.23): C, 78.89; H, 10.59. Found: C, 78.61; H, 10.39.

Peak 3 was not identified.

Registry No.—Selenium dioxide, 7446-08-4; **4**, 23758-22-7; **7**, 23758-23-8; **7** (2,4-dinitrophenylhydrazone), 23758-24-9; **7** (semicarbazone), 23829-43-8; **8**, 23758-25-0; **9**, 23758-26-1; **13**, 23713-60-2; **15**, 23758-27-2; **16**, 23713-61-3; **20**, 23713-62-4; **22**, 23746-53-4; **23**, 23713-63-5; **24**, 23713-64-6; **26**, 23713-65-7; **31**, 23713-66-8; **32**, 23713-67-9; **33**, 23713-68-0; **34**, 23713-69-1; **40**, 23713-70-4; **41**, 23713-71-5.

Acknowledgment.—Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research.

Mechanism of Selenium Dioxide Oxidation of Olefins[1]

EDWARD N. TRACHTENBERG, CHARLES H. NELSON,[2] AND JANE RUMFORD CARVER[3]

Department of Chemistry, Clark University, Worcester, Massachusetts 01610

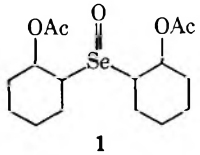
Received September 4, 1969

The mechanism of allylic oxidation of olefins by selenium dioxide is discussed. Evidence is presented in favor of an initial oxaselenocyclobutane intermediate forming an allylic selenite ester, which then solvolyzes.

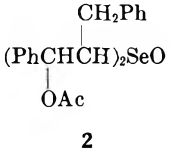
The mechanism of allylic oxidation of olefins by selenium dioxide has been the subject of several studies over the past 30 years.[4] The first hypothesis, that of Guillemonat,[5] invoked the intermediacy of tetraalkyl and dialkyl selenides in which the selenium is bonded to an allylic carbon. The gross inadequacy of this proposal has already been commented upon adequately,[4,6] but it should be recognized that Guillemonat's comprehensive studies of the behavior of selenium dioxide in acetic acid–acetic anhydride led to the formulation of many useful and still valid generalizations with respect to the site of attack in unsymmetrical alicyclic and acyclic olefins.

Another early suggestion put forth by Waters without any experimental support was that the reaction involves neutral radical species.[7] This was based on analogy to the allylic oxidation observed with benzene diazonium acetate, lead tetraacetate, or air catalyzed by osmium and on the fact that many oxidations involve radical-chain mechanisms. Although Wiberg and Nielsen[8] credit Waters with suggesting that the reaction proceeds "*via* a hydrogen atom abstraction from the alkene," Waters did recognize that the 2-cyclohexenol acetate produced by selenium dioxide oxidation of cyclohexene could also be formed by addition of two acetoxy radicals followed by elimination of acetic acid. No support has, however, been forthcoming for a free-radical process. Quite the contrary, Schaefer, Horvath, and Klein[9] have shown that the reaction is unaffected by inhibitors and, therefore, cannot be radical chain. We wish to report that the reaction does not involve free radicals at all. Thus, we find that an oxidizing system is incapable of initiating polymerization of acrylonitrile under conditions of temperature and concentration where acrylonitrile is rapidly polymerized if a source of free radicals is present.

There is now evidence that the oxidation proceeds by two different mechanisms, a low energy solvolytic pathway and a pyrolytic one. Guillemonat[5] had early observed that the organoselenium intermediates which he postulated as selenides thermally decompose to regenerate olefin and to produce allylic oxidation products. Wiberg[8] established that these compounds are selenoxides, rather than selenides, by isolating **1** from the oxidation of cyclohexene in acetic acid–acetic anhydride. Schaefer, Horvath, and Klein,[9] however, showed that the analogous compound **2** isolated from



1



2

the oxidation of 1,3-diphenylpropene (**3**) decomposes to 1,3-diphenyl-2-propen-1-ol acetate (**4**) at too slow a rate to account for the main course of the oxidation.

The main pathway must involve the solvolysis of an allylic selenite ester, although the structure of the latter has not been rigorously established. Schaefer[9]

(1) A preliminary report of some of this work was made at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1962, Abstract, p 78Q.

(2) Extracted in part from the Ph.D. dissertation submitted by C. H. N. to Clark University in 1964. A National Science Foundation Cooperative Graduate Fellowship for 1961–1962 is gratefully acknowledged.

(3) Extracted in part from the Ph.D. dissertation submitted by J. R. C. to Clark University in 1969.

(4) For a review of the scope and limitations of this reaction, see (a) E. N. Trachtenberg in "Oxidation," Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969, pp 119–187; (b) N. Rabjohn, *Org. React.*, **5**, 331 (1949); (c) G. R. Waitkins and C. W. Clark, *Chem. Rev.*, **36**, 235 (1945).

(5) A. Guillemonat, *Ann. Chim.* (Paris), **11**, 143 (1939).

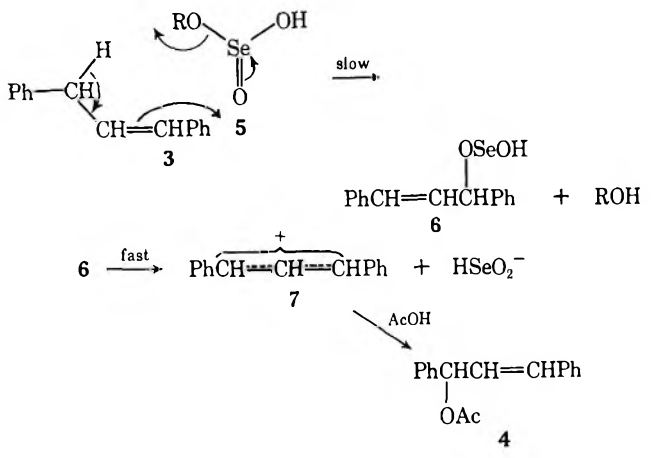
(6) T. W. Campbell, H. G. Walker, and C. M. Coppinger *Chem. Rev.*, **50**, 279 (1952).

(7) W. A. Waters, *J. Chem. Soc.*, 1805 (1939).

(8) K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

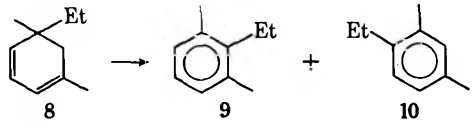
(9) J. P. Schaefer, B. Horvath, and H. P. Klein, *ibid.*, **33**, 2647 (1968).

SCHEME I

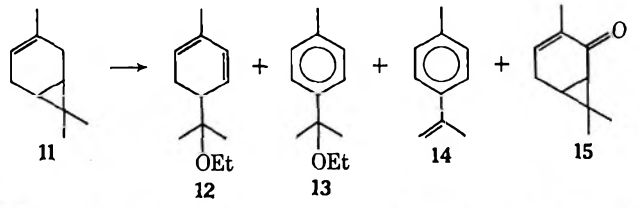


has suggested the mechanism shown in Scheme I. The rapid SN1 of **6** is in agreement with the observation that **3** deuterium labeled at C-3 shows equilibration of C-1 and C-3. Furthermore, the presence of a final solvolytic step is in agreement with observations on many systems. Thus, one obtains alcohols, acetates, and ethers when the selenium dioxide oxidation is performed in water, acetic acid (or acetic acid–acetic anhydride), or alcohol, respectively.[4] Since alcohols formed under the mildly acidic reaction conditions would not be converted into ethers, it follows that the latter must be formed directly in a solvolytic step; by analogy, the same should also be true for acetate formation. In further support of a solvolytic mechanism, at least part of which must be SN1 in character, is our observation that, whereas D-(+)-1-*p*-menthene in wet dioxane yields optically active, albeit partially racemized, *cis*- and *trans*-carvotanacetols and carvotanacetone, the acetates produced in the better ionizing solvent, acetic acid–acetic anhydride, are completely racemic. This accords with a competition between uni- and bimolecular solvolysis.

The observation of rearranged products in a system such as **8** agrees with the formation of an allylic cation at C-6 which then undergoes Wagner–Meerwein rearrangement followed by proton loss to generate the



aromatic system **9**.[10] The formation of **10** is similarly explicable. Another example involves the oxidation of 3-carene (**11**) in ethanol to give **12**–**15**.[11] Finally, the

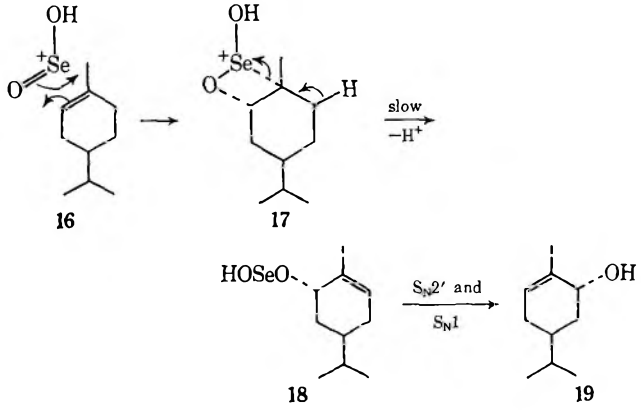


observed formation of dienes in systems in which the preferred site of oxidation is tertiary is in accord with the expectation of E1 competing with SN1 in such systems.[5,12]

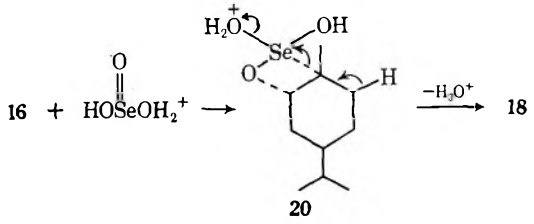
The first step of the Schaefer mechanism (Scheme I) is harder to justify. If what is implied is a synchronous electrocyclic reaction, one cannot explain the large kinetic deuterium isotope effect of 3.1 for reaction of PhCHDCH=CHPh in refluxing acetic acid. This effect clearly implies that, in the cleavage of the allylic C–H bond, bond breaking markedly leads over bond making. If this is so, and the proposed mechanism is to be generally true, one is faced with the dilemma of explaining why the C-6 and not the C-3 position is oxidized in 1-alkyl-, 1-halo-, and, above all, 1-aryl-cyclohexenes. Irrespective of whether the hydrogen is removed as proton, atom, or hydride ion, the extra resonance stability available to a C-3 anion, radical, or cation over that available in the cross-conjugated C-6 position should favor its oxidation. Finally, the Schaefer mechanism does not explain the stereochemical results which are reported in this and the accompanying paper[13] (*vide infra*).

We wish to propose a different mechanism which appears to accommodate our stereochemical findings as well as all other information in the literature. It is shown in Scheme II with D-(+)-1-*p*-menthene (**16**) as substrate. Although the oxidant is here written as

SCHEME II



protonated selenium dioxide, it may instead well be some hydrated (or solvated) form of this, in which case the first two steps of the mechanism would be altered as shown below. Evidence in favor of a protonated



oxidant has previously been presented.[9] It should be noted that the first step does not imply a concerted 2 + 2 cycloaddition but rather a typical Markovnikov-type electrophilic addition with attack occurring through oxygen to generate positive character at the

(10) M. Zaidlewicz, A. Uzarewicz, and W. Zacharewicz, *Rocz. Chem.*, **40**, 437 (1966) (English summary).

(11) Z. G. Isaeva, B. A. Arbuzov, and V. V. Ratner, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 475 (1965); *Bull. Acad. Sci. USSR, Ser. Chem.* (Engl. Transl.), 458 (1965).

(12) R. K. Callow, *J. Chem. Soc.*, 462 (1936).

(13) E. N. Trachtenberg and J. R. Carver, *J. Org. Chem.*, **35**, 1646 (1970).

tertiary carbon, followed by cyclization. In agreement with electrophilic attack are the observations that dienes are more reactive than olefins, olefin reactivity increases with alkyl substitution,[4] and electron-feeding groups slightly accelerate the rate of oxidation of **3**.[9] It is essential to the mechanism shown in Scheme II that the closure of the four-membered ring occur either before full carbonium-ion character develops at C-1 or more rapidly than a Wagner–Meerwein rearrangement can occur if carbonium-ion character does develop. If this were not the case, one would anticipate Wagner–Meerwein rearrangement in the oxidation of systems such as α- and β-pinene and typical camphene–isobornyl rearrangement in the oxidation of camphene. The latter is not observed, and only a small amount of rearranged product is formed in the pinene case.[14]

The postulated slow conversion of **17** (or **20**) into **18** is in agreement with the primary deuterium isotope effect reported by Schaefer.[9] It seems reasonable that this process should be slow for, although the breaking of the four-membered ring might provide some steric acceleration, the carbon–selenium bond which must be cleaved is very similar to that present in an alkylseleninic acid, and even benzylseleninic acid proves unreactive toward solvolysis.[15] It should be noted that, if the deprotonation step is slow in an acyclic system such as **3**, this will be accentuated in a cyclic system such as in the conversion of **17** (or **20**) into **18**. The carbon–hydrogen bond undergoing cleavage cannot become *trans* diaxial to the carbon–selenium bond in the preferred conformation for the transition state for elimination unless the isopropyl group also becomes axial. Thus, the molecule either is forced into this unfavorable conformation or else must undergo elimination through a less favorable conformational arrangement of departing groups. The latter might well happen if the necessary chair–chair interconversion introduces 1,3-*syn*-diaxial interactions or is otherwise prevented from occurring in *trans*-decalin or other conformationally frozen systems.

Finally, the postulated combined S_N2'–S_Ni solvolysis of **18**, similar to a suggestion made by Schaefer, Horvath, and Klein,[9] is required by our observation that the major product from D-(+)-1-*p*-menthene is partially racemized D-(+)-*trans*-carvotanacetol when the reaction is carried out in wet dioxane. Since there is overall retention of configuration with respect to C-4, it follows that either zero or an even number of allylic rearrangements is occurring. Wiberg, who did a similar study, has nicely explained why it must be the latter.[8] It should be emphasized that the well-established stereochemistry of the S_N2' [16] requires that **18** have *trans* stereochemistry if the observed major product is *trans*-carvotanacetol. We cannot at this point eliminate another alternative for the last step of Scheme II in which S_N2' is replaced by S_Ni'; the stereochemical result is, however, the same.

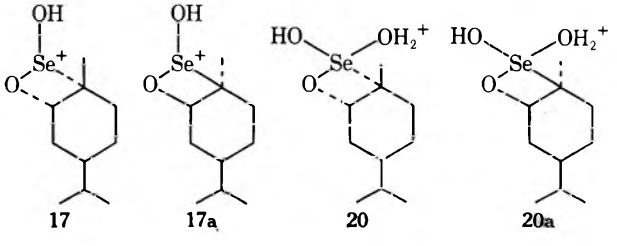
The main reason for favoring the mechanism shown in Scheme II is that it permits us to explain the stereochemistry of the products observed in the oxidation of a number of cyclohexenyl systems. The results are shown in Table I; the details on **16** are given in the

TABLE I

Olefin oxidized	Allylic alcohols produced and yields
21	**22**, 41%; **23**, 18%
16	**19**, 48%; **24**, 20%; **25**, 23%
26	**27**, 39%; **28**, 12%; **29**, 7%
30	**31**, 20%; **32**, 4.3%; **33**, 5.2%
34	**35**, 19%; **36**, 7%; **37**, 7%; **38**, 5%
39	**40**, 35%; **41**, 3%; **42**, 4.5%; **43**, 0.6%
44	**45**, 42%; **46**, 24%

Experimental Section; and those on the other compounds are given in the accompanying paper.[13]

If one makes the reasonable assumption that the steric requirements of selenium are greater than those of oxygen in intermediates such as **17** or **20** and that oxygen must attack the less substituted end of a trisubstituted double bond to get to the observed product with allylic substitution at C-6 and not C-3, there are two stereochemical possibilities, **17** and **17a** (or **20** and **20a**). Since **17** (or **20**) involves 1,3-diaxial interaction between oxygen at C-2 and hydrogen at C-4 and C-6,



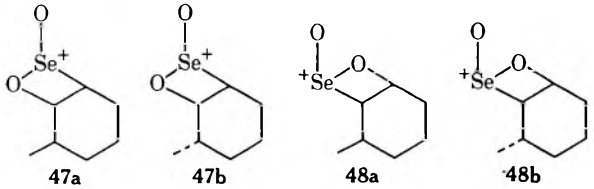
17 **17a** **20** **20a**

whereas **17a** (or **20a**) necessitates more serious interaction of selenium at C-1 with the C-3 and C-5 hydrogens, one predicts and finds that the preferred intermediate is that leading eventually to *trans*-carvotanacetol. The same argument applies to other 1,4-disubstituted cyclohexenes such as **21** and **26**, and again the results agree with the predictions based on the proposed intermediacy of an oxaselenocyclobutane. The 2.4-fold preference for **19** over **24** observed in the oxidation of **16** in wet dioxane is in substantial agreement with the ratio of 1.5 reported by Wiberg[8] who carried out the reaction in acetic acid–acetic anhydride. Under the

(14) See ref 4a, 4b, and 4c and references cited therein.
(15) C. L. Jackson, *Ann.*, **179**, 13 (1875).
(16) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

latter conditions, in contrast to ours, there is no further oxidation to carvotanacetone. Since we have observed that *cis*-carvotanacetol **24** is oxidized more rapidly than its epimer, the ratio when adjusted for selective further oxidation of **24** agrees exactly with Wiberg's result.

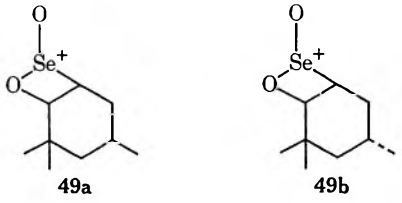
The situation becomes more complex with **30** since it is now possible, on electronic grounds, to add across the double bond in either direction as well as from either side. If one considers the preferred conformations for the four stereochemical possibilities (shown only for intermediates of the type **17** since the stereochemical arguments are the same for those of the type **20**), **47a** introduces a skew interaction between methyl and oxygen and two 1,3-diaxial interactions between oxygen



47a **47b** **48a** **48b**

and hydrogen, whereas epimer **47b** suffers from 1,3-diaxial interactions between selenium and hydrogen. Apparently, these about balance for the yields of **32** and **33**, derived from **47a** and **47b**, respectively, show almost no stereoselectivity. Of the two possible intermediates derived from addition in the opposite sense, **48a** has little to recommend it, but **48b** only involves 1,3-diaxial interactions between oxygen and hydrogen. In agreement with this, the yield of **31** is over twice the combined yields of **32** and **33**. It should be noted that it is not possible in this system to demonstrate that **48b**, rather than **48a**, is the precursor of **31**, but such distinction becomes possible in a study of *cis*-3,5-dimethylcyclohexene (**34**). Here again, there is almost no stereoselectivity observed in the secondary carbinol products **37** and **38**, and the tertiary products **35** and **36** are favored by over twofold. What is interesting is that the axial tertiary carbinol **35** derived from the analog of **48b** is favored over its epimer by almost threefold.

Equally interesting are the results with 3,3,5-trimethylcyclohexene (**39**). For steric reasons, the direction of addition is again fixed so that only the intermediates **49a** and **49b** are possible. Since **49a** introduces two 1,3-diaxial interactions between oxygen and hydrogen, whereas **49b** in one conformation introduces

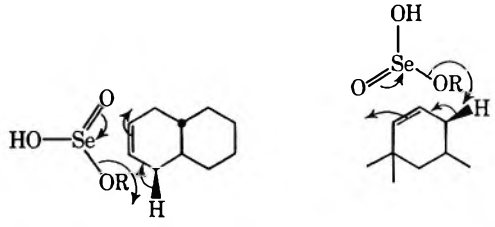


49a **49b**

1,3-diaxial interactions between methyls and in the other between methyl and selenium, the preference for **49a** should be more emphatic than in the other cases studied. Indeed, **40** is favored over **41** by over tenfold.

The case of *trans*-Δ^2-octalin (**44**) is instructive because symmetry makes the two directions of addition equivalent, conformation is fixed, and one can therefore get a measure of the difference between 1,3-diaxial interactions involving hydrogen with either selenium or oxygen. The preference for oxygen is such that the stereoselectivity is almost twofold.

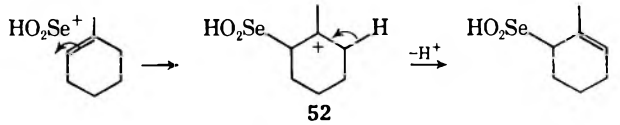
The characteristic feature of the mechanism which we are proposing is that it involves both ends of the double bond unsymmetrically. The intermediacy of an oxaselenocyclobutane had previously been considered by Schaefer and Horvath[17] but was rejected solely on the grounds that the evidence then available could be explained by a less complex intermediate. It is now useful to enquire whether other types of intermediates can accommodate our stereochemical findings as well as fit other literature evidence. We have already discussed some of the difficulties with Scheme I. As mentioned previously, this mechanism also breaks down on stereochemical grounds. If one assumes, as Schaefer did, that the attack must be axial for stereoelectronic reasons, one is unable to explain why a conformationally fixed system such as **44** shows only a twofold preference for axial product, whereas **39** gives over tenfold stereoselectivity. In the transition states for the two, **50** and **51**, respectively, axial attack would be from the top of the molecules as drawn.



50 **51**

Exactly the same types of 1,3-diaxial interactions between oxygen and hydrogen are introduced in both, but **51** additionally involves a skew interaction between oxygen and methyl. One is also unable to explain why the slightly preferred mode of attack in the case of **30** is equatorial.

Another mechanism which has previously been proposed involves attack by protonated selenium dioxide at the less substituted end of a trisubstituted double bond leading to an intermediate of the type **52**.[8]

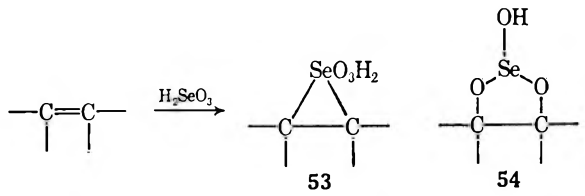


52

Some of the difficulties with this suggestion have already been pointed out elsewhere.[9] Additionally, this mechanism is unable to explain the stereochemical results whether one assumes that the group must preferentially come in axially or assumes no such preference. The same criticism applies to a similar sequence of reactions with attack through oxygen instead of selenium.[18]

Other types of mechanism which are excluded by our stereochemical findings are those involving symmetrical

(17) J. P. Schaefer and B. Horvath, *Tetrahedron Lett.*, 2023 (1964).
(18) E. N. Trachtenberg and C. H. Nelson, ref 1.



intermediates such as **53**[8] or **54**. As indicated above, stereoselectivity derives from differential steric demands of groups attached to the original olefinic carbons.

In conclusion, we find that intermediates which either involve both of the olefinic carbons symmetrically or alternately only involve one are incapable of explaining the observed stereoselectivity. We recognize that the energy factors involved must be relatively small, but all are in the right direction and relative magnitude. We also wish to reiterate that this discussion applies only to the low energy solvolytic mechanism and that we do not rule out the operation of a pyrolytic pathway leading through organoselenium compounds and also producing allylic oxidation products.

Experimental Section

Infrared spectra were obtained on thin liquid films with a Perkin-Elmer Infracord. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian HA-60 or a Jeolco JNM C-60H on samples dissolved in deuteriochloroform containing tetramethylsilane (TMS) as internal standard. Optical rotations were determined on benzene solutions (unless otherwise noted) with a Rudolph Model 80 CSPI photoelectric polarimeter, and refractive indices were measured on a Bausch and Lomb Abbe 3L refractometer. Melting points were determined in soft glass capillaries on a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by the Alfred Bernhardt Microanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany.

Gas chromatographic analyses and separations were performed on a Wilkens–Varian Model A-700 Autoprep packed with the Wilkens–Varian materials specified below and equipped with a thermal conductivity detector with helium gas as carrier. Peak areas were determined by cutting out the peaks and weighing them or, in the case of sharp symmetrical peaks, by measuring peak height. Calibration curves for each compound in the appropriate solution were prepared to determine the proportionality between peak area and concentration in the concentration range encountered in these experiments. The preparative column used was $^3/_8$ inch by 10 ft stainless steel containing 20% FFAP (free fatty acid phase of Carbowax) on 60–80 mesh Chromosorb W, acid washed and treated with DMCS (dimethyldichlorosilane). The analytical column used was $^1/_4$ inch by 10 ft aluminum containing 15% FFAP on 60–80 mesh Chromosorb W.

D-(+)-1-*p*-Menthene (16).—Redistilled D-(+)-limonene (**26**, Eastman White Label) was selectively catalytically reduced by the method of Newhall[19] with the uptake of 1 mol of hydrogen. The product was vacuum fractionated through a 100-mm Vigreux column to give **16** (91%) as a colorless liquid, bp 66–67° (1 mm), $n^{20}D$ 1.4566 (lit.[20] $n^{20}D$ 1.4570), $[\alpha]^{24}D$ +100.2° (*c* 9) (lit.[19,20] $[\alpha]^{23}D$ +95.8°, $[\alpha]^{25}D$ +109°).

Selenium Dioxide Oxidation of D-(+)-1-*p*-Menthene (16) in Wet Dioxane.—A solution of selenious acid made by warming 0.740 g (6.6 mmol) of Fairmount selenium dioxide in 0.5 ml of water and 10.0 ml of dioxane, purified by the method of Vogel,[21] was added dropwise over a 3-hr period to a magnetically stirred, refluxing solution of 7.4 g (53 mmol) of **16** in 10.0 ml of purified dioxane. It was determined in separate experiments that Fairmount selenium dioxide could be used without further purification as it gave identical results with those obtained with freshly sublimed material prepared by the oxidation of selenium metal with hot concentrated nitric acid by the method of Baker and Maxson.[22] On addition of the selenious acid, the solution rapidly yellowed and the color then intensified to orange and then red as selenium precipitated during the subsequent 12–20-hr period of refluxing. Glpc analysis showed 83.7 ± 1.1% of recovered **16** in addition to four oxidation products (*t* 142°), peak 1 (1.5%, R_t 9.0 min), peak 2 (7.7%, R_t 10.5 min), peak 3 (3.3%, R_t 13.2 min), and peak 4 (3.8%, R_t 21.9 min). The crude product was vacuum distilled through a 100-mm Claisen column to yield fraction 1, bp <25° (1–2 mm), consisting of dioxane, water, and some unreacted **16**, fraction 2, bp 37–88° (1 mm), consisting of unreacted **16** and its volatile oxidation products, and a residue consisting of selenium and organoselenium compounds. It was necessary to do this crude distillation to avoid contamination of the preparative glpc column by noneluting organoselenium by-products. The glpc peak ratios on both crude and distilled products agreed, indicating lack of decomposition or isomerization during distillation.

Peak 1 was D-(+)-carvotanacetone (**55**), identified by glpc peak enhancement and ir comparison with an authentic sample prepared by selective hydrogenation of Aldrich glpc unipeak D-(+)-carvone (**56**) over 5% Pt on carbon and having physical and spectral properties in agreement with those of **55** reported by Hallsworth.[23] If the oxidation was carried out at increasingly higher selenium dioxide/olefin ratios, peak 1 became correspondingly larger with concomitant disappearance of both peaks 2 and 3. Thus, at an olefin/selenium dioxide ratio of 3:2, peaks 2 and 3 were absent; peak 1 from a reaction with this stoichiometry was glpc collected and showed $[\alpha]^{24}D$ +37.6° (c 1.6) (lit.[23,24] $[\alpha]^{25}D$ +55.2°, $[\alpha]^{25}D$ +49.5°). Its physical and spectral properties were identical with those of authentic **55**.

Peak 2 was D-(+)-*trans*-carvotanacetol (**19**), $n^{20}D$ 1.4779 (lit.[20] $n^{20}D$ 1.4777), $[\alpha]^{25}D$ +97.8° (*c* 2) (lit.[25] $[\alpha]^{20}D$ +169.1°). Its ir[26] and nmr[27] spectra agreed with literature reports and its α-naphthylurethan had mp 129–130° which was not depressed upon admixture of a sample with that prepared from authentic **19** made by the method of Schroeter.[25]

Peak 3 was D-(+)-*cis*-carvotanacetol (**24**), $n^{20}D$ 1.4805 (lit.[25] $n^{20}D$ 1.4817), $[\alpha]^{25}D$ +32.2° (*c* 5) (lit.[23] $[\alpha]D$ +56.5°). Its ir[26] and nmr[27] spectra agreed with reported spectra and its α-naphthylurethan had mp 122.5–123.5° which was not depressed upon admixture of a sample with that prepared from authentic **24** made by the method of Schroeter.[25]

Peak 4 was D-(+)-phellandrol (**25**), $n^{20}D$ 1.4810 (lit.[28] $n^{20}D$ 1.4826), $[\alpha]^{25}D$ +76.8° (*c* 5) {lit.[29] $[\alpha]^{20}D$ +102.8° (neat)}. Its ir spectrum agreed with that reported by Mitzner;[26] its nmr ($CDCl_3$) spectrum consisted of δ 5.53 (broad s, 1, C=CH), 3.80 (s, 2, CH_2OH), 3.07 (s, 1, OH), 1.17–2.40 (broad band, 8, CH, CH_2), and 0.85 [d, 6, $CH(CH_3)_2$]. Its phenylurethan had mp 76–77° (lit.[28] mp 79°) and its α-naphthylurethan had mp 65–67° (lit.[28] mp 69.5°).

Selenium Dioxide Oxidation of D-(+)-*trans*-Carvotanacetol (19) and of D-(+)-*cis*-Carvotanacetol (24).—A solution of 0.2 g (1.8 mmol) of selenium dioxide in 0.2 ml of water and 10.0 ml of dioxane was added to a solution of 1.0 g (6.7 mmol) of an equimolar mixture of **19** and **24** in 5.0 ml of dioxane. The solution rapidly yellowed and the color intensified to orange and then red as selenium precipitated during the 1-hr period of refluxing. Glpc analysis of the crude product (*t* 142°) showed the presence of D-(+)-carvotanacetone (**55**) and of **19** but of very little **24** as determined by peak enhancement with authentic samples.

Selenium Dioxide Oxidation of D-(+)-1-*p*-Menthene (16) in Acetic Acid–Acetic Anhydride.—A solution of 23 g (0.17 mol) of **16** in 50:50 (v/v) acetic acid–acetic anhydride was oxidized with 13.9 g (0.125 mol) of selenium dioxide at room temperature for 10 hr. The reaction was quite exothermic and required cooling in an ice bath. The crude product was filtered several times

(19) W. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).
(20) R. L. Kenney and G. S. Fisher, *ibid.*, **28**, 3509 (1963).
(21) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 177.
(22) R. H. Baker and R. N. Maxson, *Inorg. Syn.*, **1**, 119 (1939).
(23) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(24) C. Harries, *Chem. Ber.*, **34**, 1924 (1901).
(25) S. Schroeter, *Ann.*, **674**, 118 (1964).
(26) B. M. Mitzner, V. J. Mancini, S. Lemberg, and E. T. Theimer, *Appl. Spectrosc.*, **22**, 34 (1968).
(27) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, **30**, 1 (1965).
(28) J. P. E. Human, A. K. Macbeth, and H. J. Rodda, *J. Chem. Soc.*, 350 (1949).
(29) F. Porsch, *Dragoco Report*, 59 (1964); *Chem. Abstr.*, **61**, 16099d (1964).

through Celite until clear and the filtrate, diluted with ether, was washed with water until the washings were neutral. The ethereal solution was then dried (sodium sulfate), filtered, and rotary evaporated to an oil which was vacuum fractionated to afford 3.65 g (15%) of a mixture of carvotanacetol acetates, bp 79–81° (5 mm), $[\alpha]^{25}D$ 0.0°.

Selenium Dioxide Oxidation of D-(+)-1-*p*-Menthene (16) in Wet Dioxane in the Presence of Acrylonitrile.—To a solution of 10 g (0.070 mol) of **16** in 80 ml of purified dioxane maintained under an atmosphere of nitrogen was added 2.0 ml (0.03 mol) of acrylonitrile [Eastman practical grade freshly distilled (bp 75–76°) just prior to use to remove inhibitor]. Both the dioxane and **16** were peroxide free as determined by negative test with acidified potassium iodide. To the solution of **16** was added dropwise a solution of 8.0 g (0.07 mol) of selenium dioxide in 200 ml of purified dioxane containing 5.0 ml of distilled water. The reaction was maintained under nitrogen at ambient temperature for several days. Under these conditions, **16** was oxidized to a mixture of *cis*- and *trans*-carvotanacetols, phellandrol, and carvotanacetone (*vide supra*) but no polyacrylonitrile precipitated. It was determined in control experiments that polyacrylonitrile is highly insoluble in this medium and would have been readily discernible had initiation of polymerization occurred. It was further established that acrylonitrile polymerizes rapidly under the same reaction conditions if a source of free radicals in introduced. Indeed, a solution of 2.0 ml of freshly distilled acrylonitrile in 280 ml of purified dioxane maintained under a nitrogen atmosphere at 40° gave an immediate precipitate when successively treated with 0.3 g of potassium persulfate in 10 ml of aqueous dioxane and 0.15 g of sodium bisulfite in 10 ml of aqueous dioxane.

Registry No.—Selenium dioxide, 7446-08-4; **16**, 1195-31-9; **21**, 23713-54-4; **26**, 23713-55-5; **30**, 23713-56-6; **34**, 23713-57-7; **39**, 23713-58-8; **44**, 2001-50-5.

Acknowledgment.—Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research.

Micellar Effects on the Hydrolysis of 2,4-Dinitrophenyl Sulfate[1]

E. J. FENDLER, R. R. LIECHTI, AND J. H. FENDLER

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, and Radiation Research Laboratories, Mellon Institute, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received November 3, 1969

Hexadecyltrimethylammonium bromide (CTAB) and poly(oxyethylene)(24)dinonylphenol (DNPE) enhance the rate of neutral hydrolysis of 2,4-dinitrophenyl sulfate by factors of 3.2 and 2.6, respectively, but sodium dodecyl sulfate (NaLS) has no effect on the rate. The rate enhancement arises from a decrease in both the enthalpy and entropy of activation. From the kinetic data at 25.00°, the binding constant between CTAB and 2,4-dinitrophenyl sulfate is calculated to be 1.9×10^5 l. mol^{-1}. The effects of these surfactants on the acid- and base-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate are less specific; both charged and uncharged micelles enhance the rate of the acid-catalyzed reaction, while the base-catalyzed rate is only affected by DNPE. The retardation of the base-catalyzed hydrolysis by DNPE is a manifestation of an increase in both the enthalpy and entropy of activation with respect to the base-catalyzed hydrolysis in the absence of surfactant. Micellar effects on the hydrolyses of sulfate esters are compared with those on aryl phosphates and are discussed in terms of electrostatic and hydrophobic interactions.

The recent vigorous interest in micellar effects on reaction rates has been stimulated by the recognized analogies between protein and micelle structures and between enzymatic and micellar catalysis.[2] The influence of surfactants on the hydrolysis of aryl phosphates has been shown to be specific. Hexadecyltrimethylammonium bromide (CTAB) increases the rate constants for the dianion hydrolysis of 2,4- and 2,6-dinitrophenyl phosphate by a factor of 25 but does not affect the hydroxide ion catalyzed reaction of the dianion or the hydrolysis of the monoanion of *p*-nitrophenyl phosphate, whereas sodium dodecyl sulfate (NaLS) and poly(oxyethylene)(24)dinonylphenol (Igepal DM-730), a nonionic amphiphile, do not significantly alter the rates of hydrolysis of dinitrophenyl phosphate dianions.[3] Since a number of analogies can be made between the mechanisms for the hydrolyses of sulfate[4] and phosphate esters and since both reactions are of vital importance in biochemical processes, we have undertaken a study of micellar effects on the neutral, acid-catalyzed, and base-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate in order to compare these two systems and to elucidate the nature of micellar catalysis.

Experimental Section

The preparation and purification of 2,4-dinitrophenyl sulfate has been described.[4] Hexadecyltrimethylammonium bromide (CTAB) and sodium dodecyl sulfate (NaLS) were purified by the method of Duynstee and Grunwald.[5] Poly(oxyethylene)(24)dinonylphenol (Igepal DM-730, General Aniline and Film Corp.) was used without further purification[6] and is denoted as DNPE in the text. Deionized distilled water was used for the preparation of the buffer, the surfactant, and the standard acid and alkali solutions. The pH of the buffer solutions was adjusted by the addition of hydrochloric acid or sodium hydroxide at 25.0° using an Orion Model 801 pH meter. The concentrations of the acid solutions were determined by titration with standard 0.100 or 1.00 *M* NaOH (BDH) using Lacmoid as the indicator. The alkali solutions were prepared from the 1.00 *M* NaOH standard by dilution.

The hydrolysis was followed spectrophotometrically on a Beckman DU-2 by measuring the absorbance of the phenoxide ion (360 nm) or the phenol (320 nm).[4] The temperature of the thermostated baths and the cell compartment was maintained within ±0.05°, as monitored by NBS thermometers. Good first-order plots were obtained in all cases for at least 75% reaction. The pseudo-first-order rate constants, k_ψ, for the hydrolysis of 2,4-dinitrophenyl sulfate have been calculated by the Guggenheim method.[7]

(1) Supported, in part, by the Health Research Services Foundation, and by the U. S. Atomic Energy Commission.

(2) For a comprehensive review of micellar effects on reaction rates, see E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(3) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K.-U. Yang, *J. Amer. Chem. Soc.*, **90**, 5512 (1968).

(4) E. J. Fendler and J. H. Fendler, *J. Org. Chem.*, **32**, 3852 (1968).

(5) E. F. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540 (1959).

(6) We are greatly indebted to Dr. L. W. Burnette of the General Aniline and Film Corp. for providing us with samples of nonionic surfactants.

(7) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

Results

The observed pseudo-first-order rate constants, k_ψ, for the hydrolysis of 2,4-dinitrophenyl sulfate at pH 8.0 in the presence of a cationic (CTAB), an anionic (NaLS), and an uncharged (Igepal DM-730, DNPE) amphiphile are collected in Table I. Sodium dodecyl sulfate has no effect on the neutral hydrolysis of the substrate, but both hexadecyltrimethylammonium bromide and poly(oxyethylene)(24)dinonylphenol enhance the rate above their critical micelle concentrations (Figure 1). The following critical micelle concentrations are used in the present work: 7.8×10^{-4} M for CTAB in 2.5×10^{-3} M disodium tetraborate buffer, 8.1×10^{-3} M for NaLS, and 4.7×10^{-4} M for Igepal DM-730.[2] The concentrations of 2,4-dinitrophenyl sulfate are $1\text{–}6 \times 10^{-5}$ M and in this concentration range the observed rate constants are invariant, within the limits of experimental error, as a function of substrate concentration. The rate constants for micellar catalysis, obtained in the absence of buffers, agree well with those obtained in their presence; 2.5×10^{-3} M sodium tetraborate has no influence, therefore, on the micellar catalysis under these conditions.

TABLE I

HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE IN AQUEOUS MICELLAR SOLUTIONS AT pH 8.00[a]

	$10^5 k_\psi$, sec^{-1}		
$10^3 c_D$ M	CTAB	NaLS	DNPE
0.000		2.71[b]	
0.500			3.82
0.750			4.83
0.925	4.40		
0.950	4.52		
1.00	6.12		4.20
1.05	5.30		
1.10	5.45		
1.25	5.82		
1.50	6.61		5.45
1.75	5.95		
1.75	7.31		
2.00	6.75		
2.25	7.52		
3.00	6.95		
5.00	8.26	2.80	6.28
5.00	8.23[c]		
6.00	8.30		
6.00	3.34[d]		
6.00	23.1[e]		
8.00	8.70		6.80
10.0	8.43		6.85
10.0			19.6[e]
10.0			45.7[f]
14.0			6.90
15.0			6.72
20.0	8.65		7.30
20.0			6.40
30.0	8.65		6.50
30.0			7.20
50.0		2.75	

[a] In the presence of 2.5×10^{-3} M $Na_2B_4O_7$ buffer at 25.00°, unless specified otherwise. [b] $k_0 = 2.71 \times 10^{-5}$ sec^{-1}. [c] In the absence of buffer. [d] At 15.00°. [e] At 35.10. [f] At 46.50°.

Micellar effects on the acid- and on the base-catalyzed hydrolyses are summarized in Tables II and III, respectively.

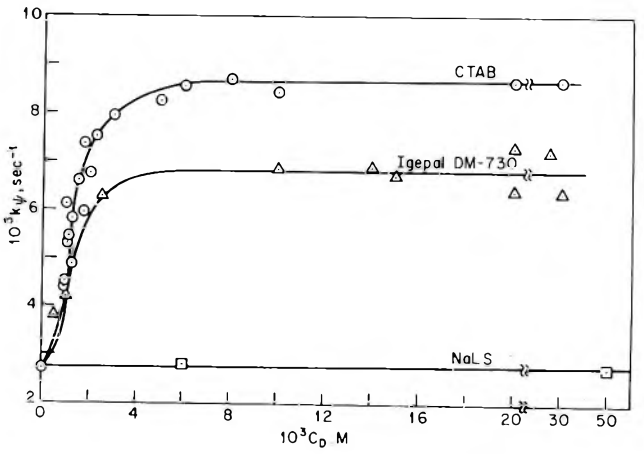


Figure 1.—Plot of the observed pseudo-first-order rate constant, k_ψ, against the surfactant concentration, c_D, for the hydrolysis of 2,4-dinitrophenyl sulfate at pH 8.00 and 25.00°.

TABLE II

MICELLAR EFFECTS ON THE ACID-CATALYZED HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE AT 25.00°

[HCl], M	Surfactant	$10^5 k_\psi$, sec^{-1}	$10^5 k_a$, M^{-1} sec^{-1} [a]
0.10	None	5.09	23.8
1.00	None	12.57	9.86
0.10	5×10^{-3} M CTAB	11.50	32.4
1.00	5×10^{-3} M CTAB	23.03	14.77
0.10	5×10^{-2} M NaLS	6.05	33.0
1.00	5×10^{-2} M NaLS	15.00	12.25
0.01	1×10^{-2} M DNPE	12.26	54.1

[a] $k_a = (k_\psi - k_n)/[HCl]$, where k_n is the observed rate constant for the neutral hydrolysis.

TABLE III

MICELLAR EFFECTS ON THE HYDROXIDE ION CATALYZED HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE AT 25.00°

Surfactant	$10^4 k_b$, M^{-1} sec^{-1} [a]
None	4.48
5.0×10^{-3} CTAB	5.9
5.0×10^{-2} NaLS	4.7
1.0×10^{-2} DNPE	1.65

[a] k_b = slope of plots of k_ψ *vs.* [NaOH] (containing at least four points) in the 0.1–0.4 M NaOH concentration range.

The Arrhenius parameters determined for the neutral and the alkaline hydrolyses of 2,4-dinitrophenyl sulfate in the presence and in the absence of surfactants are collected in Table IV. Allowing an overall 5% error in the individual rate constants, at the temperature interval used, the statistical error for the activation

TABLE IV

ARRHENIUS PARAMETERS FOR THE HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE IN THE PRESENCE OF SURFACTANTS[a]

Surfactant	$\Delta H^\pm$, kcal/mol	$\Delta S^\pm$, eu[b]
None	18.2	−18.0[c]
6.00×10^{-3} M CTAB	16.0	−23.3
1.00×10^{-2} M DNPE	16.3	−22.7
None[d]	17.3	−15.0
1.00×10^{-2} M DNPE[d]	19.7	−9.74

[a] Neutral hydrolysis, at pH 8.00, unless specified otherwise. [b] Calculated at 25.0°. [c] Data determined previously and given in ref 4. [d] Base-catalyzed hydrolysis; calculated from the second-order rate constants, k_b, at three temperatures.

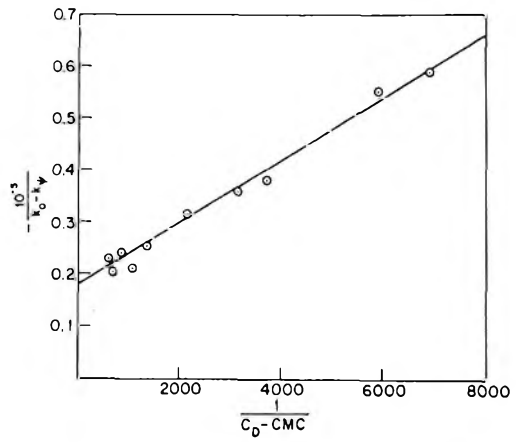


Figure 2.—Plot of $1/(k_0 - k_\psi)$ *vs.* $1/(c_D - \text{cmc})$ for the interaction of CTAB with 2,4-dinitrophenyl sulfate at pH 8.00 and 25.00°.

enthalpy is ±0.8 kcal/mol and that for the activation entropy is ±2.0 eu.[8]

Discussion

Neutral Hydrolysis.—At concentrations greater than their critical micelle concentrations both CTAB and DNPE enhance the rate of the neutral hydrolysis of 2,4-dinitrophenyl sulfate. The rate constants first increase rapidly as a function of surfactant concentration and then reach a value which remains constant over a wide range of surfactant concentration (Figure 1). Similar behavior has been observed in the CTAB-catalyzed hydrolysis of the dianions of 2,4- and 2,6-dinitrophenyl phosphates,[3] although the magnitude of the rate enhancement ($k_\psi/k_0 \cong 25$ for CTAB) is considerably greater than that observed for the micellar effects on the neutral hydrolysis of 2,4-dinitrophenyl sulfate ($k_\psi/k_0 = 3.2$ for CTAB and 2.6 for DNPE).

By making a number of assumptions and simplifications,[9] the kinetic form of micellar catalysis has been successfully treated[2,3,10-14] in terms of micelle–substrate complex formation and reaction in the aqueous and micellar phase (eq 1), where k_0 and k_m are the rate

$$\begin{array}{ccc} \text{M} + \text{S} & \overset{K}{\rightleftharpoons} & \text{MS} \\ & \downarrow{\scriptstyle k_0} \quad \downarrow{\scriptstyle k_m} & \\ & \text{P} \quad \text{P} & \end{array} \qquad (1)$$

constants for product formation in the bulk solvent and in the micellar phase, respectively, and K is the micelle–substrate binding constant. The observed rate constant, k_ψ, for product formation is given[2,3,10-14] by eq 2. The kinetic behavior for the micelle-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate obeys, at least qualitatively, eq 2 in that k_ψ increases to a constant value

$$k_\psi = \frac{k_0 + k_m K[\text{M}]}{1 + K[\text{M}]} \qquad (2)$$

which represents conditions when $K[\text{M}] \gg 1$ and $k_m K[\text{M}] \gg k_0$ and the observed rate constant in this plateau region (Figure 1) is due entirely to the reaction in the micellar phase, *i.e.*, $k_\psi = k_m$. Equation 2 can be rearranged to give eq 3,[2,3,10-14] using the relationship of

$$\frac{1}{k_0 - k_\psi} = \frac{1}{k_0 - k_m} + \left(\frac{1}{k_0 - k_m}\right)\left(\frac{1}{c_D - \text{cmc}}\right)\frac{N}{K} \qquad (3)$$

eq 4, where c_D is the total concentration of the surfactant, cmc is the critical micelle concentration, and N is the aggregation number. A plot of the left-hand side of eq 3 *vs.* $1/(c_D - \text{cmc})$ should result in a straight line, from which k_m and K/N can be calculated. As expected, such a plot for the CTAB-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate at pH 8.0 is linear (Figure 2). From the intercept, k_m is calculated to be 8.12×10^{-5} sec^{-1}, a value which is in good agreement with the observed rate constant in the plateau region (Figure 1). Assuming an aggregation number of 61 for CTAB,[2,15] the binding constant, K, for hexadecyltrimethylammonium bromide and 2,4-dinitrophenyl sulfate at pH 8.0 and 25.0° is calculated to be 1.9×10^5 l. mol^{-1}. Since this catalysis by CTAB is relatively small in magnitude and is observed at low surfactant concentrations, the value of K obtained using eq 3 is very sensitive to the actual value used for the cmc. A modified form of eq 3, eq 5, has been suggested to circumvent this problem.[16] A plot of the left-hand side of eq 5 *vs.* c_D

$$\frac{k_\psi - k_0}{k_m - k_\psi} = \frac{K}{N}(c_D - \text{cmc}) \qquad (4)$$

$$[\text{M}] = \frac{c_D - \text{cmc}}{N} \qquad (5)$$

does not involve the cmc and should give a straight line whose slope is K/N. A good straight line is obtained by plotting the data given in Table I according to eq 5 and gives a value of 1.6×10^5 l. mol^{-1} for K (once again assuming N to be 61). The reasonable agreement between the K values obtained from eq 3 and 5 justifies, at least partially, the approximations used in the derivation of eq 2.[2,9] From the intercept of the straight line obtained by using eq 5, a value of 3.6×10^{-4} M is obtained for the cmc of CTAB. This cmc value is somewhat lower than that determined by others and used in eq 3 (7.8×10^{-4} M).[2,3] The lower cmc value determined kinetically can reasonably be attributed to 2,4-dinitrophenyl sulfate induced micellization of the surfactant and hence a decrease in the cmc.[2,17,18] Similarly, the cmc values obtained, by use of eq 5, for phenyl and 2,4-dimethoxyphenyl hexadecyldimethylammonium bromide in the presence of 2,4-dinitrophenyl phosphate were lower than those obtained in the absence of the phosphate ester.[16]

Since the magnitude of the binding constant for 2,4-dinitrophenyl sulfate and CTAB ($K \cong 1.9 \times 10^5$ l. mol^{-1}) is similar to that found for 2,4-dinitrophenyl phosphate and CTAB (1.1×10^5 l. mol^{-1}),[3] the greater rate enhancement in the case of phosphate dianion

(8) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(9) A. K. Colter, S. S. Wang, G. H. Megerle, and P. S. Ossip, *J. Amer. Chem. Soc.*, **86**, 3106 (1964).
(10) F. M. Menger and C. E. Portnoy, *ibid.*, **89**, 4698 (1967).
(11) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *ibid.*, **90**, 1333 (1968).
(12) C. A. Bunton and L. Robinson, *ibid.*, **90**, 5972 (1968).
(13) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).
(14) C. A. Bunton and L. Robinson, *ibid.*, **34**, 780 (1969).
(15) E. W. Anacker, R. M. Rush, and J. S. Johnson, *J. Phys. Chem.*, **68**, 81 (1964).
(16) C. A. Bunton, L. Robinson, and L. Sepulveda, *J. Org. Chem.*, **35**, 108 (1970).
(17) P. Mukerjee and K. J. Mysels, *J. Amer. Chem. Soc.*, **77**, 2937 (1955).
(18) P. H. Elworthy, A. T. Florence, and C. B. Macfarlane, "Solubilization by Surface Active Agents and Its Applications in Chemistry and the Biological Sciences," Chapman and Hall, London, 1968.

hydrolysis compared with that for the corresponding sulfate is a manifestation of the higher reactivity of the former in the micellar phase (eq 2).

The acceleration of the rate of the neutral hydrolysis of 2,4-dinitrophenyl sulfate by cationic and nonionic micelles arises from a decrease in both the enthalpy and the entropy of activation (Table IV). In contrast, the catalysis of the dinitrophenyl phosphate dianion hydrolyses by CTAB results almost exclusively from a decrease in the activation energy.

The substrate specificity of the micellar effects are further emphasized by the observed rate enhancement on the neutral hydrolysis of 2,4-dinitrophenyl sulfate by the nonionic surfactant. A straight line is obtained by plotting the data (Table I) for the DNPE-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate at pH 8.0 according to eq 5, from the slope of which we calculate K/N to be $1.3 \times 10^3\ M^{-1}$. Since the aggregation number for this amphiphile is unavailable, a direct comparison of the binding constants for the cationic and the nonionic surfactant cannot be made; however, the values of K/N for CTAB (3.1×10^3) and DNPE ($1.3 \times 10^3\ M^{-1}$) suggest that 2,4-dinitrophenyl sulfate binds appreciably to the nonionic surfactant irrespective of the exact value of N.

Acid-Catalyzed Hydrolysis.—The rate-determining step in the acid-catalyzed hydrolysis of aryl sulfates probably involves unimolecular fission of a rapidly formed zwitterion;[4,19] however, acids, in addition to their proton-donating power, exert specific electrolyte effects on both the initial and the transition states of these hydrolyses.[4]

Both charged and uncharged micelles enhance the rate of the acid-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate, the order of effectiveness being DNPE > CTAB ~ NaLS (Table II). The absence of appreciable catalytic specificity in this reaction is obviously uninterpretable solely on the basis of electrostatic effects and indicates the importance of nonelectrostatic factors, such as hydrophobic interactions, and activity coefficient effects in the micellar catalysis of the acidic hydrolysis. Supporting this postulation is the observation of a significant rate acceleration ($k_\psi/k_0 = 20$) by nonionic poly(oxyethylene)(20)sorbitan monooleate (Polysorbate 80)[20] in the acid-catalyzed hydrolysis of 2,4-dichloronaphthyl sulfate.

Base-Catalyzed Hydrolysis.—The base-catalyzed hydrolysis of sulfate esters is somewhat complex, since this hydrolytic reaction can involve attack of hydroxide ion on both carbon and sulfur.[4] The observed rate constants may, of course, represent composites of those for these two reaction paths. Neither cationic CTAB nor anionic NaLS influences the base-catalyzed hydrolysis of 2,4-dinitrophenyl sulfate, but nonionic DNPE retards it (Table III). The rate inhibition by the nonionic surfactant is a manifestation of an increase in both the enthalpy and the entropy of activation with respect to the base-catalyzed hydrolysis in the absence of the surfactant (Table IV). The influence of an unchanged surfactant on the base-catalyzed hydrolysis, once again, points strongly to the fact that effects, in addition to those of electrostatic origin, need to be considered in micellar catalysis.

Nature of the Micellar Catalysis.—Micellar catalysis of the hydrolysis of aryl phosphates has been observed only in cases which involve unimolecular phosphorus–oxygen fission in the rate-determining step. Furthermore, catalyst specificity is apparent, since cationic micelles generally accelerate these hydrolyses whereas anionic and nonionic ones either retard them or have little effect.[2] In these cases the observed catalysis is explicable in terms of relatively simple electrostatic considerations; however, other factors undoubtedly contribute to the catalysis. Conversely, the effects of surfactants on the hydrolyses of aryl sulfates are comparatively much smaller in magnitude and less specific than those for the corresponding aryl phosphates, and nonelectrostatic factors appear to play a significant role in the micellar catalyses.

Registry No.—2,4-Dinitrophenyl sulfate, 17396-93-9; CTAB, 57-09-0.

(19) J. L. Kice and J. M. Anderson, *J. Amer. Chem. Soc.*, **38**, 5242 (1966).

(20) T. H. Baxter and H. B. Kostenbauder, *J. Pharm. Sci.*, **58**, 33 (1969).

Notes

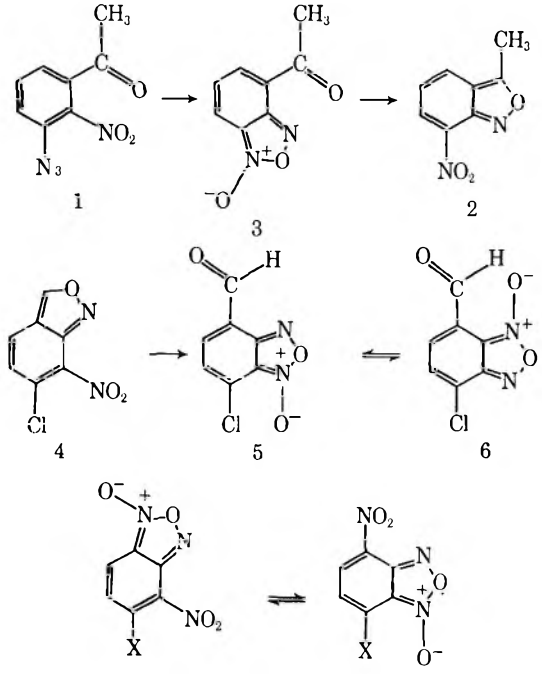
Heterocyclic Rearrangements. XII.[1] The Formation of a Formylbenzofurazan Oxide from a Nitroanthranil

A. J. Boulton and R. C. Brown

School of Chemical Sciences, The University of East Anglia, Norwich, Norfolk, NOR 88C, England

Received August 13, 1969

A few years ago a new anthranil synthesis was reported, in the decomposition of the nitroazidoacetophenone (**1**) to form 3-methyl-7-nitroanthranil (**2**), *via* the presumed intermediate acetylbenzofurazan oxide (**3**).[2]



We now find that nitration of 6-chloroanthranil leads to its 7-nitro derivative **4**, which rearranges on heating to 7-chloro-4-formylbenzofurazan oxide (**5**). The nmr spectrum of **4** (in acetone) shows, as expected, an AB system (τ_A 1.80, τ_B 2.63, J_{AB} = 9.5 Hz) and a singlet (τ −0.02). Compound **5**, on the other hand, gives at room temperature a very broad, indistinct spectrum, owing to the tautomerism of the furazan oxide ring, which places the formyl and ring protons in rapidly changing environments. On cooling to 0°, **5** shows two distinct AB spectra (τ_A 1.77, τ_B 2.31, J_{AB} = 8.0 Hz; $\tau_{A'}$ 2.01, $\tau_{B'}$ 2.12, $J_{A'B'}$ = 7.0 Hz) and two singlets from the aldehyde groups (τ −0.30; τ' −0.50), while at 80° one AB and a singlet are observed. The ratio of tautomers (**5**:**6**) was *ca.* 3:4 at 0°, the assignment of spectra to isomers (primed symbols refer to structure **6**) being made on the basis of the chemical shifts of the formyl protons (that in **6** is expected to be deshielded owing to the proximity of the N-oxide group) and of the aromatic protons.[3]

The rearrangement of nitrobenzofurazan oxides (**7** ⇌ **8**) has been described, and the apparent completeness of the conversion of **7** (X = Cl) into **8** (X = Cl) was suggested to be due to steric inhibition of resonance of the nitro group with the ring in **7**.[4,5] The present work establishes the first example of a benzofurazan oxide being formed by a rearrangement of this type from a system other than another benzofurazan oxide; probably steric inhibition again provides the energy to drive the rearrangement in the unexpected direction.

Experimental Section

Melting points are uncorrected. Nmr spectra of acetone solutions were measured on a Perkin-Elmer R10 60-MHz instrument with a variable-temperature probe.

6-Chloro-7-nitroanthranil (**4**).—6-Chloroanthranil[6] (1.0 g, 0.065 mol), mp 64° (lit.[6] mp 65°), was carefully dissolved in 10 cc of cold (0°), concentrated sulfuric acid. To the stirred solution at −5° was added dropwise a solution of potassium nitrate (0.9 g, 0.1 mol) in 20 cc of H_2SO_4. The mixture was stirred at 0° for ½ hr, then at 50° for a further 0.5 hr. The red solution was poured onto ice and extracted with methylene chloride. The organic layer was washed with water, dilute Na_2CO_3 solution, and again with water and then dried (Na_2SO_4). Removal of the solvent left a dark orange solid which was carefully crystallized from ethanol as orange plates (0.5 g, 40%): mp 96–97°; ir (Nujol) 1642 (anthranil), 1530, and 1350 cm^{-1} (NO_2).

Anal. Calcd for $C_7H_3ClN_2O_3$: C, 42.3; H, 1.5. Found: C, 42.0; H, 1.5.

7-Chloro-4-formylbenzofurazan Oxide (**5** ⇌ **6**).—6-Chloro-7-nitroanthranil (0.9 g) was heated 30 min under reflux in 20 ml of glacial acetic acid. The solution was cooled, and an equal volume of water was added. The precipitated solid was crystallized from aqueous ethanol as yellow prisms (0.7 g, 77%): mp 103–104°; ir (Nujol) 1692 (C=O), 1618, 1580, 1545, and 1490 cm^{-1} (benzofurazan oxide).[7]

Anal. Found: C, 42.5; H, 1.2.

Registry No.—**4**, 22950-43-2; **5**, 22950-44-3.

(1) Part XI: A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *Chem. Commun.*, 62 (1968).

(2) A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc., B*, 1011 (1966).

(3) R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 197 (1963).

(4) A. J. Boulton and A. R. Katritzky, *Rev. Chim.* (Acad. R. P. Roumaine), **7**, 691 (1962).

(5) P. B. Ghosh, *J. Chem. Soc., B*, 334 (1968).

(6) Altaf-ur-Rahman and A. J. Boulton, *Tetrahedron Suppl.*, **7**, 49 (1966).

(7) J. H. Boyer, D. I. McCane, W. J. McCarville, and A. T. Tweedie, *J. Amer. Chem. Soc.*, **75**, 5290 (1953).

Reaction of Substituted 2-Carbethoxyacetylaminopyridines and Similar Compounds with Triethyl Orthoformate and Zinc Chloride

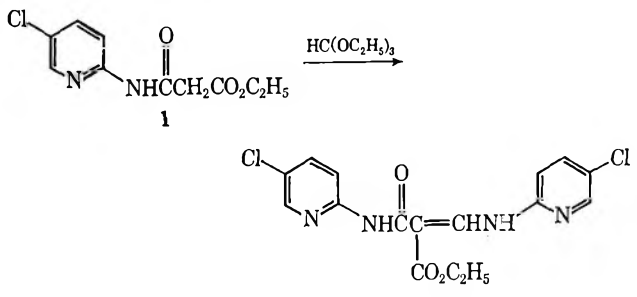
Michael C. Seidel, Glenn C. Van Tuyle, and W. David Weir

Rohm and Haas Company, Spring House, Pennsylvania 19477

Received April 2, 1969

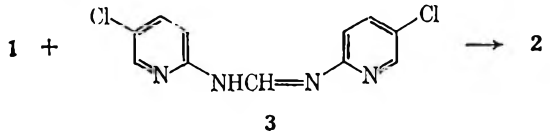
In an attempt to prepare the ethoxymethylene derivative of 2-(carbethoxyacetylamino)-5-chloropyr-

idine (1) by reaction of 1 with triethyl orthoformate, acetic anhydride, and zinc chloride, the expected product was not obtained. Instead, when the reaction mixture was cooled, a crystalline product formed which was assigned structure 2 on the basis of elemental analysis, spectral data, and a molecular weight determination.

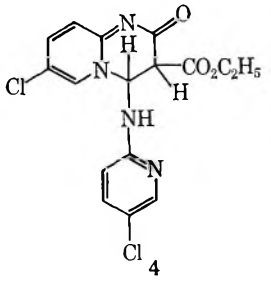


The yield of 2 was 24%, and it could be raised to 41% by conducting the reaction in ethanol instead of acetic anhydride. This result is unusual, since we have found that carbethoxyacetylanilines normally give good yields of ethoxymethylene derivatives.

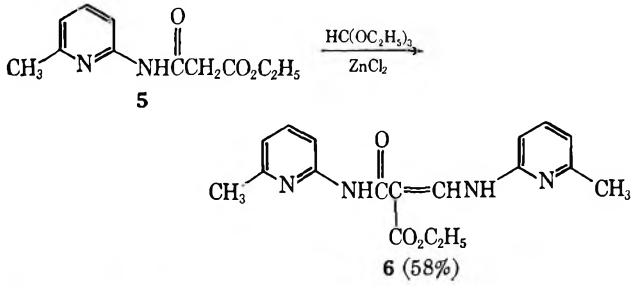
It is known that formamidines derived from aromatic amines react with acidic methylene groups to form compounds such as 2,[1] and this method was used to synthesize 2 independently. The formamidine 3 was prepared by heating 2-amino-5-chloropyridine with triethyl orthoformate, and reaction of 3 with 1 in boiling diglyme gave 2 in 24% yield.



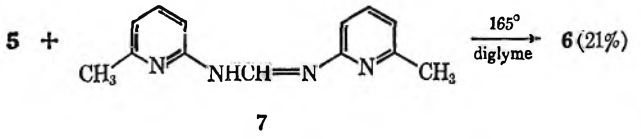
To examine the possibility that 2 possessed a cyclic structure such as 4, the 6-methyl derivative 6, in which



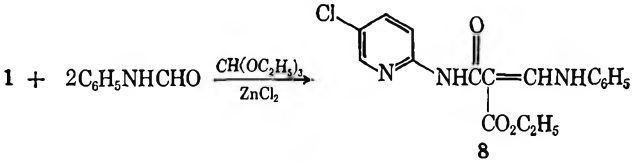
cyclization is very unlikely, was made in the two ways indicated below; the spectral properties of 2 and 6 are very similar and indicate the same structural type.



(1) F. B. Dains, *Ber. Deut. Chem. Ges.*, **35**, 2496 (1902).

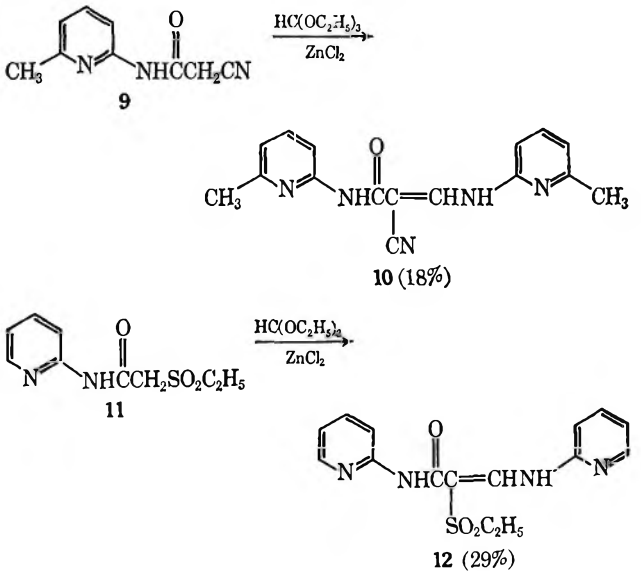


To ascertain whether a simple anilide can replace the second mole of 1 in the production of compounds of type 2, the reaction was run in the presence of a 2 molar excess of formanilide. The product 8 was



obtained in higher yield (58%) than 2 in the original reaction. No traces of 2 were found. In none of these reactions could a simple ethoxymethylene derivative be isolated.

The reaction of triethyl orthoformate and zinc chloride with the cyanoacetyl derivative 9 and the ethylsulfonylacetyl derivative 11 gave the analogous products 10 and 12 in the yields indicated.



Mechanism.—The first step of the reaction is probably the same as in normal preparations of ethoxymethylene derivatives of active methylene compounds.

The favorable steric arrangement of the pyridine nitrogen in 13 could make the ethoxy group labile,

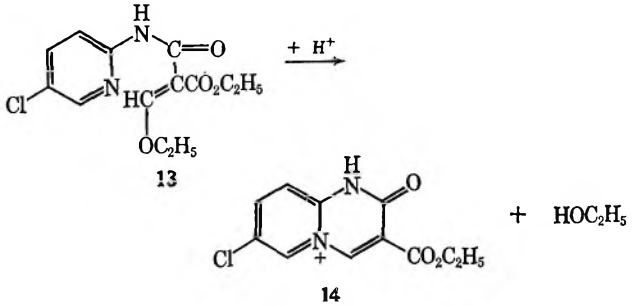


TABLE I

CARBETHOXYACETYL, CYANOACETYL, AND SULFONYLACETYL DERIVATIVES OF 2-AMINOPYRIDINES, 2-PYRIDYLFORMAMIDINES

Compound	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	$C_{10}H_{11}ClN_2O_3$[a]	38	108.5–110	49.48	4.57	11.55	49.22	4.80	11.73
5	$C_{11}H_{14}N_2O_3$[a]	41	87–89	59.46	6.35	12.61	59.28	6.10	12.64
9	$C_9H_9N_3O$[a]	16	97.5–99.5	61.70	5.18	23.99	61.71	5.00	24.24
11	$C_9H_{12}N_2O_3S$	30	110–112	47.35	5.30	12.27	47.51	5.37	12.27
3	$C_{11}H_8Cl_2N_4$	57	197.5–199.5	49.46	3.00	20.98	49.27	3.12	20.89
7	$C_{13}H_{14}N_4$	54	110.5–112.5	69.00	6.24	24.76	68.77	6.19	24.78

[a] Preparation was according to E. A. Ingalls and F. D. Popp, *J. Heterocycl. Chem.*, **4**, 523 (1967), and literature quoted therein.

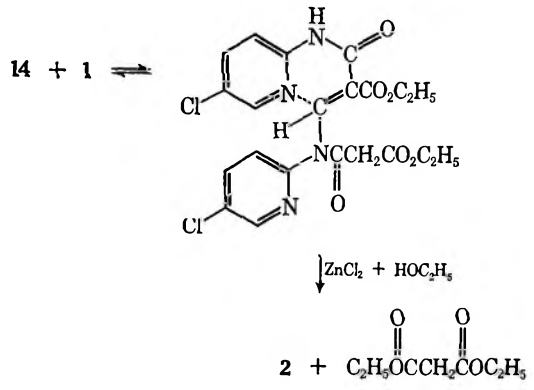
TABLE II

2-CARBETHOXY-3-2-PYRIDYLAMINOACRYL(2-PYRIDYL)AMIDES AND ANALOGS

Compound	Empirical formula	Yield, %	Mp, °C	Calcd, % C	H	N	O	Cl	S	mol wt	Found, % C	H	N	O	Cl	S	mol wt	Nmr aldimino proton, ppm
2	$C_{16}H_{14}O_2N_4O_3$	41	195–197	50.41	3.70	14.70	12.59	18.60		381	50.54	3.72	14.71	12.59	18.60		385 ± 2[a]	9.38
6	$C_{18}H_{20}N_4O_3$	58	150–152	63.52	5.92	16.46					63.40	5.93	16.68					8.97
10	$C_{16}H_{16}N_5O$	18	182–186	65.51	5.16	23.88					65.47	5.13	24.03					8.57
12	$C_{15}H_{16}N_4O_3S$	29	183–184	54.20	4.85	16.86			9.65		54.39	4.75	16.67			9.42		
8	$C_{17}H_{16}ClN_3O_3$	58	170–172	59.05	4.67	12.15					59.00	4.74	12.04					8.35

[a] Ebullioscopic determination in benzene.

facilitating its departure as an anion leading to **14** as the reactive intermediate. This intermediate should be more reactive than an ethoxymethylene derivative and should be capable of reacting with the amide nitrogen of another molecule of starting material **1**.



Zinc chloride catalyzed removal of the malonyl group would then yield **2**.

Another possibility is partial solvolysis of **1** under the reaction conditions and reaction of free 2-amino-5-chloropyridine with either **13** or **14** to yield **2**. However, some **2** is formed even in the presence of an excess of acetic anhydride, which makes it likely that at least part of the reaction goes *via* attack on **14** by an amide nitrogen.

Experimental Section

All melting points are uncorrected. The microanalyses (see Tables I and II) were carried out by Mr. C. W. Nash and his associates.

Spectral Data.—The ir spectra of **2**, **6**, **8**, **10**, and **12** are quite straightforward. The ester band is shifted to longer wavelengths compared with those of the starting materials and occurs at 5.95 μ; the amide I bands and >C=N- bands occur at 6.05 and 6.15 μ.

In the nmr spectra only the hydrogen on the aldimino group is interesting. It is extremely deshielded, almost as much as an aldehydic proton. This proton is easy to spot since it is coupled to the proton on the neighboring nitrogen (J = 12 to 14 Hz). Its location ranges from 8.35 to 9.38 ppm (see Table II).

2-Carbethoxy-3-(5-chloro-2-pyridylamino)acryl(5-chloro-2-pyridyl)amide (2) (Table II, the Other Compounds Listed in Table II Were Made in the Same Way).—A solution of 27.4 g (0.1 mol) of **1** and 1.0 g of $ZnCl_2$ in 70 ml of triethyl orthoformate and 100 ml of absolute ethanol was refluxed for 15 hr. The mixture was then cooled and the product was filtered off. After recrystallizing from Methyl Cellosolve a yield of 15.5 g was obtained.

1,3-Bis(5-chloro-2-pyridyl)formamidine (3) (Table I, the Same Method Was Used for 7).—A solution of 38.5 g (0.3 mol) of 2-amino-5-chloropyridine and 22 g (0.15 mol) of triethyl orthoformate in 150 ml of diglyme was refluxed for 2 hr. After that, the mixture was cooled and diluted with 100 ml of ethanol. The precipitated product was recrystallized from ethanol. The yield was 23 g.

2-Ethylsulfonylacetylaminopyridine (Table I).—A mixture of 90 g (0.43 mol) of $C_2H_5SO_2CH_2CO_2C_4H_9$-*n* (made by peracetic acid oxidation of the corresponding sulfide) and 41 g (0.43 mol) of 2-aminopyridine was heated with stirring to 180° for 2 hr when 40 ml of liquid had distilled off. The mixture was then cooled and diluted with 100 ml of 2-propanol. The product crystallized and was recrystallized from 2-propanol. The yield was 30 g.

Registry No.—**2**, 23595-75-5; **3**, 23595-76-8; **6**, 23595-77-9; **7**, 23646-50-6; **8**, 23595-78-0; **10**, 23646-51-7; **11**, 23595-79-1; **12**, 23595-80-4; triethyl orthoformate, 122-51-0; zinc chloride, 7646-85-7.

Acknowledgment.—We would like to gratefully acknowledge the encouragement of this work by Dr. Charles L. Levesque.

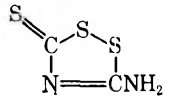
The Basicity of Isoperthiocyanic Acid

RAYMOND SELTZER[1] AND WILLIAM J. CONSIDINE[1]

M & T Chemicals Inc., Subsidiary of American Can Company, Corporate Research Laboratories, Rahway, New Jersey 07065

Received February 11, 1969

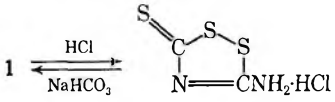
Isoperthiocyanic acid, or 3-amino-5-thione-1,2,4-dithiazole (**1**), was first isolated by Wöhler,[2] but its



1

structure was proven only recently.[3,4] The literature[5] contains many examples illustrating the "acid" character of **1**; it reacts with amines and hydroxide ion to give ring-opening products. However, there is only one questionable example[6,7] relating to the expected basic properties of **1**. In this note, we provide evidence for the basicity of **1** *via* reactions at the exocyclic amino group.

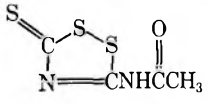
The addition of gaseous HCl to a solution of isoperthiocyanic acid (**1**) in acetonitrile gave the hydrochloride (**2**) in 46% yield. Compound **1** can be recovered in



2

80% yield by adding **2** to aqueous sodium bicarbonate. Attempts to dissolve **2** for recrystallization or nmr measurements led to **1**. However, the ir spectrum showed broad multiple NH absorption at 3200–3090 cm^{-1} and a strong NH deformation frequency at 1615 cm^{-1}, characteristic of primary amine hydrochlorides.[8]

An acetyl derivative of **1** was reported,[6,7] but its structure was not proven. We have treated **1** with acetic anhydride, and isolated a compound to which we assign structure **3**. Acid hydrolysis of **3** regenerated **1**



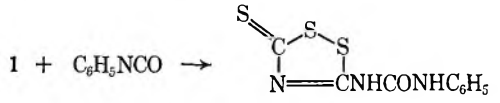
3

in 71% yield. The nmr spectrum (acetone-d_6) of **3** showed methyl and NH proton absorptions, in the correct ratio, at 2.41 and 3.62 ppm, respectively. The ir spectrum showed the amide I band at 1695 cm^{-1}, NH stretching frequency for secondary amides at 3110 and 3220 cm^{-1},[8] an amide II band at 1510 cm^{-1},[9] and imine absorption at 1500 cm^{-1}.[10]

(1) Geigy Chemical Co., Ardsley, N. Y. 10502.
(2) A. Wöhler, *Ann. Phys.*, **69**, 273 (1821).
(3) A. Hordvik, *Acta Chem. Scand.*, **15**, 1186 (1961).
(4) H. J. Emeléus, A. Haas, and N. J. Shepperd, *J. Chem. Soc.*, 3165 (1963).
(5) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. 4, Interscience Publishers, New York, N. Y., 1952, p 35.
(6) M. P. de Clermont, *Bull. Soc. Chim. Fr.*, **25**(2), 525 (1876).
(7) A. Hantzsch and M. Wolvekamp, *Ann. Chem.*, **331**, 265 (1904).
(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1960, pp 249, 259.

The acetyl derivative (**3**) is soluble in 6 *N* aqueous ammonia and can be recovered unchanged on acidification with aqueous hydrochloric acid. However, we have confirmed Hantzsch's observation that **3** undergoes a ring-opening reaction with 10% aqueous sodium hydroxide; sulfur was isolated. Isoperthiocyanic acid (**1**) undergoes ring-opening reactions with hydroxide ion and ammonia. Thus hydrolysis of the amide linkage is undoubtedly required for the opening of the dithiazole ring in **3**.

A urea derivative (**4**) of isoperthiocyanic acid was prepared in 53% yield by allowing a mixture of **1** and phenyl isocyanate to react in refluxing dioxane. At-



4

tempts to hydrolyze **4** to **1** led to decomposition of the dithiazole ring. Sulfur was the only product isolated. This result is not surprising in view of the vigorous conditions required for the hydrolysis of a urea linkage. The infrared spectrum of **4** is consistent with the assigned structure; it showed broad NH stretching absorption in the 3120–3000-cm^{-1} region and carbonyl absorption at 1680 cm^{-1}. The nmr spectrum (dimethyl sulfoxide-d_6) shows multiple absorption at 7.10–7.60 ppm, characteristic of the phenyl protons, and additional absorption at 8.10 and 9.50 ppm, consistent with the two amide protons. The absorptions were in the appropriate ratio.

In contrast to the amide derivative **3**, the urea derivative **4** can be recovered unchanged from 10% aqueous sodium hydroxide solution, demonstrating the stability of the urea linkage. Thus we have additional evidence that substitution at the exocyclic amino group in isoperthiocyanic acid stabilizes the dithiazole nucleus to ring-opening reactions.

Experimental Section

The infrared spectra were determined on a Beckman IR-8 spectrophotometer in Nujol and Fluorolube. The nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal standard. The spectrum of **4** was determined at 70° for solubility reasons.

Isoperthiocyanic Acid (1).—Klason's[11] procedure was used to prepare **1**. To a solution of 1000.0 g (13.2 mol) of ammonium thiocyanate in 400 ml of water was added dropwise 1000 ml (11.8 mol) of 36% hydrochloric acid. A solid deposited during the addition which turned yellow on standing. Gas evolution was observed after the addition was complete, and the reaction mixture was allowed to stand at room temperature for 3 days. The latter step was taken as a precaution, as hydrogen cyanide is liberated in the reaction. The reaction mixture was filtered, and the residue was washed with water until chloride free. Air drying gave 317.0 g (54%), mp 200° dec. Recrystallization from a dimethyl sulfoxide–water solution gave an analytical sample, mp 202° dec.

Anal. Calcd for $C_2H_2N_2S_3$: N, 18.6; S, 64.0. Found: N, 18.3; S, 63.9.

3-Acetamido-5-thione-1,2,4-dithiazole (3).—A mixture of 150.0 g (1.0 mol) of isoperthiocyanic acid and 1500 ml of acetic anhydride was heated with stirring at 110° for 2 hr. After cooling, the mixture was filtered and the residue was washed with methanol and dried to give 141.0 g (73%) of a yellow solid, mp 211–

(9) Reference 8, pp 205–208.
(10) Emeléus assigned the band at 1515 cm^{-1} in **1** to the imine linkage.
(11) P. Klason, *J. Prakt. Chem.*, **38** (2), 366 (1883).

213° dec. Recrystallization of a sample from acetonitrile gave pure **3**, mp 212–213° dec.

Anal. Calcd for $C_4H_4N_2OS_3$: N, 14.6; S, 49.9. Found: N, 14.6; S, 49.4.

Hydrolysis of 3.—A mixture of 4.5 g (0.023 mol) of **3**, 10 ml of concentrated HCl, and 20 ml of ethanol was heated to the reflux temperature. The mixture turned homogeneous, but solids deposited on continued reaction at the reflux temperature. After heating for 2.5 hr, the mixture was cooled and filtered. The residue was washed chloride free with water and dried, yield 2.5 g, mp 200° dec. A mixture melting point with an analytical sample of **1** was not depressed. The ir spectrum was identical with that of **1**. Therefore, a 71% yield of isoperthiocyanic acid was recovered.

3-Amino-5-thione-1,2,4-dithiazole Hydrochloride (2).—A mixture of 20.0 g of isoperthiocyanic acid (**1**) and 2 l. of acetonitrile was refluxed for 2 hr and allowed to cool overnight. The mixture was filtered; 5.3 g (0.035 mol) of **1** remained in solution. To the solution, at room temperature, was added HCl gas for 40 min. Solids precipitated which were filtered, washed with acetonitrile, and dried, yield of **2** 3.0 g (46%), mp 190° dec. Attempts to recrystallize **2** regenerated **1**.

Anal. Calcd for $C_2H_3ClN_2S_3$: Cl, 18.9; N, 15.0; S, 51.5. Found: Cl, 18.4; N, 15.2; S, 51.0.

To a solution of 0.08 g (0.01 mol) of sodium bicarbonate in 10 ml of water was added in small portions 0.18 g (0.01 mol) of **2**. Immediate gas evolution occurred, and the mixture was stirred at room temperature for 30 min. The mixture was filtered, and the residue was washed with water and then air-dried to give 0.12 g (80%) of **1**, mp 200° dec. A mixture melting point with an analytical sample of **1** was not depressed. The ir spectra of the two samples of **1** were identical.

N-Phenyl-N′-(5-thione-1,2,4-dithiazyl-3)urea (4).—A mixture of 75.0 g (0.50 mol) of **1** and 59.5 g (0.50 mol) of phenyl isocyanate in 3 l. of dioxane was refluxed for 3.5 hr. After cooling, the mixture was filtered, and the residue was washed with dioxane until the filtrate was colorless. Drying the product at 100° under vacuum gave 105.0 g of a yellow solid, mp 227–229° dec. Recrystallization from dimethylformamide followed by washing the product with ethyl ether gave 61.0 g (45%) of pure **4**, mp 220–221° dec.[12] An additional recrystallization did not change the melting point. Cooling the mother liquor gave an additional 10.0 g (8%) of pure **4**, mp 220–221° dec.

Anal. Calcd for $C_9H_7N_3OS_3$: C, 40.2; H, 2.6; N, 15.6; S, 35.7. Found: C, 40.3; H, 2.7; N, 15.7; S, 35.2.

Registry No.—**1**, 14453-29-3; **2**, 23405-39-2; **3**, 23405-40-5; **4**, 23405-41-6.

Acknowledgment.—The authors are grateful to Mr. Patrick Branigan, Mr. Ivor Simmons, and their staffs for the elemental and spectral analyses, respectively.

(12) The higher melting point of the crude product is undoubtedly due to the presence of unreacted isoperthiocyanic acid (**1**). Compound **1** melts with decomposition at 202°.

Studies of Organoindium Compounds. The Reaction of Triethylindium with an Excess of Phenyl Isocyanate

HISASHI TADA AND ROKURO OKAWARA

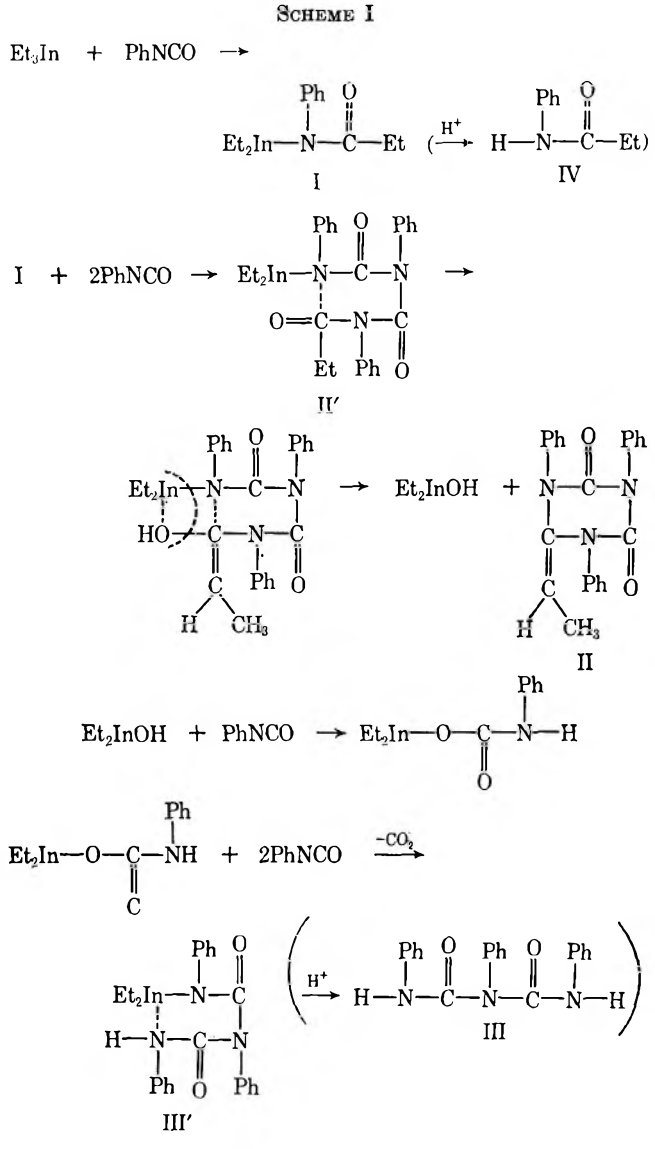
Department of Applied Chemistry, Osaka University, Yamadakami, Suita, Osaka, Japan

Received July 29, 1969

In a previous paper, we reported the reaction of triethylindium with an equimolar amount of phenyl isocyanate to give N-diethylindium-N-phenylpropionamide (I, 89%) and a small amount of unknown compounds.[1]

In this paper we describe the reaction of triethylindium with an excess of phenyl isocyanate to give 2,4-dioxo-6-ethylidene-1,3,5-triphenylhexahydro-1,3,5-triazine (II), N,N′,N″-triphenylbiuret (III), N-phenylpropionamide (IV), and 2,4-dioxo-6,6-diethyl-1,3,5-triphenylhexahydro-1,3,5-triazine (V). Although many organometallic compounds have been known to catalyze the trimerization of isocyanates,[2] the type of reaction described here has never been observed for other organometallic compounds. The results are shown in Table I and the probable reaction scheme is presented below (Scheme I).

SCHEME I



In the reaction of triethylindium and phenyl isocyanate in a 1:3 molar ratio, the yields of II and III were low and that of IV was moderate, but, in the case of a 1:6.3 molar ratio, the yields of II and III increased and that of IV decreased remarkably. These changes in the yield of products with different molar ratios can be reasonably explained by assuming that I is formed at first and is then consumed by the successive insertion of

(1) H. Tada, K. Yasuda, and R. Okawara, *J. Organometal. Chem.*, **16**, 215 (1969).

(2) (a) A. J. Bloodworth and A. G. Davies, *J. Chem. Soc.*, 6858 (1965); (b) S. Herbstman, *J. Org. Chem.*, **30**, 1259 (1965); (c) J. G. Noltes and J. Boersma, *J. Organometal. Chem.*, **7**, P6 (1967).

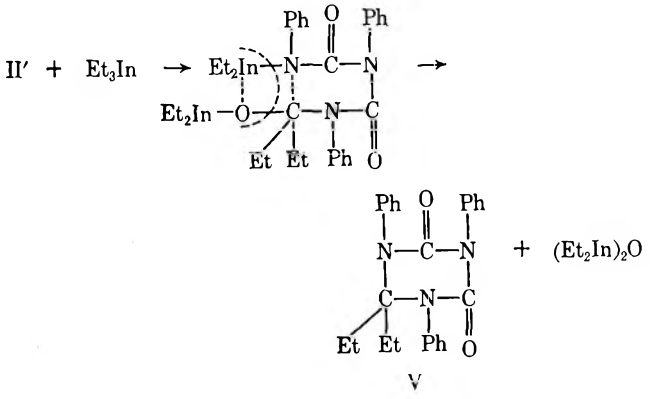
TABLE I
RESULTS OF THE REACTION OF TRIETHYLINDIUM WITH PHENYL ISOCYANATE

Reactants			Products[a]			
Et_3In, g (mmol)	PhNCO, g (mmol)	Molar ratio	II, g (%)	III, g (%)	IV, g (%)	V, g (%)
1.34	2.37	1:3	0.50	0.45	0.60	0.10
(6.63)	(19.96)		(20.4)	(20.5)	(60.7)	(3.8)
1.70	6.33	1:6.3	2.00	1.30	0.00	0.40
(8.42)	(53.2)		(64.3)	(46.6)	(0.00)	(11.9)

[a] Calculation of yields are based on the amount of triethylindium used.

two molecules of isocyanate[3] and that the residual phenyl isocyanate is consumed by both I and diethylindium hydroxide.[4] The reaction of I (prepared by another route) with 5.3 mol of phenyl isocyanate gave II and III in good yield without formation of V. This result supports the scheme in which II is formed from I and the participation of the resulting, not yet characterized, triethylindium fragment, probably diethylindium hydroxide, to form III′.[5] Considering that V was not obtained in the reaction of I with isocyanate,[6] it is reasonable to suppose that V was formed from the reaction of II′ and triethylindium, as shown below (Scheme II).

SCHEME II



V

Experimental Section

General preparative methods were described in the previous paper.[1]

Reaction of Triethylindium with Phenyl Isocyanate. A. In the Molar Ratio of 1:3.—When phenyl isocyanate (2.37 g, 19.96 mmol) in *n*-hexane (20 ml) was treated with triethylindium (1.34 g, 6.63 mmol) in *n*-hexane (20 ml) with stirring at 0°, carbon dioxide containing a small amount of ethane was slowly evolved.[7] After 20 hr the precipitate was filtered off, washed with *n*-hexane, and fractionally recrystallized from acetone, yielding II and V. Data for II follow: mp 226°; ir (Nujol) 1732, 1690, and 1673 cm^{-1} (C=O and C=C); nmr (CH_2Cl_2) τ 2.63 (multiplet, aromatic protons), 5.66 (quartet, methine proton), and 9.00 (doublet, $J_{=CHCH_3} = 7.2$ Hz, methyl protons) of relative intensity 15:1:3; mass spectrum *m/e* 369 (M^+, $C_{23}H_{19}N_3O_2$).

Anal. Calcd for $C_{23}H_{19}N_3O_2$: C, 74.77; H, 5.18; N, 11.37; mol wt, 369. Found: C, 74.68; H, 5.24; N, 11.36; mol wt, 353 (0.403% in benzene).

Data for V follow: mp 222°; ir (KBr) 1707, and 1669 cm^{-1} (C=O); nmr (CH_2Cl_2) τ 2.56 (singlet, aromatic protons), 2.63 (singlet, aromatic protons), and 8–9 (multiplet, A_3B_2-type ethyl protons) of relative intensity 10:5:10; mass spectrum *m/e* 399.5 (M^+, $C_{25}H_{25}N_3O_2$).

Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52; mol wt, 399.5. Found: C, 74.66; H, 6.48; N, 10.42; mol wt, 385 (0.797% in CH_3CN).

The solvent and the slight excess of phenyl isocyanate (0.1 g recovered as ethyl-N-phenylcarbamate) were removed from the filtrate under reduced pressure. The remaining solid was dissolved in *n*-hexane. Addition of methanol (2 ml) gave a white precipitate immediately, which was filtered off, washed with *n*-hexane, and recrystallized from methylene chloride, yielding III: mp 147° (lit.[8] mp 147–148°); ir (KBr) 3322 (NH), 1707, and 1674 (C=O); nmr (CH_2Cl_2) τ 1.09 (broad singlet, amide proton) and 2.7 (multiplet, aromatic protons) of relative intensity 2:15.

Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68; mol wt, 331. Found: C, 72.54; H, 5.09; N, 12.89; mol wt, 323 (1.085% in benzene).

The filtrate was hydrolyzed by aqueous hydrogen chloride, giving N-phenylpropionamide (IV), mp 107° (lit.[9] mp 105°), whose ir spectrum was identical with that of an authentic sample.

B. In the Molar Ratio of 1:6.3.—The above procedure was followed. Unreacted phenyl isocyanate was recovered as ethyl-N-phenylcarbamate (1.70 g).

Preparation of N-Diethylindium-N-phenylpropionamide (I).—When triethylindium (1.26 g, 6.24 mmol) in *n*-hexane (15 ml) was added to N-phenylpropionamide (0.93 g, 6.24 mmol) suspended in *n*-hexane (30 ml), ethane was evolved. After the clear solution had been heated under reflux for 1 hr, the solvent was removed under reduced pressure to give I (2.00 g), whose ir spectrum and melting point were identical with those of an authentic sample.[1]

Reaction of N-Diethylindium-N-phenylpropionamide (I) with Phenyl Isocyanate in the Molar Ratio of 1:5.3.—When phenyl isocyanate (3.94 g, 33.1 mmol) in *n*-hexane (15 ml) was treated with N-diethylindium-N-phenylpropionamide (I, 2.00 g, 6.24 mmol) in *n*-hexane (45 ml), carbon dioxide was slowly evolved, and, after the usual treatment, II (1.50 g, 65%) and III (2.0 g, 96%) were obtained. Unreacted phenyl isocyanate was recovered as ethyl-N-phenylcarbamate (1.5 g).

Registry No.—Triethylindium, 923-34-2; phenyl isocyanate, 103-71-9; II, 23405-35-8; III, 2645-39-8; V, 23405-37-0.

Acknowledgment.—Thanks are due to Professor C. R. Dillard of Brooklyn College of the City University of New York for his help in improving our manuscript.

(3) Triethylindium did not react with isocyanate dimer and trimer.

(4) (a) It has been reported that triethylsilanol reacts with isocyanate to give the corresponding triethylsilicon carbamates,[4b] and that tributyltin N-ethylcarbamate reacts with phenyl isocyanate, giving N-ethyl-N′-phenyltributylstannylurea and carbon dioxide.[4c] These results lend some support to the scheme to form biuret from diethylindium hydroxide and phenyl isocyanate. (b) V. V. Atakhin, I. P. Losev, and K. A. Andrianov, *Dokl. Akad. Nauk SSSR*, **113**, 581 (1957); *Chem. Abstr.*, **51**, 14582 (1957). (c) A. J. Bloodworth and A. G. Davies, *J. Chem. Soc., C*, 229 (1966).

(5) If bisdiethylindium oxide is formed from diethylindium hydroxide by dehydration, the water should react with the remaining phenyl isocyanate (*cf.* Experimental Section) to give N,N′-diphenylurea, but we could not obtain urea in these reactions. Consequently, the possibility of the participation of bisdiethylindium oxide to form biuret as in the case of bistributyltin oxide[4c] was eliminated.

(6) In this case, there was no triethylindium present.

(7) Gas analysis was performed by glpc (2-m column packed with activated charcoal using helium as carrier gas).

(8) B. Kuhn and E. Henschel, *Chem. Ber.*, **21**, 504 (1888).

(9) C. G. Rerick and J. H. Bornmann, *J. Amer. Chem. Soc.*, **35**, 1284 (1913).

Small-Ring Heterocyclic Compounds. IV. Attempted Synthesis of 1,2-Thiazetidines and Thiazetes[1a-c]

NORMAN E. HEIMER AND LAMAR FIELD[1d]

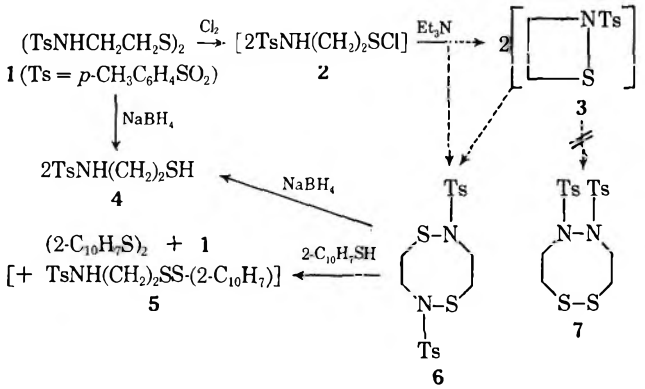
Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

Received September 15, 1969

Although the 1,2-thiazetidine ring system, exemplified in structure **3** of Scheme I, is readily available in oxidized form through cycloaddition of N-sulfinyl- or N-sulfonylamine derivatives to olefins or ketenes,[2] we are unaware of any 1,2-thiazetidines, *per se*. Such systems are of interest for several reasons. (1) Both the sulfur and the nitrogen atoms of an aminoethanethiol moiety are latentiated, so that such compounds might be attractive antiradiation drugs.[3] (2) The nitrogen and sulfur lone pairs may be forced into essentially eclipsed positions in which electron repulsion should be high, so that the N–S bond might be unusually labile. (3) A benzothiazete such as **10** of Scheme II might be considered a bis heteroanalog of benzocyclobutadiene and consequently might have unusual chemical and physical characteristics. This paper reports the outcome of attempts to prepare the ring systems **3** and **10**.

In seeking **3**, we converted 2-tosylamidoethyl disulfide (**1**) into the sulfenyl chloride **2**, which was treated *in situ* with triethylamine (Scheme I).

SCHEME I



Sulfonamide **1** was used because of its acidity and because previous experience suggested that an acetamide would function less well.[4] The disulfide **1** was prepared conventionally from 2-aminoethyl disulfide with tosyl chloride, and its structure was assured by its spectra. Chlorinolysis of **1** and addition of triethylamine gave a crude product that showed only a weak ir absorption for NH. Analysis of the crude product by mass spectrometry showed only compounds of molecular weight 458 (**6**) and 460 (**1**); no ion was seen at *m/e* 229, the molecular weight of the thiazetidine **3**. Analysis of the crude product by tlc revealed the presence of only two compounds. One was identified as the original disulfide **1** by comparison with authentic **1**. No material remained at the origin, which would have indicated a polymer of **3**. Purification of the other product by fractional crystallization entailed large losses, but ultimately gave a new compound to which we assign structure **6**, that of a dimer of **3** (13–18% yield).

The assignment of structure **6** is based both on spectral and chemical considerations. The nmr spectrum showed the expected pattern for the aromatic protons (A_2B_2), for the methyl group (a singlet), and for the adjacent methylene protons (two multiplets approximating triplets). The ir spectrum showed no NH absorption, but did show bands corresponding to the aromatic ring and $>SO_2$ moieties. The mass spectrum showed a molecular ion at *m/e* 458 (with proper isotope abundancies at 459 and 460), a base peak at *m/e* 91 ($C_7H_7^+$), and an intense ion at *m/e* 155 ($C_7H_7SO_2^+$). The chemical reactions of **6** seem inconsistent with structure **7**. Thus **6** oxidized iodide ion to iodine, a characteristic of sulfenamides unlikely for **7**.[4] Reduction of **6** with sodium borohydride gave thiol **4** in 93% yield identical (essentially identical spectrum) with **4** prepared by reduction of **1** (Scheme I). The structure of **4** follows from its spectra. The nmr spectrum of **4** showed an A_2B_2 pattern for the aromatic protons, a methyl group, multiplets for the methylene protons, and the amide and thiol protons as multiplets both removable by D_2O exchange. The mass spectrum showed a molecular ion (*m/e* 231) with other ions at *m/e* 184 ($C_7H_7SO_2NHCH_2^+$), 155 ($C_7H_7SO_2^+$), and 91 ($C_7H_7^+$). Furthermore, **6** showed the behavior expected of a sulfenamide[4,5] in reacting with 2-naphthalenethiol to give the two possible symmetrical disulfides (*i.e.*, 2-naphthyl disulfide and **1**), together with a third product presumed to be 2-tosylamidoethyl 2-naphthyl disulfide (**5**).

That the yields of **6** isolated are much lower than the actual yield was indicated by reaction of 2-naphthalenethiol with crude product left after the isolation of **6** in 13% yield. Titration of the excess thiol, after its reaction, corresponded to the presence of **6** in 89% yield. The total yield of **6** calculated thus was 102%.

The failure to find any evidence for the thiazetidine **3** itself, taken along with the apparent high yield of the dimer **6**, requires comment. The dimer **6** seems unlikely to be the primary product, since a high yield would not be anticipated from condensation of two molecules of **2** followed by cyclization to give the eight-membered ring of **6**. It seems considerably more likely that the initial product is **3** and that it then dimerizes to **6**, as shown in Scheme I, to minimize ring strain and lone-pair–lone-pair repulsion.

Synthesis of the benzothiazete **10** was attempted as shown in Scheme II. Reaction of tosyl chloride with

(1) (a) Paper III: T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 656 (1962). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Presented in part at the Third International Cork Mechanisms Conference, University College, Cork, Ireland, Sept 29–Oct 3, 1969. (d) To whom inquiries should be addressed.

(2) (a) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, pp 307, 336; (b) G. M. Atkins, Jr., and E. M. Burgess, *J. Amer. Chem. Soc.*, **89**, 2502 (1967); (c) F. Effenberger and R. Gleiter, *Chem. Ber.*, **99**, 3903 (1966).

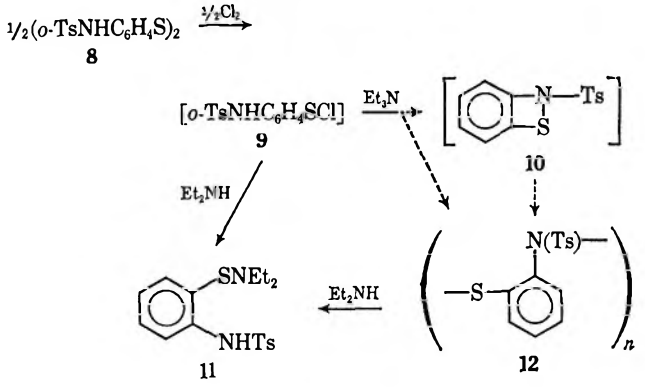
(3) For leading references on antiradiation drugs and latentiation, see L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969).

(4) N. E. Heimer and L. Field, to be published.

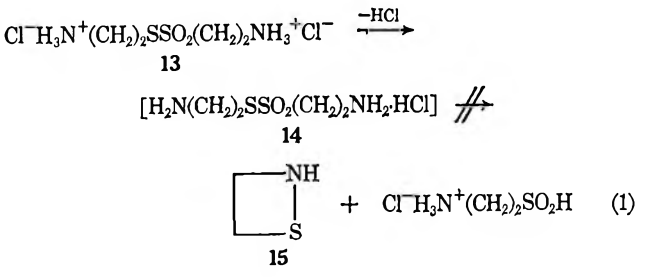
(5) (a) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968); (b) A. Fontana, F. Marchiori, L. Moroder, and E. Scoffone, *ibid.*, 2985 (1966).

o-aminophenyl disulfide gave **8**, which had appropriate spectra. Chlorinolysis of **8** to give the sulfenyl chloride **9** was followed by reaction *in situ* with triethylamine to give an insoluble white solid (**12**). This solid (**12**) showed no ir absorption for NH and was soluble only in secondary amines or in pyridine containing thiols. The mass spectrum of **12** showed no ion at *m/e* 277, as expected for **10**. Ions seen at *m/e* 556 corresponded to the disulfide **8** and at *m/e* 554 probably to the dimer of **10** analogous to **6**. The virtual insolubility of **12**, the absence of an ir band for NH, the relatively high intensity of the disulfide peak (**8**) in the mass spectrum of **12**, and the peak at *m/e* 554 suggest that **12** is polymeric, with small amounts of **8** and the dimer of **10** entrapped. This probability was enhanced by dissolution of **12** in diethylamine, followed by tlc and mass spectra analysis, both of which showed the presence of sulfenamide **11**. Attempts to purify **11** unfortunately led to its decomposition. For substantiation of its structure, the unstable sulfenamide **11** was prepared by reaction of diethylamine with the sulfenyl chloride **9** (Scheme II).

SCHEME II



Another possible route to a thiazetidine was suggested by the rapid decomposition after neutralization of **13**;[6] attack of an amino group on the bivalent sulfur atom (eq 1) might lead to **15** (or perhaps to a sulfenamide).[7]



However, weight loss after neutralization of **13** to **14**, then drying, was less than calculated from eq 1, and there was no ammoniacal odor. Tlc showed two products. Tosylation indicated that one was 2-aminoethyl disulfide. The other seemed to be taurine. Use of 2 mol of alkali with **13** also gave no **15** and, like eq 1, seemed unattractive for further study.

(6) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(7) *Cf.* J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

Experimental Section[8]

2-Tosylamidoethyl Disulfide (**1**).—A solution of 14.2 g (75 mmol) of tosyl chloride in 200 ml of CH_2Cl_2 was added during *ca.* 90 min to 6.40 g (0.16 mol) of sodium hydroxide and 8.45 g (37.5 mmol) of 2-aminoethyl disulfide dihydrochloride in 200 ml of H_2O. The mixture was stirred overnight, and the CH_2Cl_2 layer then was separated, dried (Na_2SO_4), and evaporated: yield of **1**, 17.0 g (99%); mp 69–74°. Recrystallization twice from CH_3OH gave pure **1** with a constant melting point of 79–80°: nmr δ 2.37 (s, 3), 2.65 (t, 2), 3.20 (q, 2), 5.33 (t, 1), 7.20 (m, 2), and 7.69 (m, 2); ir (KBr) 1330 (s), 1150 (s), 1080, and 1055 cm^{-1}; mass spectrum *m/e* (rel intensity) 462 (1), 461 (1), 460 (4), 289 (6), 259 (4), 231 (5), 198 (22), 185 (6), 184 (57), 156 (7), 155 (73), 139 (7), 92 (12), 91 (100), 74 (5), and 65 (21).

Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93; H, 5.25. Found: C, 47.25; H, 5.40.

2-Tosylamidoethanethiol (**4**).—A solution of 1.70 g (3.70 mmol) of 2-tosylamidoethyl disulfide (**1**) in 30 ml of dioxane was reduced with 0.67 g (17.8 mmol) of $NaBH_4$ at 90° for 3 hr and then was let stand overnight at *ca.* 25°. Addition of 10% HCl to destroy the excess hydride, filtration, evaporation to near dryness and extraction with $CHCl_3$ gave 1.30 g (76%) of a pale yellow oil. Short-path distillation [*ca.* 100° (0.002 mm)] gave **4** as a colorless oil, $n^{25}D$ 1.5681. One more distillation gave **4**: $n^{25}D$ 1.5683; ir 3280, 2560 (w), 1600, 1500, 1420, 1325 (s), 1160 (s), 1085, 810, and 650 cm^{-1}; nmr δ 1.42 (m, 1, SH), 2.42 (s, 3, CH_3Ar), 2.63 (m, 2 CH_2S), 3.13 (m, 2, CH_2N), 5.63 (t, 1, NH), 7.32 (m, 2, ArH), and 7.79 (m, 2, ArH); mass spectrum *m/e* (rel intensity) 233 (0.2), 232 (2.2), 231 (1.5), 184 (39), 155 (56), 92 (10), 91 (100), 65 (24), 51 (5), 47 (6), 42 (5), and 41 (6).

Anal. Calcd for $C_9H_{13}NO_2S_2$: C, 46.74; H, 5.66. Found: C, 46.91; H, 5.73.

1,5-Ditosyl-2,6-dithia-1,5-diazocine (**6**). **A. Preparation.**—A solution of 3.22 g (7.0 mmol) of 2-tosylamidoethyl disulfide (**1**) in 30 ml of CH_2Cl_2 was cooled in Dry Ice and 0.42 ml (8.9 mmol) of Cl_2 was evaporated into the solution. After 1 hr at −30°, an excess (3 ml, 21 mmol) of Et_3N was added, and stirring was continued until the solution warmed to *ca.* 25°. The CH_2Cl_2 solution was washed thrice with water, dried (Na_2SO_4), and evaporated to give 3.7 g of thick oil; tlc showed the presence of two compounds, **1** (by comparison with authentic material) and a new compound (**6**). Trituration with EtOAc and recrystallization (Me_2CO) gave 0.4 g (13%) of **6** having a constant melting point of 233° dec (sample inserted at 225°, heated at *ca.* 3°/min). The remaining 2.8 g of material was dissolved in 25 ml of CH_2Cl_2, and 80.8 mg (0.505 mmol) of 2-naphthalenethiol and a trace of Et_3N were added to a 1.00-ml aliquot in 15 ml of EtOH. After 0.5 hr at *ca.* 25°, the solution was acidified with 50% AcOH (1 ml) and the excess thiol (0.01 mmol) was determined by titration with standard KI_3, yield of dimer **6** 6.19 mmol (89%), making a total yield of **6** of 102%. Data for the solid **6** follow: ir (Nujol) 1600, 1500, 1330 (s), 1150 (s), 1090, 870, 810, 700, and 675 cm^{-1}; nmr δ 2.43 (s, 3), 3.24 (m, 2), 3.81 (m, 2), 7.34 (m, 2), and 7.84 (m, 2); mass spectrum *m/e* (rel intensity) 460 (3), 459 (3), 458 (12), 303 (9), 184 (17), 156 (5), 155 (44), 139 (10), 123 (4), 120 (9), 106 (21), 92 (10), 91 (100), 79 (6), 74 (17), 65 (34), 64 (6), 63 (8), 60 (12), 51 (6), 46 (5), 45 (10), 42 (16), and 41 (6).

Anal. Calcd for $C_{18}H_{22}N_2O_4S_4$: C, 47.14; H, 4.84. Found: C, 47.08; H, 5.18.

B. Reduction of 6 with $NaBH_4$.—A suspension of 0.46 g (1.0 mmol) of **6** and 0.19 g (5 mmol) of $NaBH_4$ in dioxane was stirred overnight at *ca.* 25° and then was heated at 90° for 3 hr. The excess $NaBH_4$ then was decomposed with 10% HCl. The mixture was filtered, evaporated to near dryness, and extracted with CH-

(8) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Mass spectra were obtained at 70 eV using the direct inlet system for **1**, **6**, **8**, and **11** and the glpc-inlet system (glass, 9-ft 1% SE-30 on Gas-Chrom Q column) for **4** on an LKB Model 9000 instrument, which was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to Mr. Charles Wetter for these spectra. Ir spectra were obtained using a Beckman Model IR-10 with films of liquids and KBr pellets or Nujol mulls of solids; "s" signifies strong absorption (others reported are medium). Nmr spectra were obtained using a Varian Model A-60 spectrometer, with TMS as internal standard and $CDCl_3$ as solvent. We thank the National Science Foundation for Departmental Grant GP-1683 toward purchase of this instrument. Evaporation of solvents was done under reduced pressure using a rotary evaporator.

Cl_3 to give 0.43 g (93%) of 2-tosylamidoethanethiol (**4**) as a colorless oil having ir and mass spectra nearly identical with those of **4** obtained from the reduction of **1**.

C. Reaction with 2-Naphthalenethiol.—A suspension of 100 mg (0.22 mmol) of **6** and 74 mg (0.46 mmol) of 2-naphthalenethiol in 1:1 EtOH–CH_2Cl_2 was treated with 5 drops of Et_3N. The solid dissolved immediately. After *ca.* 16 hr, the solvent was evaporated and the residue was crystallized from EtOH. Analysis of both the solid and the filtrate by tlc (silica gel–benzene) showed the solid to be a mixture of two compounds; one of these, the more mobile, was evidently 2-naphthyl disulfide by tlc comparison; the other probably was 2-tosylamidoethyl 2-naphthyl disulfide (**5**) but was not positively identified. The filtrate contained three compounds; tlc comparison with authentic materials indicated two of them to be **1** and 2-naphthyl disulfide; the third presumably was **5**.

***o*-Tosylamidophenyl Disulfide (8).**—A solution of 10.0 g (40.3 mmol) of *o*-aminophenyl disulfide and 17.4 g (91 mmol) of tosyl chloride in 125 ml of pyridine was allowed to stand for 4 days. Filtration of the solution, dilution with EtOAc, and filtration removed a hygroscopic, water-soluble solid (presumably pyridine·HCl). The filtrate was washed several times with aqueous 10% HCl, dried, and evaporated to give a thick oil that slowly crystallized. Recrystallization from EtOAc and from Me_2CO gave 14.0 g (62%) of **8**: mp 162–167°; ir (Nujol) 3320, 1603, 1580, 1340 (s), 1280, 1165 (s), 1090, 1060, 925, 812, 767, and 660 cm^{-1}; nmr δ 2.16 (s, 3), and 6.7–7.9 (m, 9); mass spectrum *m/e* (rel intensity) 558 (6), 557 (8), 556 (29), 402 (5), 246 (20), 215 (10), 214 (45), 200 (10), 199 (60), 181 (7), 180 (6), 167 (5), 156 (5), 155 (8), 154 (14), 140 (8), 139 (13), 125 (11), 124 (67), 122 (7), 97 (8), 96 (17), 95 (5), 92 (20), 91 (100), 90 (5), 89 (6), 79 (28), 77 (7), 76 (7), and 65 (38).

Anal. Calcd for $C_{26}H_{24}N_2O_4S_4$: C, 56.09; H, 4.34. Found: C, 55.93; H, 4.48.

Attempted Synthesis of the Benzothiazete 10.—A solution of 4.90 g (8.80 mmol) of **8** in 50 ml of CH_2Cl_2 was cooled to −30°, and 8.8 mmol of Cl_2 in CCl_4 was added. The solution was stirred and allowed to warm to 0°. Then 3 ml of Et_3N was added (a considerable amount of solid appeared quickly, although Et_3N·HCl is soluble in the medium). Stirring was continued for 0.5 hr. The suspension was shaken twice with H_2O (solid remained in the organic phase), and then solid was separated to give 1.90 g (39%) of **12** as a white solid: mp >250° (insoluble in $CHCl_3$, CH_2Cl_2, EtOH, C_6H_6, C_5H_5N, H_2O, DMF, and $C_2H_2Cl_4$, soluble in secondary amines and in pyridine solutions of thiols); ir (Nujol) 1603, 1333 (s), 1300, 1170 (s), 1090, 915, 890, 851, 810, 731, and 669 cm^{-1}; mass spectrum *m/e* (rel intensity) 556 (24), 554 (4), 443 (15), 260 (5), 246 (18), 244 (9), 214 (50), 199 (57), 181 (6), 180 (6), 156 (8), 155 (14), 139 (17), 124 (43), 92 (10), 91 (100), and 65 (40). The filtrate contained only **8** (tlc).

Reaction of 12 with Diethylamine.—When 200 mg of **12** was placed in 30 ml of Et_2NH and heated under reflux for 5 min, dissolution occurred. After a reflux period of 3 hr, the excess Et_2NH was removed and the resulting oil was analyzed by tlc (silica gel, EtOAc) and by mass spectrometry, giving the same spectrum as authentic **11**. After 2 days at *ca.* 25°, analysis of the hardened oil by mass spectrometry showed only Et_2NH (trace) and disulfide **8**, consistent with virtually complete decomposition of **11**.

o-Tosylamidobenzenesulfenyl Diethylamide (11).—A stirred solution of **8** (556 mg, 1.00 mmol) in 20 ml of CH_2Cl_2 was cooled to −30°, and Cl_2 (1.05 mmol) was added. After 0.5 hr, the solution was allowed to warm to *ca.* 25°, and 0.5 ml (4.9 mmol) of Et_2NH was added. After 0.5 hr, the solution was diluted with 30 ml of CCl_4, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give 0.75 g (107%) of **11** as a light brown oil; tlc showed the same characteristics as solutions of **11** prepared from **12** and Et_2NH, *viz*, one large spot and two small ones. Attempted distillation resulted only in decomposition, and chromatography over Florisil (*ca.* 50% recovery) failed to provide **11** more pure than the crude product: ir (thin film) 3280, 2990, 1600, 1470, 1345, 1173 (s), 1090, 923, 820, 792, 760, and 665 cm^{-1}; nmr δ 1.10 (t, 6, CH_3CH_2), 2.27 (s, 3, CH_3Ar), 2.84 (q, 4, CH_2CH_3), 6.6–7.8 (m, 8, ArH), and 8.06 (s, 1, NH); mass spectrum *m/e* (rel intensity) 350 (36), 214 (19), 199 (19), 155 (6), 125 (7), 124 (42), 96 (7), 91 (42), 80 (16), 73 (23), 72 (92), 65 (14), 63 (5), 57 (100), 56 (9), 45 (5), 44 (23), 43 (6), 42 (20), and 41 (8).

Decomposition of 2-Aminoethyl 2-Aminoethanethiolsulfonate Monohydrochloride (14).—A solution (pH 4) of 10.0 mmol of **13** in water was neutralized with 10.0 mmol of NaOH (the pH increased to 7–8). Tlc (Brinkmann Polygram MN Polyamide, with 10:1:0.15 EtOH–Me_2CO–Et_2NH) showed two ill-defined spots, R_f 0.5 (by fluorescence) and 0.3 (by I_2 vapor). Evaporation and vacuum drying gave 2.73 g of residue (92% of the 2.97 g of **13** and NaOH used). Ethanol separated 0.35 g of taurine, mp > 210° (lit.[9] mp 300–305° dec); the ir spectrum was virtually identical with that of authentic taurine. The crude residue from an identical experiment was dissolved in H_2O, and 0.80 g of NaOH was added. The mixture then was treated with tosyl chloride. After 6 hr, a CH_2Cl_2 solution was washed thrice with water and evaporated to give 1.20 g, identified as **1** by tlc comparison with authentic **1** (silica gel–*n*-butyl acetate).

Registry No.—**1**, 23516-74-7; **4**, 23516-75-8; **6**, 23516-76-9; **8**, 3982-42-1; **11**, 23516-78-1.

(9) F. Cortese, *J. Amer. Chem. Soc.*, **58**, 191 (1936).

Thallium in Organic Synthesis. XI. Preparation of Azoxy Compounds[1,2]

ALEXANDER MCKILLOP AND RICHARD A. RAPHAEL

School of Chemical Sciences, University of East Anglia, Norwich, England

EDWARD C. TAYLOR

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received October 20, 1969

Thallium is abundant, inexpensive, and readily available in bulk in a high state of purity. Surprisingly, the literature is virtually devoid of descriptions of direct applications of the metal to organic synthesis. We wish to describe in this paper the use of thallium in a simple, high-yield procedure for the preparation of aromatic azoxy compounds.

During studies on the use of thallium salts in the synthesis of biaryls,[3] we were able to confirm an early report by Spencer and Wallace[4] that small amounts of biphenyl and thallium(I) iodide were formed when thallium and iodobenzene were heated together under reflux. Although more detailed investigation of this reaction has established that the overall process is of little synthetic value as a route to biaryls,[5] an interesting side reaction was observed when nitrobenzene was employed as solvent. In refluxing nitrobenzene thallium underwent slow oxidation to give thallium(III) oxide, with concomitant formation of significant amounts of azoxybenzene (eq 1). The conversion out-

$$2C_6H_5NO_2 + 2Tl \longrightarrow C_6H_5\overset{+}{N}(O^-)=NC_6H_5 + Tl_2O_3 \qquad (1)$$

lined in eq 1 also proceeds smoothly in a number of high boiling solvents such as dimethylformamide, *o*-dichlorobenzene, and diglyme, but extended reaction

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) Part X: A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(3) A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, **90**, 2423 (1968).

(4) J. F. Spencer and M. L. Wallace, *J. Chem. Soc.*, **93**, 1827 (1908).

(5) A. McKillop, J. S. Fowler, and E. C. Taylor, unpublished results.

TABLE I
CONVERSION OF SUBSTITUTED NITROBENZENES INTO AZOXY COMPOUNDS

Nitrobenzene derivative	Azoxy compound	Registry no.	Time, hr[a]	Yield, %[b]	Mp, °C	Lit. mp, °C
Nitrobenzene	Azoxybenzene	495-48-7	6	76	34.5–35.5	35[c]
2-Nitrotoluene	2,2′-Dimethylazoxybenzene	956-31-0	6	73	57–58	60[c]
3-Nitrotoluene	3,3′-Dimethylazoxybenzene	19618-06-5	6	77	33–35	38–39[d]
4-Nitrotoluene	4,4′-Dimethylazoxybenzene	955-98-6	5	77	66–68	68[c]
4-Ethylnitrobenzene	4,4′-Diethylazoxybenzene	23595-86-0	8.5	80	Bp 180–185 (0.7 mm)	bp 244 (16 mm)[e]
2,5-Dimethylnitrobenzene	2,2′,5,5′-Tetramethylazoxybenzene	14381-98-7	7.5	64	110–112	111.5–112.5[f]
2-Nitrobiphenyl	2,2′-Diphenylazoxybenzene	7334-10-3	4.5	84	158–160	160–163[g]
2-Nitroanisole	2,2′-Dimethoxyazoxybenzene	13620-57-0	5.5	80	79–80	81–82[c]
4-Nitroanisole	4,4′-Dimethoxyazoxybenzene	1562-94-3	5.5	76	116.5–118.5, 134.5–135.5	118.5, 135[h]
4-*n*-Butyloxynitrobenzene	4,4′-Di-*n*-butyloxyazoxybenzene	17051-01-3	12	80	102–104, 136.5–137	107, 134[i]
4-*n*-Hexyloxynitrobenzene	4,4′-Di-*n*-hexyloxyazoxybenzene	2587-42-0	7	71	80–81.5, 128.5	81, 127[j]
4-Fluoronitrobenzene	4,4′-Difluoroazoxybenzene	326-04-5	12	89	84–86	86–87[c]
2-Chloronitrobenzene	2,2′-Dichloroazoxybenzene	13556-84-8	1.5	86	53.5–55	55–56[c]
3-Chloronitrobenzene	3,3′-Dichloroazoxybenzene	139-24-2	4.5	84	95.5–97	96[c]
4-Chloronitrobenzene	4,4′-Dichloroazoxybenzene	614-26-6	5	93	154–156	155–156[c]

[a] In most cases about 5–10% of the thallium was *not* consumed during the reaction. Increasing the time of reaction had no significant effect on the yield, and resulted in minor amounts of decomposition. [b] No attempt was made to optimize yields. [c] P. H. Gore and O. H. Wheeler, *J. Amer. Chem. Soc.*, **78**, 2160 (1956). [d] L. Zechmeister and P. Rom, *Ann.*, **468**, 117 (1929). [e] B. T. Newbold and D. Tong, *Can. J. Chem.*, **42**, 836 (1964). [f] E. Bamberger, *Chem. Ber.*, **59**, 418 (1926). [g] E. Wenkert and B. F. Barnett, *J. Amer. Chem. Soc.*, **82**, 4671 (1960). [h] R. S. Porter and J. F. Johnson, *J. Phys. Chem.*, **66**, 1826 (1962). [i] C. Weygand and R. Gabler, *Chem. Ber.*, **71B**, 2399 (1938). [j] C. Weygand and R. Gabler, *J. Prakt. Chem.*, **155**, 332 (1940).

times are necessary (24–60 hr) and yields of azoxy compounds are only moderate in most cases (20–60%).

A particularly important feature of the above transformation is the conversion of thallium into thallium(III) oxide, presumably *via* the intermediacy of the much less stable thallium(I) oxide. It was apparent that use of a solvent which could intercept the initially formed thallium(I) oxide, preferably by formation of a soluble thallium(I) derivative, might simplify considerably the experimental procedure. In justification of this simple rationalization, we have found that oxidation of thallium by aromatic nitro compounds proceeds smoothly in refluxing ethanol.[6] The metal dissolves rapidly to give a homogeneous solution containing thallium(I) ethoxide and the corresponding azoxy compound (eq 2). Addition of potassium

$$2ArNO_2 + 6Tl + 6EtOH \longrightarrow ArN(O^-)=NAr + 6TlOEt + 3H_2O \quad (2)$$

iodide to the reaction mixture results in precipitation of thallium(I) iodide. Removal of the inorganic salt by filtration followed by evaporation of the filtrate under reduced pressure gives the azoxy derivative directly. Yield and experimental data for typical conversions are listed in Table I.

The formation of azoxy compounds by treatment of nitroarenes with various specially prepared modifications of thallium has been noted previously by McHatton and Soulal.[7] Unlike these authors, however, we observed no tar formation in any of the examples quoted. Further, the speed and experimental simplicity of the present procedure, in which commercial thallium is used, contrast favorably with the prolonged reaction times (usually 14–28 days) reported by McHatton and Soulal; the necessity of employing a specially prepared form of the metal is also avoided.

In addition to the examples listed in Table I, investigation of a wide range of substituted nitro compounds has defined the scope and limitations of the present synthesis. Electron-withdrawing substituents (–CHO, –COR, –COOH, –COOR, and –CN) totally inhibit the reaction, as do phenolic hydroxyl groups and both substituted and unsubstituted amino groups. High yields of azoxy compounds are obtained from nitro aromatics with ether or alkyl substituents (see Table I), the positional relationship of the substituents in no way influencing the overall reaction. Both fluoro- and chloro-substituted nitro aromatics react smoothly with retention of the halogen, but bromo- and iodo-substituted compounds give complex mixtures from which only low yields of haloazoxy derivatives could be isolated.

Within these limitations, the present method constitutes a useful alternative to the more commonly accepted procedures for the synthesis of azoxy compounds.[8] In particular, it should be noted that a single pure product was obtained in each of the examples listed in Table I and that, under the reaction conditions indicated, standard control experiments established that azoxy compounds were stable to further reduction either by thallium or thallium(I) ethoxide.[9] It is interesting to note also that, unlike the alkali metal alkoxides, thallium(I) ethoxide does not reduce nitroarenes; 4-nitroanisole, for example, was recovered in quantitative yield after being heated under reflux for 12 hr with an excess of thallium(I) ethoxide in ethanol.

(6) The role of ethanol in this reaction is apparently specific. No azoxy compound was isolated when methanol, 2-methyl-2-propanol, or cyclohexanol was employed as solvent. It should be noted that no appreciable conversion of thallium metal into thallium(I) ethoxide takes place in refluxing ethanol in the *absence* of the nitro compound (see Experimental Section).

(7) L. P. McHatton and M. J. Soulal, *J. Chem. Soc.*, 4095 (1953).

(8) See, for example, P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 321–323; S. Swann, Jr., in "Technique of Organic Chemistry," Vol. II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp 478–481; R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1965, pp 765–768; K. H. Schündehütte in Houben-Weyl's "Methoden der Organischen Chemie," Vol. 10, Part 3, E. Müller, Ed., G. Thieme Verlag, Stuttgart, 1965, pp 752–770.

(9) Formation of small amounts of 2,2′-dichloroazobenzene could be detected when a solution of 2-chloronitrobenzene in ethanol was heated under reflux with thallium for longer than 12 hr. Polyhalonitro compounds, on the other hand, are apparently reduced directly to the corresponding azo compounds. 2,4-Dichloronitrobenzene, for example, gave 2,2′,4,4′-tetrachloroazobenzene in 80% yield on treatment with thallium in refluxing ethanol for 12 hr.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer; the normal Nujol mull technique was used for solids, and liquids were recorded as liquid films.

Reagents.—All of the aromatic nitro compounds were commercial samples and were purified prior to use either by distillation or crystallization. Commercial grade absolute ethanol was employed.

Reaction of Thallium with Ethanol.—Thallium (12 g) was added to 75 ml of ethanol and the mixture was stirred and heated under reflux for 7 days. The clear colorless solution was decanted free of unchanged thallium (10.8 g, 90% recovery) and the volume was made up to 100 ml with ethanol. Titration of 20-ml portions of this solution (diluted with 80-ml portions of water) against 0.1 *N* hydrochloric acid using screened methyl orange as indicator showed that a total of 1.2 g of thallium had been converted into thallium(I) ethoxide.[10]

Reaction of Thallium with Aromatic Nitro Compounds. Preparation of Azoxy Compounds.—A mixture of the aromatic nitro compound (0.014 mol) and thallium (8.5 g, 0.042 mol) in 75 ml of ethanol was stirred and heated under reflux for the appropriate period of time (see Table I). The cooled solution was decanted to remove any unchanged thallium, potassium iodide (8 g) was added, and the mixture was stirred at room temperature for 1 hr. The precipitated thallium(I) iodide was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and the solution was filtered through a short column of alumina (4 × 1 in.) to remove traces of inorganic salts, chloroform being used as eluent. The pure azoxy compound was obtained by evaporation of the chloroform eluate under reduced pressure and crystallization of the residue.

Thallium(I) ethoxide was identified as the inorganic by-product of the reaction in the following manner. A mixture of 4-nitrotoluene (3 g, 0.022 mol) and thallium (13.5 g, 0.066 mol) was heated under reflux for 5.5 hr in 75 ml of ethanol. Unchanged thallium was removed by decantation. A solution of phenol (6.2 g, 0.066 mol) in ethanol was added to the resulting solution, and the precipitated thallium salt was filtered and dried. This gave 16 g (92%) of thallium(I) phenoxide, mp 230–232°, identical in all respects with a genuine sample (lit.[11] mp 231–235°).

Registry No.—Thallium, 7440-28-0.

(10) R. C. Menzies and E. M. Wilkins, *J. Chem. Soc.*, **125**, 1148 (1924).
(11) G. H. Christie and R. C. Menzies, *ibid.*, **127**, 2369 (1925).

Thallium in Organic Synthesis. XII. Improved Syntheses of the 1-Acyloxy-2(1H)-pyridone Class of Active Esters[1,2]

EDWARD C. TAYLOR AND FRANK KIENZLE[3]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

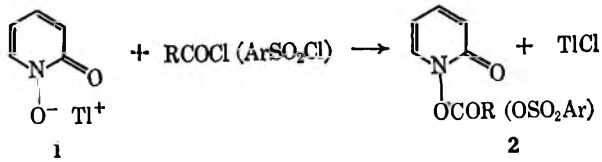
ALEXANDER MCKILLOP[3c]

School of Chemical Sciences, University of East Anglia, Norwich, England

Received October 20, 1969

1-Acyloxy-2(1H)-pyridones (2) have been found by Paquette[4] to be useful, extremely reactive active esters, which he has successfully applied to the synthesis of a number of peptides. The procedure used by Paquette for the preparation of 2 involved heating 2-ethoxypyridine 1-oxide, usually at steam-bath temperature, with the appropriate acid chloride; the resulting 1-acyloxy-2(1H)-pyridones were purified by subsequent recrystallization. Previous studies on the use of thallium in organic synthesis have shown that acylation of thallium(I) salts of carboxylic acids,[5] phenols,[5] cyclic lactams,[6] and β-dicarbonyl compounds[7] by treatment with acid halides proceeds extremely rapidly at room temperature in a heterogeneous ether suspension. We now report a simple synthesis of 1-acyloxy-2(1H)-pyridones (2) by the reaction of acid chlorides with the thallium(I) salt of 1-hydroxy-2(1H)-pyridone (1).

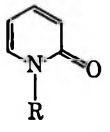
Thus, addition of 1 equiv of an acyl or a sulfonyl chloride to a suspension of the thallium(I) salt of 1-hydroxy-2(1H)-pyridone (1) in anhydrous ether at room



1 2

temperature resulted in the immediate separation of thallium(I) chloride, which was removed by filtration. Evaporation of the ether filtrate gave pure 1-acyl- (or -sulfonyl-) oxy-2(1H)-pyridones (2) in essentially quantitative yield. Representative conversions are given in Table I.

TABLE I
SYNTHESIS OF 1-ACYL- (OR -SULFONYL-) OXY-2-(1H)-PYRIDONES



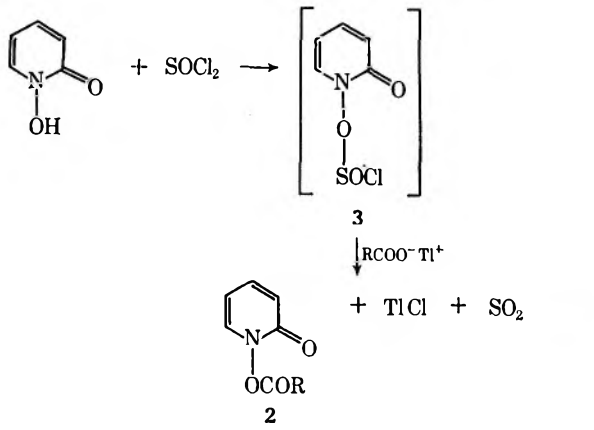
R	% yield Method A[a]	Method B[b]
CH_3COO	95	69
C_6H_5COO	95	60
p-$NO_2C_6H_4COO$	98.5	57
$C_6H_5SO_2$	96	
p-$CH_3C_6H_4SO_2$	95	29

[a] Method A: reaction of the thallium(I) salt of 1-hydroxy-2(1H)-pyridone with the acid halide. [b] Method B: reaction of the thallium(I) carboxylate with 1-hydroxy-2(1H)-pyridone/$SOCl_2$.

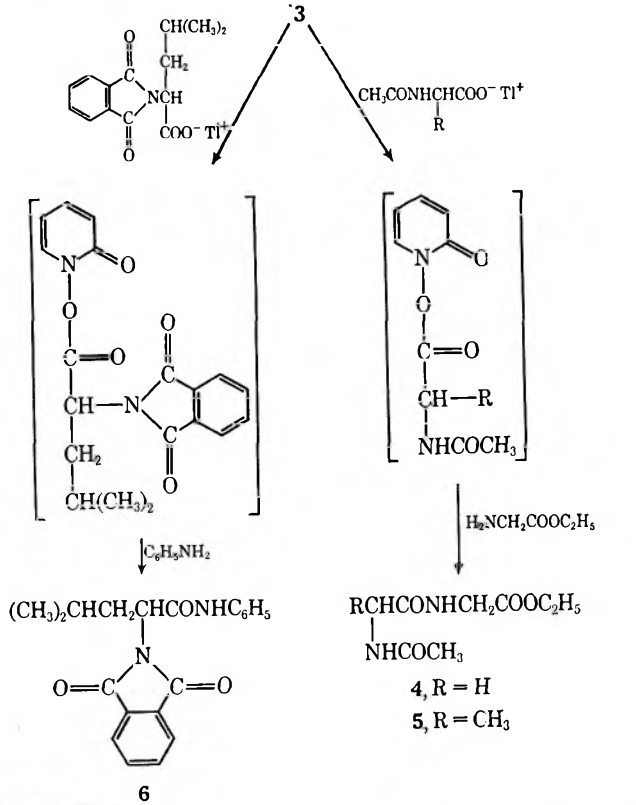
The principle disadvantage of the above synthesis of these active esters (a disadvantage also shared by Paquette's method of synthesis) for the preparation of peptides is the necessity of initial conversion of the amino acid into its corresponding (protected) acid chloride. A synthetic method avoiding the intermediacy of the acid chloride, and allowing the *direct* conversion of the amino acid into the active ester, would have obvious manipulative advantages. We report a method for the direct conversion of the thallium(I) salts of carboxylic acids and N-protected α-amino acids into 1-acyloxy-2(1H)-pyridone active esters (2).

(1) Part XI: A. McKillop, R. A. Raphael, and E. C. Taylor, *J. Org. Chem.*, **35**, 1670 (1970).
(2) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.
(3) NRCC Postdoctoral Fellow, 1968–1970.
(4) L. A. Paquette, *J. Amer. Chem. Soc.*, **87**, 5186 (1965).
(5) E. C. Taylor, G. W. McLay, and A. McKillop, *ibid.*, **90**, 2422 (1968).
(6) A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Lett.*, 4945 (1968).
(7) E. C. Taylor, G. H. Hawks, III, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

This procedure has been successfully applied to the preparation of acetylglycylglycine ethyl ester (**4**) and N-acetyl-DL-alanylglycine ethyl ester (**5**) directly from the corresponding thallium(I) carboxylates, without isolation of the intermediate active esters. Thus, treatment of 1-hydroxy-2(1H)-pyridone with excess thionyl chloride[8] at room temperature, followed by evaporation, gave an unstable oil which we presume to be the N-chlorosulfite **3** (see Experimental Section).

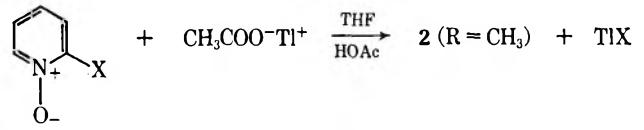


Addition of a thallium(I) carboxylate to a tetrahydrofuran solution of this oil resulted in evolution of sulfur dioxide, immediate deposition of thallium(I) chloride, and the formation of the desired active ester [which could be isolated in crystalline form by filtration of thallium(I) chloride and evaporation of the ether filtrate—see Table I]. For the preparation of amides or dipeptides (*i.e.*, **4** and **5**), however, the active ester was simply treated *in situ* with the desired amine or amino acid ester.



In order to investigate whether optically active amino acids could be converted to their active esters by this procedure with retention of optical purity, the thallium(I) salt of N-phthaloyl-L-leucine was condensed with the chlorosulfite **3** and the resulting active ester, formed *in situ*, was treated with aniline. The optically pure anilide **6** was obtained in 51% yield.

We have briefly investigated an alternate procedure for the direct conversion of thallium(I) carboxylates into the active esters **2**, based on the known propensity for rearrangement of 2-acyloxypyridine 1-oxides to 1-acyloxy-2(1H)-pyridones.[9] Treatment of 2-chloropyridine 1-oxide (**7**) or 2-bromopyridine 1-oxide (**8**) with thallium(I) acetate in tetrahydrofuran containing 20% acetic acid resulted in the formation of 1-acetoxy-2(1H)-pyridone (**2**, R = CH_3) in 58% yield. However, this reaction failed in the absence of excess acetic acid, and also failed in a wide variety of solvent systems (heptane, chloroform, ethyl acetate, pyridine, ether, dimethyl sulfoxide, and dimethylformamide), even in the presence of acid catalysts such as *p*-toluenesulfonic acid. It would thus appear that the effective nucleophile in the conversion of **7** or **8** into **2** (R = CH_3) was acetic acid, and this alternative approach was therefore not further investigated.



7, X = Cl
8, X = Br

Experimental Section[10]

Thallium(I) Salt of 1-Hydroxy-2(1H)-pyridone (1).—Thallium(I) ethoxide (7.47 g, 0.03 mol) was added to a stirred solution of 1-hydroxy-2(1H)-pyridone (3.33 g, 0.03 mol) in 75 ml of tetrahydrofuran. The thallium salt **1** precipitated immediately. Stirring was continued for 10 min, and the solid then was collected and washed well with tetrahydrofuran. The thallium salt, 9.05 g (96.5%), was analytically pure, mp 191–192°.

Anal. Calcd for $C_6H_4NO_2Tl$: C, 19.06; H, 1.28. Found: C, 19.18; H, 1.47.

Thallium(I) Salts of N-Substituted α-Amino Acids. General Procedure.—Thallium(I) ethoxide (0.01 mol) was added to a stirred solution of the amino acid (0.01 mol) in 150–250 ml of acetone. The thallium salt which precipitated immediately was filtered off after 10 min of vigorous stirring, washed well with acetone, and dried *in vacuo*.

Thallium(I) salt of acetylglycine was obtained in 92% yield, mp 76–78° (before drying) and 113° (after drying at 50° *in vacuo* for 5 hr).

Anal. Calcd for $C_4H_6NO_3Tl$: C, 14.99; H, 1.89; N, 4.37. Found: C, 15.04; H, 2.09; N, 4.29.

Thallium(I) salt of N-acetyl-DL-alanine was obtained in 98% yield, mp 165–167°.

Anal. Calcd for $C_5H_8NO_3Tl$: C, 17.95; H, 2.41; N, 4.19. Found: C, 18.29; H, 2.52; N, 4.20.

(8) Open-chain hydroxamic acids are known to rearrange to isocyanates on treatment with thionyl chloride: R. Marquis, *Compt. Rend.*, **143**, 1163 (1906); G. B. Bachman and J. E. Goldmacher, *J. Org. Chem.*, **29**, 2576 (1964). Under milder conditions, however, we have found that N-chlorosulfites analogous to **3** are apparently formed. The synthesis and properties of these interesting intermediates will form the subject of a later report.

(9) A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **11**, 1586 (1963); F. J. Dinah and H. Tieckelman, *J. Org. Chem.*, **29**, 1650 (1964).

(10) Unless otherwise indicated, evaporations were done *in vacuo* at 35–40° (bath temperature). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Infrared data refer to Nujol mull spectra taken on a Perkin-Elmer Model 237B grating infrared spectrometer. Nmr spectra were obtained on a Varian A-60A instrument. The term petroleum ether refers to the fraction of bp 30–60°. Colorless thionyl chloride of bp 75.5–76.5° (Matheson Coleman and Bell) was distilled before use.

Thallium(I) salt of N-phthaloyl-L-leucine was obtained in 78.5% yield, mp 197–198°.

Anal. Calcd for $C_{14}H_{14}NO_4Tl$: C, 36.19; H, 2.97; N, 3.02. Found: C, 36.14; H, 3.38; N, 3.22.

1-Acyl- (or -Sulfonyl-) oxy-2(1H)-pyridones (2). Method A. From 1 and Acyl or Sulfonyl Halides.—The thallium salt **1** (5 mmol) was suspended in 100 ml of anhydrous ether and an equimolar quantity of the acyl or sulfonyl halide was added. The mixture was stirred for 30 min at room temperature and filtered and the filtrate was evaporated. The residue was suspended in petroleum ether to which a small amount of ethyl acetate (10%) had been added; filtration then gave the pure products[11] in practically quantitative yield.

Method B. From Thallium(I) Carboxylates.—A suspension of 1-hydroxy-2(1H)-pyridone (2 g) in 20 ml of thionyl chloride was stirred at room temperature for 20 min with exclusion of moisture. Some 1-hydroxy-2(1H)-pyridone hydrochloride, mp 113–134° dec, was filtered off and the filtrate was evaporated. Excess thionyl chloride was removed by keeping the sample for 10 min *in vacuo* (16 mm) and the residual brown syrup was dissolved in 25 ml of anhydrous tetrahydrofuran. The thallium(I) carboxylate (0.9 equiv, based on the assumption[12] that the syrup constituted pure chlorosulfite **3**, mol wt 193) was added and the mixture was stirred vigorously for 30 min at ambient temperature. Thallium(I) chloride was then filtered off and washed well with anhydrous tetrahydrofuran, the combined filtrates were evaporated, the residue was taken up in 15 ml of anhydrous ethyl acetate, and the solution was left at 5° for several hours. After some insoluble material had been removed by filtration, the 1-acyloxy-2(1H)-pyridone crystallized from the evaporated filtrate on scratching. Stirring in ethyl acetate–petroleum ether followed by filtration gave the crude product, which was purified by crystallization from ethyl acetate. Yields of the various active esters prepared in this way are listed in Table I.

Acetylglycylglycine Ethyl Ester (4).—The chlorosulfite **3** (2.50 g, 13 mmol) was obtained from 2.70 g of 1-hydroxy-2(1H)-pyridone as described above (method B) and dissolved in 25 ml of anhydrous tetrahydrofuran. To the stirred solution was added 3.85 g (12 mmol) of thallium(I) acetylglycinate and stirring was continued for 30 min. After the precipitated thallium(I) chloride had been filtered off, glycine ethyl ester (1.24 g, 12 mmol) and 5 drops of triethylamine were added and the mixture was stirred at room temperature for 2.5 hr. A small amount of solid material was removed by filtration and the filtrate was evaporated to yield a syrup which was dissolved in 20 ml of water. The aqueous solution was passed through a column containing (lower half) of 10 g of Dowex 50W-X4 (H^+) and (upper half, separated by a plug of glass wool) 10 g of Dowex 21K (OH^-). The column was thoroughly washed with water and the combined eluates were evaporated. Two coevaporations with absolute ethanol followed by treatment with activated charcoal gave 1.02 g (42%) of a colorless solid, mp 139–141°. Recrystallization from absolute ethanol raised the melting point to 147–148° (lit. mp 152[13] and 150°[14]). The nmr spectrum (in D_2O) confirmed structure **4**.

N-Acetyl-DL-alanylglycine Ethyl Ester (5).—The dipeptide **5** was obtained from **3**, the thallium(I) salt of N-acetyl-DL-alanine, and glycine ethyl ester, in a similar manner to that described for the synthesis of **4**. Crystallization of the crude product, mp 109–111°, from chloroform–petroleum ether gave pure material, mp 113–115°, yield 29%.

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.98; H, 7.46; N, 13.25. Found: C, 49.64; H, 7.29; N, 13.08.

The nmr spectrum of **5** ($CDCl_3$) showed a triplet at τ 8.73 (3 H), a doublet at 8.60 (3 H), a singlet at 8.00 (3 H), a singlet at 6.02 (2 H), a quartet at 5.80 (2 H), and a quartet at 5.38 (1 H).

N-Phthaloyl-L-leucine Anilide (6).—The chlorosulfite **3** (1.0 g, 5.2 mmol) was dissolved in 20 ml of anhydrous tetrahydrofuran and 1.57 g (4.65 mmol) of the thallium(I) salt of N-phthaloyl-L-leucine added. The mixture was stirred at room temperature for 1 hr, then, without filtration, aniline (510 mg, 5.5 mmol) was added, and stirring was continued for 2 hr. The syrup which was obtained after filtration and evaporation was dissolved in methylene chloride (60 ml), the solution was extracted twice with 20-ml portions of a 5% aqueous sodium bicarbonate solution, the organic layer was dried over anhydrous sodium sulfate, treated with activated charcoal, and filtered, and the filtrate was evaporated. The residue was dried *in vacuo* to give 970 mg of crude product, mp 130–135°. Crystallization from benzene–petroleum ether gave 795 mg (51%) of beautiful needles, mp 154–155°, $[\alpha]_D$ −21° (c 0.9, glacial acetic acid).[15]

1-Acetoxy-2(1H)-pyridone (2, R = CH_3).—2-Bromopyridine 1-oxide (**8**) hydrochloride (1.2 g, 6.1 mmol) was suspended in 10 ml of anhydrous tetrahydrofuran and 10 g of sodium bicarbonate was added. The slurry was mixed well and filtered after 10 min; the residue was thoroughly washed with tetrahydrofuran. The volume of the filtrate was then approximately 50 ml. Thallium(I) acetate (1.6 g, 6.1 mmol) was added together with 10 ml of glacial acetic acid [to dissolve the thallium(I) salt] and 5 ml of acetic anhydride (to remove traces of water). The clear solution was then heated under reflux; after 30 min a fine precipitate of thallium(I) bromide started to separate. Heating was continued for 18 hr, thallium(I) bromide (1.19 g, 66.9%) was removed by filtration, and the filtrate was evaporated. The syrupy residue was dissolved in anhydrous ethyl acetate and unreacted insoluble thallium(I) acetate was removed by filtration. Addition of petroleum ether resulted in slow crystallization of 510 mg (59%) of **2** (R = CH_3), mp 92–93°. Recrystallization from ethyl acetate–petroleum ether gave beautiful prisms, mp 94–95° (lit.[4] mp 93–94°).[16]

2-Chloropyridine 1-oxide (**7**) under the same conditions gave (R = CH_3) in 58% yield.

Registry No.—Thallium (I) salt of acetylglycine, 23715-40-4; thallium (I) salt of N-acetyl-DL-alanine, 23715-41-5; thallium (I) salt of N-phthaloyl-L-leucine, 23715-42-6; **1**, 23715-39-1; **4**, 3757-98-0; **5**, 23595-74-6.

(11) Identity and purity were determined by comparison of physical data (melting point and ir and uv spectra) with reported values.[4]

(12) Attempted purification of this syrup led to extensive decomposition. We assume that it is the N-chlorosulfite **3** rather than N-chloro-2(1H)-pyridone because reaction with the thallium(I) carboxylate results in vigorous evolution of sulfur dioxide. Gas evolution is almost explosive in the absence of solvent, but is readily controlled if the N-chlorosulfite is dissolved in tetrahydrofuran before the thallium(I) carboxylate is added.

(13) E. Fischer, *Chem. Ber.*, **35**, 1095 (1902).

(14) R. G. Petrova, L. N. Akinova, and N. I. Gavrilov, *Zh. Obshch. Khim.*, **24**, 2239 (1954).

(15) J. C. Sheehan, D. W. Chapman, and R. W. Roth [*J. Amer. Chem. Soc.*, **74**, 3822 (1952)] reported mp 154.5–156°, $[\alpha]_D$ −21° (acetic acid).

(16) Uv and ir spectra were also identical with the reported values.[4]

The Addition of N-Bromosuccinimide to 3-Sulfolene

J. M. LANDESBERG AND M. SIEGEL

Adelphi University, Garden City, New York 11530

Received November 13, 1969

The use of N-bromosuccinimide (NBS) as an allylic brominating agent has been known for some time and has enjoyed wide applicability.[1] A lesser known, but not entirely unknown, reaction of NBS is the addition of this reagent to the double bond.[1b,2-4] This latter process is usually observed when electron-withdrawing groups[3] or steric factors[2] make stabilization of the allylic radical difficult. Succinimido radicals have been suggested.[2,3]

In connection with the above, we have reexamined the reaction of NBS with 2,5-dihydrothiophene-1,1-dioxide (3-sulfolene, **1**). Backer, *et al.*,[5] reported that

(1) (a) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); (b) L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

(2) L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **29**, 1290 (1964), and references cited therein.

(3) W. J. Bailey and J. Bello, *ibid.*, **20**, 525 (1955).

(4) J. R. Shelton and C. Ciadella, *ibid.*, **23**, 1128 (1958).

(5) H. J. Backer, W. Stevens, and N. Dost, *Rec. Trav. Chim. Pays-Bas*, **67**, 451 (1948); *Chem. Abstr.*, **43**, 558 (1948).

the reaction of these reagents in CCl_4, both with or without the addition of benzoyl peroxide (or ultraviolet irradiation), led to the recovery of starting material along with 3,4-dibromosulfolane and succinimide. The lack of any allylic bromination product suggested a destabilizing influence from the sulfone. One might then anticipate addition to the double bond, and the presence of adduct in the reaction mixture was sought.

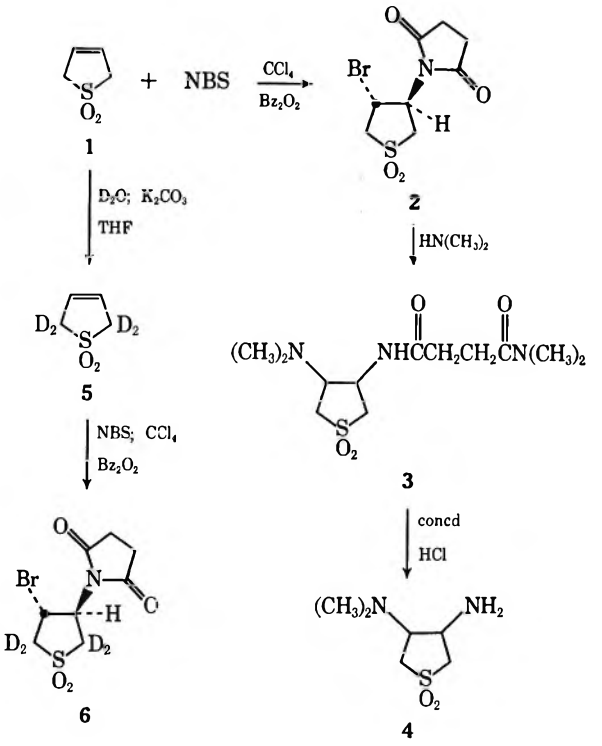
When **1** and NBS are heated in CCl_4 in the presence of benzoyl peroxide, as Backer describes, a solid separates. Examination of this solid by tlc showed the presence of succinimide and a second component which was found to be a 1:1 adduct. Spectral data confirmed the gross structure of the adduct as **2**. An attempt to form the adduct without any benzoyl peroxide in solution was unsuccessful; only the products reported by Backer were isolated.[5]

The positions of substitution and the geometry of the substituents at these positions were established by the nmr spectrum of the adduct **6** obtained from NBS addition to 2,2,5,5-tetradeuteriothiophene 1,1-dioxide (**5**).[6] The nmr spectrum of **6** shows a two-proton signal centered at δ 5.10 for the protons at C_3 and C_4, compared with the chemical shift of analogous protons of 3,4-dibromosulfolane at δ 4.85–5.10 (m).[7] The δ 5.10 absorption could be resolved into two signals with a separation of only 2 cps. The lack of any significant coupling constant is consistent with a *trans*-substitution pattern on a five-membered ring.[8] Thus, the 3-bromo and 4-succinimido groups are situated *trans* in the five-membered sulfone ring.

While the mechanism of addition is not known with certainty, the fact that the reaction only takes place when benzoyl peroxide is present is suggestive of a free-radical process[2] rather than one of polar addition. The intermediacy of succinimido radicals is implied.[9] This reaction is analogous to one observed by Kharasch, *et al.*[10] Here bromotrichloromethane ($BrCCl_3$) reacts with 3-sulfolene in the presence of peroxides to yield 3-bromo-4-(trichloromethyl)sulfolane in a free-radical process.

Further transformations of **2** were possible. Thus dimethylamine displaced bromine and opened the succinimide ring; concentrated hydrochloric acid hydrolyzed the side chain and led to diamine **4**. Scheme I summarizes these reactions.

SCHEME I



Experimental Section

General.—All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer grating infrared spectrophotometer, Model 257. The 1601-cm^{-1} peak of polystyrene is used as the reference standard. Nuclear magnetic resonance spectra were measured on a Varian A-60, with chemical shifts recorded in δ units downfield from tetramethylsilane. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

***trans*-3-Bromo-4-succinimidotetrahydrothiophene 1,1-Dioxide (2).**—2,5-Dihydrothiophene 1,1-dioxide (20.0 g, 0.169 mol), N-bromosuccinimide (33.2 g, 0.188 mol), and benzoyl peroxide (1.00 g) were refluxed in carbon tetrachloride (500 ml) for 12 hr. The solution was then cooled to room temperature and filtered. The solid material was stirred with chloroform (100 ml) for 15 min before filtering; this yielded 3.90 g (7.8%) of **2**, mp 217–218.5°. A single recrystallization from methanol raised the melting point to 218–219°.

Anal. Calcd for $C_8H_{10}BrNO_4S$: C, 32.44; H, 3.40; N, 4.73; Br, 26.98; S, 10.83. Found: C, 32.59; H, 3.28; N, 4.69; Br, 26.85; S, 10.84.

The spectral characteristics of **2** are as follows: ir (Nujol) 1700 (broad, amide C=O), 1315 (broad, SO_2), 1130, and 1145 cm^{-1} (strong, SO_2); nmr (DMSO-d_6) δ 5.30–4.75 [m, 2, $-CH(Br)CH(N<)-$], 4.08–3.40 (m, 4, $-CH_2SO_2CH_2-$), and 2.73 [s, 4, $-C(O)CH_2CH_2C(O)-$].

N-[4-(3-Dimethylaminotetrahydrothiophene 1,1-dioxide)]-N′,N′-dimethylsuccinimide (3).—Compound **2** (7.94 g, 26.8 mmol) was slowly added as a solid to a cooled, stirred solution of dimethylamine (48.8 g, 1.08 mol) in benzene (265 ml). This mixture was then stirred for 3 days at room temperature. The solution was then filtered, excess dimethylamine was removed under vacuum, and the remaining benzene solution was washed with 15% hydrochloric acid. The aqueous phase was washed with chloroform, cooled, and neutralized with concentrated sodium hydroxide. This was washed with chloroform, and the combined chloroform extracts were dried ($MgSO_4$) and concentrated while the temperature was maintained below 30°. An oil remained. The oil, when taken up in benzene–ether, deposited crystals, mp 142–143°. Recrystallization from ethyl acetate gave 74 mg (9%) of **3**, mp 143.5–144.5°.

Anal. Calcd for $C_{12}H_{23}N_3O_4S$: C, 47.19; H, 7.59; N, 13.76. Found: C, 46.92; H, 7.75; N, 13.60.

The spectral characteristics of **3** are as follows: ir (Nujol) 3240 (broad, NH), 1620 (broad, amide C=O), 1340, 1150, and 1130 cm^{-1} (strong, SO_2); nmr ($CDCl_3$) δ 7.33–7.0 (broad, 1, –NH–), 4.85–4.23 [m, 1, $-CH(NH-)-$], 3.90–3.08 [m, 5, $-CH_2-SO_2CH_2CH(N<)-$], 3.03, 2.95, [s, 6, $O=CN(CH_3)CH_3$], 2.60 [s, 4, $-C(O)CH_2CH_2C(O)-$], and 2.33 [s, 6, $-N(CH_3)_2$].

3-Amino-4-dimethylaminotetrahydrothiophene 1,1-Dioxide (4).—Compound **3** (245 mg, 0.802 mmol) was refluxed in concentrated hydrochloric acid (10 ml) for 12 hr. The solution was then washed with chloroform; the aqueous phase was cooled, neutralized with concentrated sodium hydroxide, and washed with chloroform. The chloroform extract was dried ($MgSO_4$)

(6) D. S. Weinberg, C. Stafford, and M. W. Scoggins, *Tetrahedron*, **24**, 5409 (1968).

(7) "The Sadtler Standard Spectra," Vol. 2, Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 586.

(8) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 117.

(9) T. R. Beebe and F. M. Howard [*J. Amer. Chem. Soc.*, **91**, 3379 (1969)] have demonstrated the intermediacy of succinimido radicals.

(10) M. S. Kharasch, M. Freiman, and W. H. Urry, *J. Org. Chem.*, **13**, 570 (1948).

and concentrated to yield an oil. This oil was taken up in ether, an equal volume of petroleum ether (bp 30–60°) was added, and the solution was cooled; 70 mg (49%) of **4** separated, mp 79–80.5°.

Anal. Calcd for $C_6H_{14}N_2O_2S$: C, 40.43; H, 7.92; N, 15.72. Found: C, 40.25; H, 7.95; N, 15.43.

The spectral characteristics of **4** are as follows: ir (Nujol) 3360 (strong, NH), 1350, 1160, 1135, and 1120 cm^{-1} (strong, SO_2); nmr ($CDCl_3$) δ 3.80–2.67 (m, 6, ring protons), 2.33 [s, 6, $-N(CH_3)_2$], and 1.67 (broad, 2, $-NH_2$).

2,2,5,5-Tetradeuteriothiophene 1,1-Dioxide (5).—This compound was prepared according to the method of Weinberg, *et al.*[6] 2,5-Dihydrothiophene 1,1-dioxide (1.18 g, 9.98 mmol) was dissolved in tetrahydrofuran (10 ml); to this solution was added deuterium oxide (20.4 g, 99.7%, Merck Sharp and Dohme of Canada, Ltd.) and anhydrous potassium carbonate (0.5 g). The mixture was stirred for 2 days at room temperature. Solvent was removed under vacuum. Deuterium oxide (13 g) and tetrahydrofuran (7 ml) were added and the procedure was repeated. Solvent was then removed. The residue was triturated with chloroform, and the chloroform was dried ($MgSO_4$), filtered, and evaporated to yield 0.945 g (77.5%) of **5**, mp 63–64°. The nmr spectrum showed greater than 95% deuterium incorporation: nmr ($CDCl_3$) δ 6.05 (s).

***trans*-3-Bromo-3,4-dihydro-4-succinimido-2,2,5,5-tetradeuteriothiophene 1,1-Dioxide (6).**—Compound **5** (820 mg, 6.71 mmol), N-bromosuccinimide (670 mg, 3.76 mmol) and benzoyl peroxide (570 mg) were refluxed in carbon tetrachloride (15 ml) for 3 hr. The solution was then cooled and filtered. The collected solid material was taken up in chloroform and the solution was filtered. The filtrate was concentrated, methanol was added and heated, and the hot solution was filtered. Upon cooling, the filtrate deposited light yellow crystals. Recrystallization from methanol gave white needles: mp 214–215°; nmr (DMSO-d_6) δ 5.10 (two resolved signals which are separated by 2 cps, two hydrogens on C_3 and C_4) and 2.77 [s, 4, $-C(O)CH_2CH_2C(O)-$].

Registry No.—**1**, 77-79-2; **2**, 23740-31-0; **3**, 23740-32-1; **4**, 23740-33-2; **5**, 20966-34-1; **6**, 23829-44-9; N-bromosuccinimide, 128-08-5.

Acknowledgment.—We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant 1061-G).

Potential Folic Acid Antagonists. IV. Synthetic Approaches to Analogs of Aminopterin and Methotrexate. IV. The Preparation of *p*-{[(2,4-Diamino-6-pteridinyl)methyl]amino}-benzoic Acids[1,2]

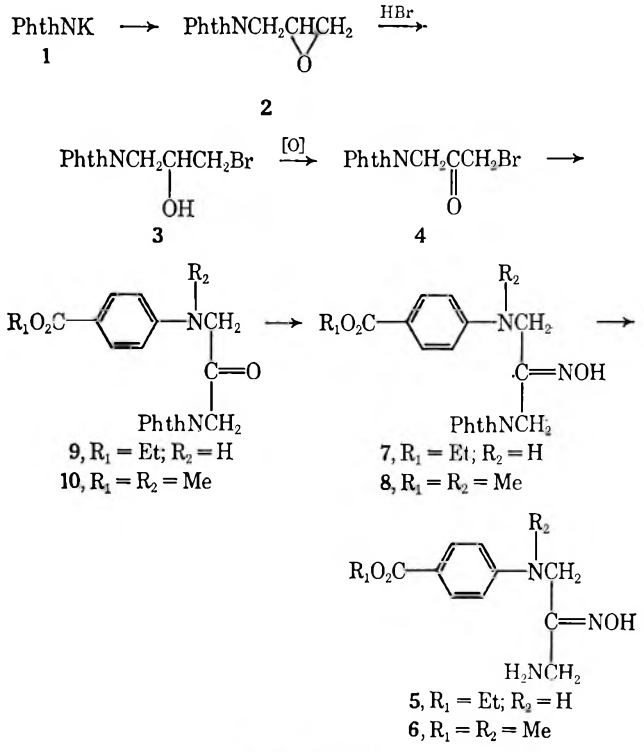
ROBERT D. ELLIOTT, CARROLL TEMPLE, JR., AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received October 27, 1969

As part of our program on the synthesis of folic acid antagonists, methods were needed for the construction of the pyrazine ring containing the *p*-(methyleneamino)-benzoyl moiety of folic acid, and of its analogs aminopterin and methotrexate. Although the preparation of the pteroic acid analogs **21**[3] and **23**[4] by the reaction of 2,4,5,6-tetraaminopyrimidine with a *p*-aminobenzoic acid in the presence of a halogenated three-carbon aldehyde or ketone has been reported, the former was obtained in a crude mixture and the latter as a dihydrate in unspecified yield. This method of preparation is unattractive in that the desired product is obtained in low yield and is difficult, if not impossible, to purify. Previously, Boon and Leigh[5] developed an unambiguous route to 6-substituted pteridines that involved the reduction of [(5-phenylazo-4-pyrimidinyl)amino]acetones. However, the synthesis by this method of a 6-(phenoxymethyl)pteridine for use as an intermediate for the preparation of compounds like **21** and **23** was unsuccessful when the phenoxy group underwent reductive cleavage. We report the preparation of some *p*-{[(2,4-diamino-6-pteridinyl)methyl]amino}benzoic acids by a modification of the Boon and Leigh procedure, which will also be used to prepare other analogs in which the pyrimidine ring has been replaced with the pyridine ring to give the corresponding 1- and 3-deazapteridine ring systems.

The intermediate N-3-(bromoacetonyl)phthalimide (**4**) was prepared in three steps in 24% yield from potassium phthalimide (**1**) *via* **2** and **3**.[6] Alkylation of



Phth = phthaloyl

ethyl *p*-aminobenzoate and methyl *p*-(methylamino)-benzoate,[7] respectively, with the bromo ketone **4** gave the diaminoacetones **9** (72%) and **10** (34%). The condensation of these keto compounds with $NH_2OH \cdot HCl$ in a refluxing mixture of pyridine and EtOH gave the corresponding oximes **7** (43%) and **8** (72%), both isolated as a mixture of the *syn* and *anti* isomers. The

(1) This work was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) For a related paper in this series, see R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 533 (1949).

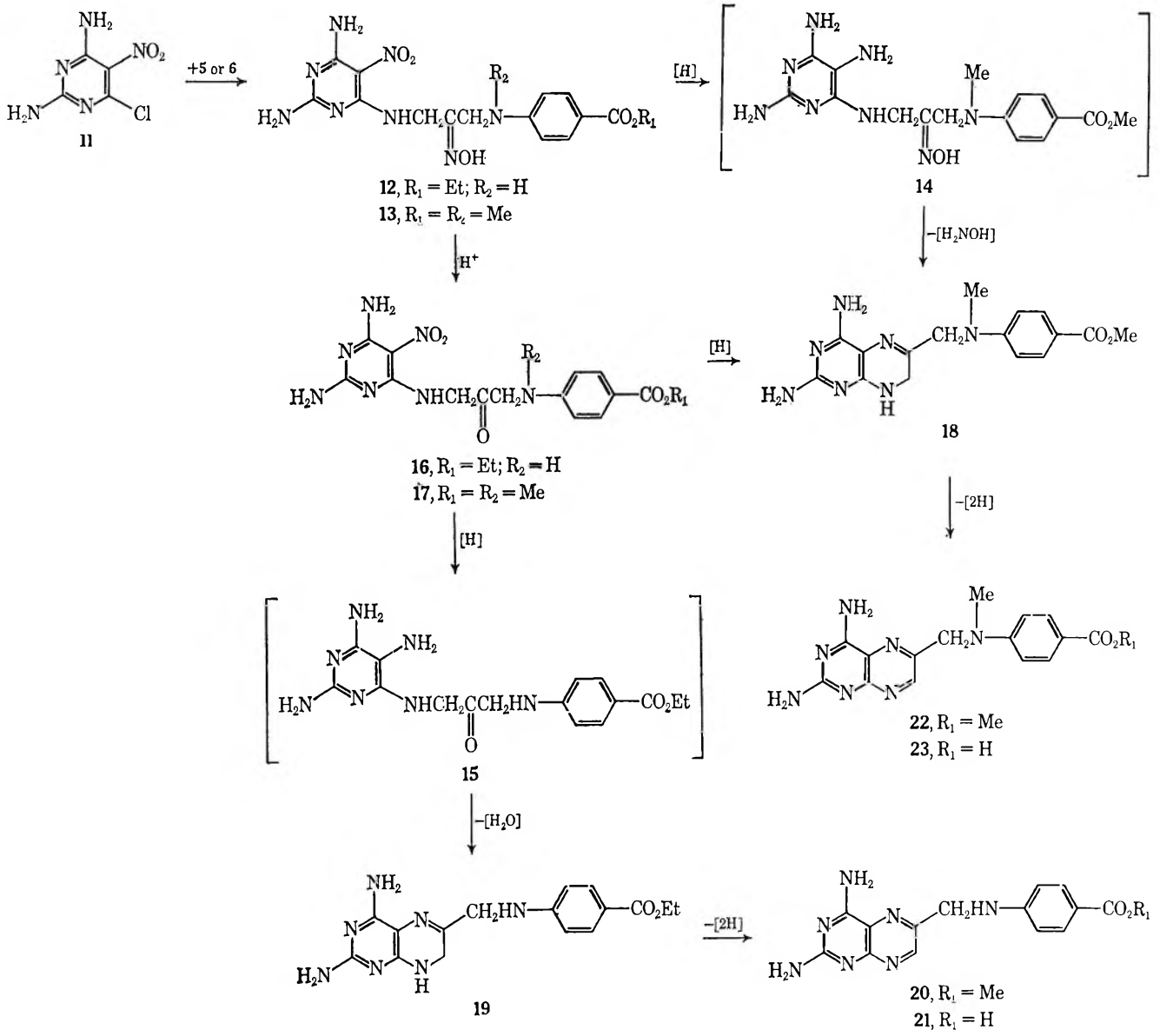
(3) D. R. Seeger, U. S. Patent 2,568,597 (1947).

(4) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949).

(5) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(6) D. P. Tschudy and A. Collins, *J. Org. Chem.*, **24**, 556 (1959).

(7) F. Klaus and O. Baudisch, *Ber.*, **51**, 1044 (1918).



phthaloyl protecting group of **7** and **8**, respectively, was cleaved with anhydrous N_2H_4 in EtOH to give the oximes of the diaminoacetones **5** (72%) and **6** (71%).

The known 2,4-diamino-6-chloro-5-nitropyrimidine (**11**) was prepared by the nitration of 2,4-diamino-6-chloropyrimidine.[8] The alkylation of the aminoacetone oxime **5** with **11** was carried out in ethanolic Et_3N to give a homogeneous sample of the 3-[(4-pyrimidinyl)-amino]acetone oxime **12** (tlc). The latter was not purified but was hydrolyzed with HCl to give the hydrochloride of the 3-[(4-pyrimidinyl)amino]acetone **16**. The nitro group of the latter was reduced with Raney nickel in a large volume of EtOH, and the resulting 5-aminopyrimidine (**15**) was cyclized *in situ* to give the 7,8-dihydropteridine **19**. This product analyzed correctly for **19**, but its tlc indicated the presence of a trace amount of the heteroaromatic pteridine **20**. Oxidation of this material with $KMnO_4$ in Me_2CO gave a pure sample of the heteroaromatic compound **20**. Hydrolysis of the ester moiety of the latter to the benzoic acid **21** was attempted with NaOH in DMSO, but this reaction appeared to give only decomposition products.[9] Also treatment of **20** with NaOAc in HOAc for an extended period of time provided an eight-component mixture containing **20** (tlc). The conversion of **20** to **21** was also attempted by transesterification with refluxing HCO_2H, but this reaction resulted in formylation of the amino groups without affecting the ester function (pmr).

The alkylation of **6** with the chloropyrimidine **11** gave the oxime **13** (91%), which was treated with HCl to give **17** (75%). The hydrogenation of **17** in the presence of Raney nickel in EtOH gave the dihydropteridine **18** (39%). However, this reduction required a long period of time (6 days), which was attributed to the low solubility of ketone **17** in EtOH.

Another route to **18** involved the reduction of the nitro group of the oxime **13**. The reduction mixture from this hydrogenation gave an analytically pure sample of the dihydropteridine **18**, *in situ* cyclization presumably resulting from a transamination-type reaction between the pyrimidine 5-amino group and the side-chain oxime function of **14**. The low yield of **18** suggested that reduction of the oxime function was a

(8) D. E. O'Brien, C. C. Cheng, and W. Pfleiderer, *J. Med. Chem.*, **9**, 573 (1966).

(9) Alkaline aerobic treatment of related compounds resulted in cleavage at the 9,10 bond and hydrolysis of the 4-amino group; see ref 4.

competing reaction. Oxidation of **18** with $KMnO_4$ gave the heteroaromatic pteridine **22**, and careful hydrolysis of the ester function of the latter with NaOH in DMSO gave the benzoic acid **23**. Although this sample was shown to be homogeneous by its chromatographic behavior and its pmr spectrum, analysis for chlorine showed that this material was a partial hydrochloride.[10] The stability of the 9,10 bond in the 10-N-methyl compound to alkaline conditions has been noted previously.[4]

Experimental Section

Melting points were determined on a Kofler Heizbank or when indicated on a Mel-Temp apparatus. The ultraviolet absorption spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer, whereas the infrared absorption spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 521 spectrophotometer. The pmr spectra were determined in deuterated DMSO with a Varian A-60A spectrometer at a probe temperature of about 40° using tetramethylsilane as an internal reference. The relative peak areas are given to the nearest whole number. Thin layer chromatograms were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of $CHCl_3$ and MeOH.

Ethyl *p*-[(3-Aminoacetonyl)amino]benzoate Oxime (5).—A stirred solution of **7** (10.8 g, 28.3 mmol) in EtOH (425 ml) at 70° was treated dropwise under N_2 with 95% NH_2NH_2 (0.98 ml, ~29 mmol). The solution was cooled to 43° and maintained at this temperature for 16 hr. The resulting mixture was refluxed for 30 min, cooled to 25°, and treated dropwise with 1 *N* HCl (28.3 ml, 28.3 mmol). After stirring for 1 hr the mixture was cooled to 0° and filtered to remove phthalhydrazide. The filtrate was evaporated to dryness *in vacuo* at ~40°, the residue was stirred with H_2O (44 ml), and the evaporation was repeated. A solution of the residue in warm H_2O (71 ml) was filtered, cooled to 25°, and treated with charcoal. The resulting filtrate was cooled in an ice bath and treated dropwise with concentrated NH_4OH (1.8 ml) to give a gummy precipitate, which crystallized to a homogeneous powder on stirring. The light tan product was collected by filtration, washed with cold H_2O, and dried *in vacuo* over P_2O_5: yield 5.09 g (72%); mp 122–124°. Tlc showed that this product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 223 (8.88), 300 (23.2); $\bar{\nu}_{max}$, cm^{-1}, 3410 3360, 3310, 3160 (NH, OH), 1683 (C=O), 1605 (NH), 1595, 1525 (C=C), 1280 (COC).

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.33; H, 7.01; N, 16.86.

Methyl *p*-[(3-Aminoacetonyl)methylamino]benzoate Oxime (6).—Similarly, a solution of **8** (23.7 g, 62.4 mmol) in EtOH (950 ml) at 50° was treated dropwise with 95% N_2H_4 (2.2 ml, ~64 mmol) and stirred at 39° for 16 hr: yield 11.3 g (71%); mp ~141°. Tlc showed that this product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 226 (7.88), 309 (25.7); $\bar{\nu}_{max}$, cm^{-1}, 3360, 3295, 3170 (NH), 3040, 2940, 2830 (CH), 1672 (C=O), 1600, 1575, 1520 (C=C), 1283 (COC).

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.19; H, 6.63; N, 16.53.

Ethyl *p*-[(3-Phthalimidoacetonyl)amino]benzoate Oxime (7).—A solution of **9** (7.87 g, 21.5 mmol), hydroxylamine hydrochloride (2.24 g, 32.2 mmol), pyridine (20 ml), and EtOH (20 ml) was refluxed under N_2 for 2 hr. The resulting mixture was evaporated to a viscous syrup under reduced pressure (1 mm) at 60°. The syrup was triturated with water (two × 10-ml portions) at 0° and stirred with EtOH (25 ml) until a homogeneous suspension was formed. The mixture was cooled to 15° and the product was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5: yield 3.55 g (43%); mp 186°. Tlc showed that the product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (10.0), 304 (21.1); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3375 (NH), 2980, 2950, 2935, 2900 (CH), 1760, 1695, 1670 (C=O), 1595, 1570, 1530 (C=C), 1275 (COC).

Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 63.11; H, 5.09; N, 11.18.

(10) This material was previously reported as the dihydrate; see ref 4.

Methyl *p*-[Methyl(3-phthalimidoacetonyl)amino]benzoate Oxime (8).—Similarly, a solution of **10** (34.8 g, 95.1 mmol), hydroxylamine hydrochloride (9.92 g, 143 mmol), EtOH (85 ml), and pyridine (85 ml) gave a pale yellow crystalline product, which was collected by filtration, washed with cold EtOH, and dried *in vacuo* at 78° over P_2O_5: yield 25.7 g; mp 131°. Tlc showed that this material was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 314 (22.1); $\bar{\nu}_{max}$, cm^{-1}, 2950, 2900, 2830 (CH), 1765, 1710, 1700 (C=O), 1600, 1550, 1520 (C=C), 1280 (COC).

Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 62.92; H, 4.93; N, 10.98.

The mother liquor deposited additional product (0.40 g), which was shown by tlc to be a single isomer, mp 148°. The total yield was 26.1 g (72%).

Ethyl *p*-[(3-Phthalimidoacetonyl)amino]benzoate (9).—A mixture of **4** (4.00 g, 14.2 mmol), ethyl *p*-aminobenzoate (2.34 g, 14.2 mmol), $NaHCO_3$ (1.19 g, 14.2 mmol), and anhydrous DMF (50 ml) was stirred at 54° for 16 hr. The resulting solution was filtered and treated dropwise with H_2O (200 ml) at 0°. The pale yellow precipitate was collected by filtration, washed with cold H_2O, and dried *in vacuo* over P_2O_5: yield 3.72 g (72%); mp 216°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (16.0), 247 (sh), 295 (10.7); $\bar{\nu}_{max}$, cm^{-1}, 3440, 3380 (NH), 2965, 2920, 2880 (CH), 1775, 1725, 1710, 1690 (C=O), 1600, 1520 (C=C), 1270 (COC).

Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.38; H, 4.79; N, 7.82.

Methyl *p*-[Methyl(3-phthalimidoacetonyl)amino]benzoate (10).—Similarly, a mixture of **4** (50.7 g, 180 mmol), methyl *p*-(methylamino)benzoate (29.6 g, 180 mmol), $NaHCO_3$ (15.1 g, 180 mmol), and anhydrous DMF (628 ml) was stirred at 58° for 16 hr. After cooling to 25°, the mixture was filtered (charcoal), and the filtrate was treated dropwise with H_2O (718 ml). The resulting mixture was cooled to 20°, and the product was collected by filtration, washed with 1:1 DMF–H_2O (25 ml) followed by H_2O, and dried *in vacuo* over P_2O_5: yield 22.4 g (34%); mp 195°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 308 (24.0); $\bar{\nu}_{max}$, cm^{-1}, 3020, 2995, 2945, 2825 (CH), 1773, 1713, 1690 (C=O), 1600, 1555, 1518 (C=C), 1282 (COC).

Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.60; H, 5.00; N, 7.58.

Methyl *p*-({3-[(2,6-Diamino-5-nitro-4-pyrimidinyl)amino]acetonyl}methylamino)benzoate Oxime (13).—Finely powdered **11** (6.04 g, 31.9 mmol) was added in small portions to a stirred suspension of **6** (8.00 g, 31.9 mmol) in EtOH (160 ml). The suspension was treated dropwise with Et_3N (3.02 g, 33.5 mmol) and stirred at 42° for 16 hr. The resulting mixture was cooled to 0°; the product was collected by filtration, washed with cold EtOH, and dried at 78° *in vacuo* over P_2O_5: yield 11.7 g (91%); mp ~140–145° with presoftening from 135° (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 226 (27.6), 317 (30.5); pH 7, 317 (32.8); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3395, 3345, 3190 (NH, OH), 2945, 2910, 2840 (CH), 1695 (C=O), 1605 (NH_2), 1545 (C=C, C=N), 1290 (COC).

Anal. Calcd for $C_{16}H_{20}N_8O_5$: C, 47.52; H, 4.99; N, 27.71. Found: C, 47.29; H, 5.18; N, 27.91.

Ethyl *p*-[3-(2,6-Diamino-5-nitropyrimidin-4-ylamino)acetonylamino]benzoate Hydrochloride (16).—Finely powdered **11** (2.58 g, 13.6 mmol) was added in small portions to a stirred suspension of powdered **5** (3.42 g, 13.6 mmol) in EtOH (68 ml). The suspension was treated dropwise with Et_3N (1.38 g, 13.6 mmol) and stirred at 40° for 17 hr. The resulting mixture was cooled in an ice bath, and the precipitate of **12** was collected by filtration under N_2, washed with cold EtOH, and dried *in vacuo* over P_2O_5: yield 4.71 g (86%); mp 141°. Tlc showed that the product was homogeneous. A portion of the oxime (0.624 g, 1.54 mmol) was added in small portions with stirring to 1 *N* HCl (15.0 ml, 15.0 mmol) at 60°. The mixture was stirred at 60° for 20 min, cooled to 25°, and neutralized by addition of $NaHCO_3$ (1.26 g, 15 mmol). The tan product was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 0.600 g (92%); mp ~204° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 303 (24.2), 340 (19.5); $\bar{\nu}_{max}$, cm^{-1}, 3380, 3325, 3275, 3230, 3150 (NH), 3050, 2970 (CH), 1728, 1670 (sh) (C=O), 1655 (NH_2), 1600, 1525 (C=C, C=N), 1278 (COC).

Anal. Calcd for $C_{16}H_{19}N_7O_5 \cdot HCl$: C, 45.13; H, 4.73; N, 23.02; Cl, 8.33. Found: C, 45.25; H, 4.53; N, 23.33; Cl, 8.46.

Methyl *p*-({3-[(2,6-Diamino-5-nitro-4-pyrimidinyl)amino]acetonyl}methylamino)benzoate (17).—A stirred solution of **13** (404

mg, 1.00 mmol) in DMAC (10 ml) at 62° was treated dropwise with 1 *N* HCl (10 ml). The resulting mixture was stirred at 62° for 20 min, cooled to 25°, and treated with $NaHCO_3$ (756 mg, 9.00 mmol). The yellow product was collected, washed with H_2O, and dried at 65° *in vacuo* over P_2O_5: yield 290 mg (75%). This sample undergoes slow decomposition above 200°: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 313 (29.8); $\bar{\nu}_{max}$, cm^{-1}, 3477, 3385, 3350, 3320, 3120 (NH), 2948, 2916, 2900, 2828 (CH), 1719, 1688 (C=O), 1647 (NH_2), 1603, 1551, 1520 (C=C, C=N), 1295 (COC).

Anal. Calcd for $C_{16}H_{19}N_7O_5$: C, 49.36; H, 4.92; N, 25.18. Found: C, 49.16; H, 4.64; N, 25.45.

Methyl *p*-{[(2,4-Diamino-7,8-dihydro-6-pteridinyl)methyl]methylamino}benzoate (18). A.—A suspension of **13** (4.04 g, 10.0 mmol) and EtOH (1 l.) was hydrogenated in the presence of Raney nickel (24 g, weighed wet with EtOH). After 21 hr 995 ml (40 mmol) of H_2 was absorbed. The suspended product was decanted from the catalyst under N_2 and additional product was obtained by rinsing the catalyst with boiling EtOH (five 100-ml portions). The combined EtOH wash was heated to boiling to dissolve most of the solid. After filtration through Celite, the resulting blue solution was treated with charcoal at 25°, filtered through Celite, and evaporated to dryness *in vacuo* to give crude **18** containing **22** (tlc): yield 2.54 g (74%). A portion of the crude product (254 mg) was dissolved in boiling EtOH (80 ml), and the solution was filtered hot through a 2-cm layer of silica gel H covered with Celite in a 3.6-cm-diameter sintered disk funnel. The product was eluted with hot EtOH. The first 70 ml of eluent was discarded and the next 130 ml was refrigerated. Pure **18** separated as yellow crystals, which were collected and dried at 100° *in vacuo* over P_2O_5: yield 54 mg (16%); mp ~275° dec with darkening from ~255° (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 232 (30.2), 294 (26.0), 310 (26.1); pH 7, 294 (sh) (25.6), 313 (29.1); $\bar{\nu}_{max}$, cm^{-1}, 3450, 3370, 3130 (NH), 2940, 2890 (CH), 1693 (C=O), 1600 (NH_2), 1590 (sh), 1523 (C=C, C=N), 1285 (COC); pmr (2.5% w/v), δ 3.04 (3, NCH_3), 3.75 (3, OCH_3), 3.92, 4.14 (2, 2, CH_2), 5.55 (4, NH_2), 6.29 (1, NH), 7.27 (q, 4, C_6H_4).

Anal. Calcd for $C_{16}H_{19}N_7O_2$: C, 56.29; H, 5.61; N, 28.72. Found: C, 56.34; H, 5.57; N, 28.90.

B.—A suspension of **17** (100 mg, 0.257 mmol) in EtOH (25 ml) was hydrogenated in the presence of Raney nickel (~400 mg, weighed wet with EtOH) for 5 days at 25° and 1 day at 40°. The mixture was heated to boiling and the suspended product was decanted from the catalyst, which was then extracted with additional hot EtOH (10 ml). The suspension in EtOH was heated to boiling with charcoal, filtered through Celite, and evaporated to dryness *in vacuo*. Trituration of the residue with EtOH (1 ml) gave a pale yellow solid which was collected, washed with EtOH, and dried *in vacuo* over P_2O_5: yield 34 mg (39%); mp ~275° dec with darkening from ~252° (Mel-Temp). Comparison of the tlc and the ultraviolet, infrared, and pmr spectra of this sample with that prepared above showed that the two samples were identical.

Ethyl *p*-{[(2,4-Diamino-7,8-dihydro-6-pteridinyl)methyl]amino}benzoate (19).—A suspension of finely powdered **16** (3.62 g, 8.50 mmol) and $NaOAc \cdot 3H_2O$ (1.16 g, 8.50 mmol) in EtOH (2 l.) was stirred for 30 min under N_2, then hydrogenated at atmospheric pressure for 2 days in the presence of Raney nickel (20 g, weighed wet with EtOH). Several times during the hydrogenation, the mixture was heated in a water bath at 50°. The supernatant containing suspended product was decanted from the catalyst. The resulting residue was extracted repeatedly with portions of boiling EtOH under N_2 until no solid deposited from the extract. The combined extracts containing suspended product was evaporated to dryness *in vacuo;* the residue was dissolved in DMAC (100 ml) at 100° under N_2, filtered under N_2, and treated dropwise at 0° with H_2O (300 ml). The resulting mixture was refrigerated for 16 hr, and the product was collected by filtration, washed with cold H_2O, and dried at 78° *in vacuo* over P_2O_5: yield 1.60 g (55%); mp ~250° dec with darkening from 220° (Mel-Temp). Tlc indicated that this product contained a trace amount of **20**: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 231 (27.6), 293 (27.6); pH 7, 294 (27.4); 0.1 *N* NaOH, 294 (26.6); $\bar{\nu}_{max}$, cm^{-1}, 3390 (broad, NH), 2980 (CH), 1680 (C=O), 1600, 1523 (C=C, C=N), 1275 (COC); pmr (10% w/v), δ 1.27 (t, 3, CH_3), 4.07 (m, 6, CH_2), 5.62, 6.05 (4, NH_2), 6.38 (1, NH), 7.22 (q, 4, C_6H_4).

Anal. Calcd for $C_{16}H_{19}N_7O_2$: C, 56.29; H, 5.61; N, 28.72. Found: C, 56.03; H, 5.63; N, 28.52.

Ethyl *p*-{[(2,4-Diamino-6-pteridinyl)methyl]amino}benzoate (20).—A suspension of **19** (3.00 g, 8.80 mmol) in DMAC (88 ml) was stirred for 10 min and treated over a period of 10 min with a 0.27% solution of $KMnO_4$ in Me_2CO (326 ml, 5.57 mmol). The resulting mixture was stirred with $MgSO_4$ (18 g) for 30 sec and filtered rapidly on two 10-cm sintered disk funnels. The precipitate was washed well with Me_2CO and dried *in vacuo* over P_2O_5. This brown powder was stirred with DMSO (88 ml) in a 60° H_2O bath for 2 min and filtered under N_2, and the residue was rinsed with additional DMSO (88 ml). The filtrate was treated with H_2O (352 ml) and refrigerated for 1 hr. The yellow product was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 1.84 g (62%); mp ~264° dec (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 242 (17.5), 298 (25.2), 335 (sh) (12.6); pH 7, 259 (24.5), 298 (26.1), 372 (8.88); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3310, 3150 (NH), 2977 (CH), 1690 (C=O), 1605, 1525 (NH_2, C=C, C=N), 1275 (COC); pmr (4% w/v), δ 1.27 (t, 3, CH_3), 4.22 (q, 2, OCH_2), 4.51 (d, 2, NCH_2), 6.5, 7.0 (broad, NH), 7.24 (q, C_6H_4), 8.71 (1, ring CH).

Anal. Calcd for $C_{16}H_{17}N_7O_2$: C, 56.63; H, 5.05; N, 28.89. Found: C, 56.58; H, 5.01; N, 28.62.

Methyl *p*-{[(2,4-Diamino-6-pteridinyl)methyl]methylamino}benzoate (22).—A solution of crude **18** (341 mg, 1.00 mmol) in DMAC (10 ml) was treated dropwise with a 0.27% solution of $KMnO_4$ in Me_2CO until the color of permanganate persisted (~16 ml). The resulting mixture was stirred with $MgSO_4$ (2.0 g) for 30 sec and filtered under N_2. The residue was washed well with Me_2CO and dried *in vacuo* over P_2O_5. This solid was stirred with DMSO (10 ml) at 60° for 1 min; the residue was removed by filtration and washed with additional DMSO (10 ml). The combined DMSO extract was treated with H_2O (40 ml) and refrigerated for 1 hr. The crude red product was collected by filtration, washed with H_2O, dried *in vacuo*, and extracted in refluxing EtOH (150 ml) under N_2 for 45 min. The hot extract was filtered through a 3-mm layer of silica gel H covered with Celite in a 3.6-cm-diameter sintered disk funnel. The filtrate was concentrated by boiling to 20 ml and cooled to 25°. The orange product was collected, washed with EtOH, and dried *in vacuo* over P_2O_5: yield 122 mg (36%); mp ~277° dec (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 240 (18.0), 311 (27.9), 350 (sh) (10.4); pH 7, 258 (22.8), 312 (27.1), 373 (8.18); $\bar{\nu}_{max}$, cm^{-1}, 3450, 3300, 3235, 3200, 3100 (NH), 2940, 2830 (CH), 1712 (C=O), 1670, 1630 (NH_2), 1600, 1565, 1520 (C=C, C=N), 1277 (COC); pmr (<10% w/v), δ 3.21 (NCH_3), 3.73 (3, OCH_3), 4.77 (2, CH_2), 6.53, 7.42 (broad, NH_2), 7.28 (q, C_6H_4), 8.58 (1, ring CH).

Anal. Calcd for $C_{16}H_{17}N_7O_2$: C, 56.63; H, 5.05; N, 28.89. Found: C, 56.47; H, 4.98; N, 29.08.

***p*-{[(2,4-Diamino-6-pteridinyl)methyl]methylamino}benzoic Acid (23).**—A solution of **22** (100 mg, 0.295 mmol) in DMSO (6 ml) was treated dropwise with 1 *N* NaOH (0.443 ml, 0.443 mmol), stirred at room temperature for 24 hr, and evaporated to dryness at 50° (0.15 mm) *in vacuo*. The residue was stirred with H_2O (3 ml) for 3 min and filtered under N_2. The remaining solid was washed with H_2O (0.5 ml), and the combined filtrate and wash was adjusted to pH 10 with 1 *N* HCl. The solution was filtered under N_2 and carefully adjusted to pH 7.5 with 1 *N* NaOH. The orange precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 54 mg (52%); mp <300°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 HCl, 240 (17.3), 311 (24.8), 350 (sh), (9.77); pH 7, 258 (24.6), 285 (22.1), 372 (7.70); 0.1 *N* NaOH, 258 (24.8), 285 (22.1), 372 (7.70); $\bar{\nu}_{max}$, cm^{-1}, 3440, 3380, 3320, 3180 (NH), 2940, 2910 (CH), 1600, 1560, 1525 (NH_2, C=C, C=N); pmr (4% w/v), δ 3.23 (3, NCH_3), 4.82 (2, CH_2), 6.63, 7.51 (NH_2), 7.33 (q, C_6H_4), 8.63 (1, ring CH).

Anal. Calcd for $C_{15}H_{15}N_7O_2 \cdot 0.65HCl$: C, 51.62; H, 4.52; Cl, 6.60; N, 28.09. Found: C, 51.34; H, 4.40; Cl, 6.83; N, 28.35.

Registry No. **5,** 23852-97-3; **6,** 23852-98-4; *syn*-**7,** 23852-99-5; *anti*-**7,** 23890-39-3; *syn*-**8,** 23853-00-1; *anti*-**8,** 23853-01-2; **9,** 23853-02-3; **10,** 23853-03-4; **13,** 23853-04-5; **16**·HCl, 23853-05-6; **17,** 23853-06-7; **18,** 23890-40-6; **19,** 23853-07-8; **20,** 23853-08-9; **22,** 23853-09-0; **23,** 19741-14-1.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute who performed most of the microanalytical and spectral determinations reported.

Esters and Amides of 5-Amino-2-aryl-4-pyrimidinecarboxylic Acid

DONG HAN KIM AND ARTHUR A. SANTILLI

Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087

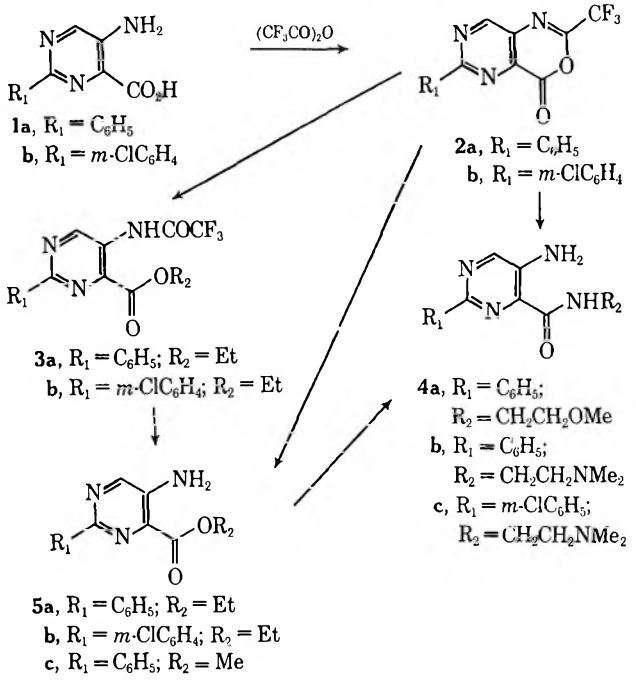
Received October 31, 1969

Although 5-amino-2-phenyl-4-pyrimidinecarboxylic acid (1)[1] has been known since 1902, surprisingly, none of its esters or amides has been reported thus far. A review of the literature, furthermore, revealed that neither esters nor amides of 5-amino-4-pyrimidinecarboxylic acids, in general, have been described. The importance of esters and amides of *o*-aminocarboxylic acids as synthetic intermediates for the construction of other heterocycles fused to the original nucleus has been widely recognized for many years.[2]

An application of the conventional Fischer esterification method to **1b** caused extensive decarboxylation, resulting in the formation of 5-amino-2-(*m*-chlorophenyl)pyrimidine. Price, *et al.*,[3] obtained 4-amino-2-methyl-5-pyrimidinecarboxylic acid methyl ester by adding a mixture of methanol and sulfuric acid to a warm solution of the corresponding carboxylic acid in sulfuric acid. An attempt to esterify **1b** by the Price method, however, caused the pyrimidine to suffer the same decarboxylation experienced with the Fischer method. Apparently, decarboxylation of these 5-amino-4-pyrimidinecarboxylic acids occurs with such facility that it presents a major problem in preparing derivatives.

We now wish to report a convenient two-step synthesis of esters and amides of 5-amino-4-pyrimidinecarboxylic acids (see Scheme I). Treatment of **1a,b** with trifluoroacetic anhydride produced in excellent yield the pyrimido[5,4-*d*][1,3]oxazines **2a,b**, the first examples of a previously undescribed heterocyclic ring system. The structures of **2a,b** were supported by elemental analyses and spectral data; their infrared carbonyl absorption bands were exhibited at 5.5 μ. When the intermediates **2a,b** were treated with an appropriate alcohol in the presence of a catalytic amount of base and HCl gas was then introduced, the desired esters **5a–c** were obtained. The products exhibited their ester carbonyl absorption bands at 5.85–5.95 μ. The conversion of **2a,b** into the esters **5a,b** appears to involve a base-catalyzed initial cleavage of the oxazine ring followed by detrifluoroacetylation in the presence of acid. Intermediates **3a,b** were isolated

SCHEME I



when the conversion reaction of **2a,b** into **5a–c** was interrupted prior to the acid treatment. Subsequent treatment of **3a,b** with ethanolic HCl produced **5a** and **5b**. Treatment of **2a** with an excess of 2-methoxyethylamine afforded, in 90% yield, the pyrimidinecarboxamide **4a**, which was identical with the compound obtained from **5a** by refluxing the latter compound with 2-methoxyethylamine. Compounds **4b,c** were prepared similarly by treating **2a,b** with appropriate amines.

Experimental Section

The melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. No effort was made to obtain optimum reaction conditions and yields.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid (1b) was prepared according to the literature method[1] from 5-bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid: yield 50%, mp 240–242° dec.

Anal. Calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; Cl, 14.20; N, 16.83. Found: C, 52.90; H, 3.33; Cl, 14.2; N, 16.77.

5-Bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid was prepared from *m*-chlorobenzamidine hydrochloride[4] and mucobromic acid according to the literature method.[5] Recrystallization from 95% EtOH gave a product with mp 162–163° dec.

Anal. Calcd for $C_{11}H_6BrClN_2O_2$: C, 42.14; H, 1.93; N, 8.94; Cl, 11.31. Found: C, 42.36; H, 1.95; N, 8.80; Cl, 11.32.

5-Amino-2-(*m*-chlorophenyl)pyrimidine.—Dry HCl gas was introduced into a mixture of **1b** (1.0 g) and absolute EtOH (70 ml) for 0.5 hr, with occasional cooling, and the resulting mixture was heated on a steam bath for 2 hr. Chilling of the reaction mixture caused separation of a precipitate, which was collected on a filter and treated with 1 *N* aqueous NaOH solution to give a product: mp 154–160° (recrystallization from EtOH–water raised the melting point to 159–161°); ir, no carbonyl absorption band.

Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.40; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 58.67; H, 3.89; N, 20.67; Cl, 17.21.

6-Phenyl-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]oxazin-4-one (2a).—5-Amino-2-phenyl-4-pyrimidinecarboxylic acid (1a)

(1) F. Kunckell and L. Zumbusch, *Chem. Ber.*, **35**, 3164 (1902).

(2) See, for example, W. Ried and R. Giesse, *Angew. Chem. Int. Ed. Engl.*, **7**, 136 (1968); W. Ried and R. Giesse, *Ann. Chem.*, **713**, 143 (1968); P. R. Levy and H. Stephen, *J. Chem. Soc.*, 985 (1956); A. G. Ismail and D. G. Wibberley, *ibid.*, 2613 (1967); E. Cohen and B. Klarberg, *J. Amer. Chem. Soc.*, **84**, 1994 (1962).

(3) D. Price, E. L. May, and F. D. Pickel, *ibid.*, **62**, 2818 (1940).

(4) T. S. Osdene, A. A. Santilli, L. E. McCardle, and M. E. Rosenthale, *J. Med. Chem.*, **9**, 697 (1966).

(5) Z. Budesinsky, *Collect. Czech. Commun.*, **14**, 223 (1949).

TABLE I

5-AMINO-N-SUBSTITUTED 4-PYRIMIDINECARBOXAMIDES

Compd	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	112–114	A	90	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58	62.09	5.99	20.30
5b	141–143	B	89	$C_{15}H_{19}N_5O$	63.14	6.71	24.55	63.19	6.78	24.73
4c	137–139	C	74	$C_{15}H_{18}ClN_5O$	56.33	5.67	21.90	56.29	5.28	21.89

[a] A = absolute ethanol, B = cyclohexane, C = ethanol + water.

(2.5 g) was added in small portions to trifluoroacetic anhydride (30 ml). The resulting mixture was refluxed for 7.5 hr and set overnight at room temperature, during which time a precipitate separated. The precipitate was collected on a filter and washed with trifluoroacetic anhyride to give 3.2 g of product, mp 210–212°.

Anal. Calcd for $C_{13}H_6F_3N_3O_2$: C, 53.25; H, 2.06; N, 14.33. Found: C, 53.33; H, 2.03; N, 14.55.

6-(*m*-Chlorophenyl)-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]-oxazin-4-one (2b) was prepared similarly from **1b** and trifluoroacetic anhydride: yield 94%, mp 176–178°.

Anal. Calcd for $C_{13}H_5ClF_3N_3O_2$: C, 47.65; H, 1.54; N, 12.82. Found: C, 47.79; H, 1.45; N, 12.77.

2-Phenyl-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic Acid Ethyl Ester (3a).—To a refluxing mixture of **2a** (7.0 g) and absolute EtOH (70 ml) was added a catalytic amount of sodium ethoxide, and the resulting solution was refluxed for 10 min. Concentration of the reaction mixture under reduced pressure and chilling in ice caused separation of a precipitate which was collected on a filter to give 7.5 g of product: mp 136.5–138.5°, ir 5.80 (CF_3CO) and 5.87 μ (ester CO).

Anal. Calcd for $C_{15}H_{12}F_3N_3O_3$: C, 53.10; H, 3.57; N, 12.39. Found: C, 53.52; H, 3.33; N, 12.29.

2-(*m*-Chlorophenyl)-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic acid ethyl ester (3b) was prepared similarly from **2b**: yield 85%, mp 172–174°.

Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_3$: C, 48.20; H, 2.97; N, 11.24. Found: C, 48.49; H, 2.93; N, 11.50.

5-Amino-2-phenyl-4-pyrimidinecarboxylic Acid Ethyl Ester (5a). From 2a.—A mixture obtained by adding 19.3 g of **2a** to 200 ml of absolute EtOH containing a catalytic amount of sodium ethoxide was refluxed for 15 min. After the reaction mixture was cooled to room temperature, dry HCl gas was introduced for 1 hr, and then the reaction material was chilled. The precipitate that was deposited was collected on a filter and transferred to a separatory funnel containing 1 *N* aqueous NaOH solution and ether. After the mixture was shaken vigorously, the ether layer was collected, dried ($MgSO_4$), and evaporated to give 12.5 g of product, mp 78–80°.

Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.22; H, 5.36; N, 17.50.

From 3a.—A slow stream of dry HCl gas was introduced into a mixture of **3a** (3.0 g) and absolute EtOH (100 ml), with stirring for 15 min. Chilling of the resulting mixture caused separation of a precipitate, which was collected on a filter. Working up as described above afforded 1.2 g of product, mp 80–82°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic Acid ethyl ester (5b) was prepared from **3b** and absolute EtOH and recrystallized from absolute EtOH, mp 130–132°.

Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13; Cl, 12.87. Found: C, 56.22; H, 4.05; N, 15.37; Cl, 12.95.

5-Amino-2-phenyl-4-pyrimidinecarboxylic acid methyl ester (5c) was prepared from **2a** and absolute methanol in 65% yield and recrystallized from cyclohexane, mp 119.5–122°.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.56; H, 4.62; N, 18.24.

5-Amino-N-(2-methoxyethyl)-2-phenyl-4-pyrimidinecarboxamide (4a) exemplifies the preparation of 5-amino-N-substituted 2-aryl-4-pyrimidinecarboxamides (**4a–c**) (Table I).

From 2a.—To 15 ml of 2-methoxyethylamine was added 2.5 g of **2a** in small portions, and the resulting mixture was heated on a steam bath for 0.5 hr. The excess amine was removed under reduced pressure, and the solid residue was recrystallized from absolute ethanol, giving 2.1 g of product (see Table I).

From 5a.—A mixture of **5a** (1.5 g) and 2-methoxyethylamine (20 ml) was refluxed for 7 hr and then the solution was concentrated under reduced pressure. Chilling caused separation of crystals which were collected on a filter and washed with EtOH to give 1.3 g of product, mp 113–115°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

Registry No.—5-Amino-2-(*m*-chlorophenyl)pyrimidine, 23788-75-2; **2a**, 23788-76-3; **2b**, 23788-77-4; **3a**, 23788-78-5; **3b**, 23877-35-2; **4a**, 23788-79-6; **4b**, 23843-57-4; **4c**, 23788-80-9; **5a**, 23788-81-0; **5b**, 23788-82-1; **5c**, 23788-83-2.

Acknowledgment.—The authors are indebted to Mr. R. A. Fieber for technical assistance.

Preparation of 16-Unsaturated Steroids by Elimination of 17α-Acyloxyl

LUDWIG SALCE, GEORGE G. HAZEN, AND ERWIN F. SCHOENEWALDT

Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey 07065

Received November 13, 1969

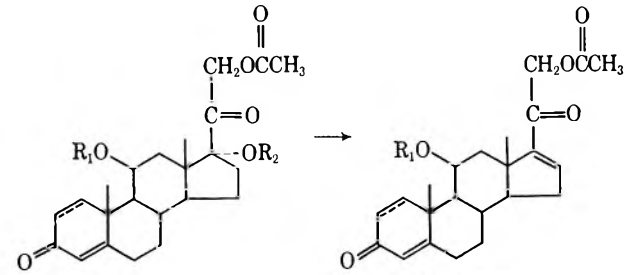
Two methods are known for elimination of the 17α-hydroxyl from the dihydroxyacetone side chain of the corticoids. Allen and Bernstein[1] have reported 16,17 dehydration of 20-dioxolane derivatives using thionyl chloride in pyridine at −5°. The dehydration yield is ~45%; the dioxolane must be subsequently converted into the 20 ketone. Slates and Wendler,[2] *et al.*, reported an improved procedure involving activation of the 17α-hydroxyl by the 20-semicarbazone. Almost quantitative dehydration is effected and conversion into the 20 ketone is facile. Both methods are unsatisfactory, however, when the 11β-hydroxyl is present. Thionyl chloride causes 9,11 dehydration. In the semicarbazone method, C-18 methyl migration[2b] takes place when an 11β-hydroxyl is present and little Δ^{16} steroid is isolated.

We wish to report the removal of a 17α-hydroxyl, in good yield, by reacting a 17α-acyloxy derivative with potassium acetate in dimethylformamide. Thus prednisolone 17,21-diacetate (**1**), when heated for 8 hr at 105° with potassium acetate in dimethylformamide, is almost quantitatively converted into 16,17-anhydroprednisolone 21-acetate (**5**). Prednisolone 17-caproate 21-acetate also gives **5** but in lesser yield, 52.6%. The

(1) W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 1028 (1955).

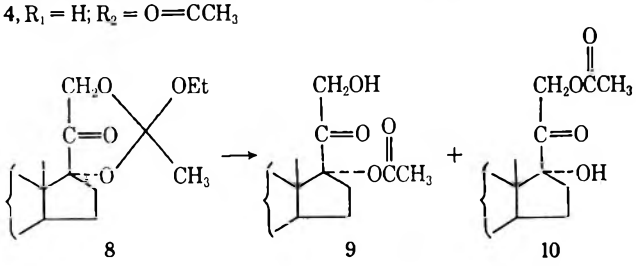
(2) (a) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957); (b) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **29**, 3486 (1964).

11β-acetate, if present, is retained, as shown by conversion of prednisolone 11,17,21-triacetate (**3**) into 16,17-anhydroprednisolone 11,21-diacetate (**6**), a new compound. The method is also applicable in the 4-en-3-one series, and cortisol 17,21-diacetate (**4**) gave 16,17-anhydrocortisol 21-acetate (**7**).



1, Δ^1; $R_1 = H$; $R_2 = O{=}CCH_3$
2, Δ^1; $R_1 = H$; $R_2 = O{=}C(CH_2)_4CH_3$
3, Δ^1; $R_1 = R_2 = O{=}CCH_3$
4, $R_1 = H$; $R_2 = O{=}CCH_3$

5, Δ^1; $R_1 = H$
6, Δ^1; $R_1 = O{=}CCH_3$
7, $R_1 = H$



8 **9** **10**

Sodium acetate was not so effective as potassium acetate. Sodium formate, calcium carbonate, and calcium acetate in dimethylformamide failed. Potassium acetate in dimethyl sulfoxide and simple pyrolysis were also ineffective.

The 17α-acylates are conveniently prepared through the 17α,21 ortho esters[3] by heating the ortho ester at 45–50° with oxalic acid–water–methanol for 5 min.[4] However, a major weakness of this reported method is formation of the isomeric 17-hydroxy-21-acylate. Gardi, *et al.*,[3] attribute formation of the isomer to acyl migration from the 17 to the 21 position after cleavage of the ortho ester. We have found that hydrolysis can be effected in a pH 3 phthalate buffer without acyl migration, even on prolonged exposure. Thus hydrolysis of prednisolone 17,21-orthoacetate (**8**), with pH 3 phthalate buffer in aqueous methanol was complete in 8 hr at 25°. The ratio of 17α-acetate to 21-acetate (**9** to **10**) was estimated to be 9:1 by thin layer chromatography. The ratio did not change in an additional 64 hr. Using the oxalic acid–aqueous methanol procedure the isomer ratio was 8:2 after 5 min of reaction.

Experimental Section

All melting points were taken in open-end glass capillary tubes and are uncorrected. Thin layer chromatograms were visualized by charring, after spraying with sulfuric acid.

1,4,16-Pregnatriene-11β-,21-diol-3,20-dione 21-Acetate (16,17-Anhydroprednisolone 21-Acetate, 5). A. From 1,4-Pregnadiene-11β,17α,21-triol-3,20-dione 17,21-Diacetate (1).—A mixture of **1** (21 g, 0.0472 mol), anhydrous potassium acetate (10.5 g, 1.07 mol), and dimethylformamide (140 ml) was stirred at 105° for 7.5 hr in an atmosphere of nitrogen. After cooling to 25°, the mixture was poured into ice water (1.2 l.) with stirring. After 15 min of stirring, the precipitated solid was collected by filtration, washed with water, and dried to constant weight *in vacuo*. The yield of 16,17-anhydroprednisolone 21-acetate (**5**) was 16.8 g (92.8%), mp 197–200°, uv max (MeOH) 242 mμ (ε 23,100), indicating 97% purity. Tlc using either chloroform–acetone (7:3) or ethyl ether–benzene (9:1) showed only a single spot.

Recrystallization from isopropyl alcohol (81.2% recovery) raised the melting point to 205–207° (lit.[5] mp 208–209°), uv max (MeOH) 242 mμ (ε 23,800).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.86; H, 7.25.

B. From 1,4-Pregnadiene-11β,17α,21-triol-3,20-dione-17-caproate 21-Acetate (Prednisolone-17-caproate 21-Acetate, 2).—Dehydrocaproxylation of **2**, prepared by the method of Gardi, *et al.*, as above, proceeded to **5** in 52.6% yield.

1,4,16-Pregnatriene-11β,21-diol-3,20-dione 11,21-Diacetate.—16,17-Anhydroprednisolone 11,21-diacetate (**6**) was obtained by dehydroacetoxylation of prednisolone 11,17,21-triacetate (**3**, 2 g). The yield of **6** was 1.72 g (92%), mp 225–230°. Tlc on silica gel G using ethyl acetate–chloroform (1:1) showed one spot with a trace of material at the origin. Charcoaling and recrystallization from isopropyl alcohol gave 1.09 g (62.4% recovery), mp 236–238°, tlc single spot. Further recrystallization increased the melting point to 238–241°; ir (KBr) 1735, 1745 (ester C=O), 1685 (16-ene, 20-C=O), 1665 (3-C=O), 1610, and 1625 cm^{-1} (1,4-diene); uv max (MeOH) 242 mμ (ε 24,950).

Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H 7.09. Found: C, 70.38; H, 7.20.

4,16-Pregnadiene-11β-21-diol-3,20-dione 21-Acetate (16,17-Anhydrocortisol 21-Acetate, 7).—4-Pregnene-11β,17α,21-triol-3,20-dione 17,21-diacetate (**4**, 5.0 g) was dehydroacetoxylated as above. The yield of **7** was 3.42 g, (80%), and the melting point after further purification was 145–147° (lit.[1] mp 148–149°).

1,4-Pregnadiene-11β,17α,21-triol-3,20-dione 17-Acetate (Prednisolone 17-Acetate, 9).—To a solution of prednisolone 17,21-ethyl orthoacetate (**8**, 2.0 g, 0.0046 mol) in methanol (12 ml) was added pH 3 acid phthalate buffer (3.0 ml) prepared by mixing 0.1 *N* HCl (20.32 ml) and 0.1 *N* potassium biphthalate (50.0 ml). After 6.5 hr at 25°, tlc on silica gel G using chloroform–acetone (7:3) showed a 9:1 ratio of **9** to **10**. Stirring for an additional 64 hr did not change the ratio.

Registry No.—**5**, 3044-42-6; **6**, 23825-05-0; **7**, 21720-47-8.

(3) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 413 (1963).
(4) R. Gardi, R. Vitali, and A. Ercoli, *ibid.*, **93**, 431 (1963).
(5) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, U. S. Patent 3,068,251 (1962); *Chem. Abstr.*, **58**, 10285c (1963).

The Isolation and Structure Elucidation of Oxoxylopine, a New Oxoaporphine Alkaloid from *Stephania abyssinica*

S. MORRIS KUPCHAN,[1a] MATTHEW I. SUFFNESS,[1b] AND ERIC M. GORDON[1c]

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

Received October 21, 1969

Stephania abyssinica Walp. is a creeping plant, native to southern and eastern Africa, which has been reported to have use as a purgative and emetic.[2] The roots are used in the treatment of roundworm, menorrhagia, and boils.[2] An examination of *S. abyssinica*

(1) (a) Department of Chemistry, University of Virginia, Charlottesville, Va. 22901. This investigation was supported by Public Health Service Grant HE-02952 from the National Heart Institute. (b) M. I. S. was a National Institutes of Health Predoctoral Fellow, 1966–1969. (c) National Institutes of Health Predoctoral Fellow, 1968–1969.

(2) J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone Ltd., London, 1962, p 458.

TABLE I
NMR SIGNALS OF OXOAPORPHINE ALKALOIDS[a]

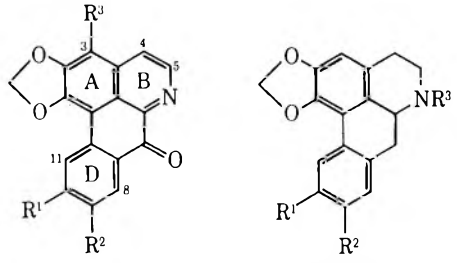
Compd	OCH_2O	C-3 H	C-3 OCH_3	C-4 H	C-5 H	C-8 H	C-9 OCH_3	C-10 H	C-11 H
Oxoxylopine (1)	3.35 (s)	2.47 (s)		1.55 (d)	1.22 (d)	1.93 (d)	5.88 (s)	2.33 (dd)	1.22 (d)
Liriodenine[b] (2)	3.28 (s)	2.37 (s)			C-4 H to C-11 H, 1.1 to 2.3 (6 H, aromatic, m)				
Atherospermidine[b] (3)	3.28 (s)		5.45 (s)		C-4 H to C-11 H, 1.1 to 2.3 (6 H, aromatic m)				
Lanuginosine[c]	3.25 (s)	2.33 (s)		2.30 (d)	1.30 (d)	1.74 (d)	5.92 (s)	2.03 (dd)	0.97 (d)

[a] All values are in τ units for CF_3COOH solutions at 60 MHz relative to tetramethylsilane. [b] Reference 4. [c] Reference 14.

from Natal revealed the presence of an alkaloid,[3] which was subsequently characterized as metaphanine,[4] originally isolated from *S. japonica*.[5]

The present communication concerns an investigation of a sample of roots and rhizomes of *S. abyssinica*, collected in Ethiopia in April 1965.[6] Examination of the alkaloidal fraction revealed the presence of a complex mixture. We report herein the isolation and structure elucidation of oxoxylopine (**1**), a new alkaloid of the oxoaporphine series.

A concentrated ethanolic extract of *S. abyssinica* roots and rhizomes was triturated with dilute hydrochloric acid. The acid solution was partially basified to pH 5 with ammonium hydroxide and extracted with chloroform to give a fraction designated as "weak bases." The weakly acidic solution (pH 5) was then further basified to yield a "strong base" fraction. The weak base fraction was chromatographed on silicic acid to yield a fraction rich in the new alkaloid. Rechromatography on alumina gave material which was crystallized from chloroform to yield oxoxylopine (**1**): mp 319–321° dec; $\lambda_{max}^{CHCl_3}$ 246 mμ (ε 28,650), 271 (21,800), 314 (5960); $\lambda_{max}^{0.1\,N\,HCl}$ 257 mμ (ε 20,570), 284 (15,500); λ_{max}^{KBr} 3.37, 6.02 μ (conjugated ketone); *m/e* 305 (M^+, 100%).



1, $R^1 = R^3 = H$, $R^2 = OCH_3$ **5**, $R^1 = R^3 = H$, $R^2 = OCH_3$
2, $R^1 = R^2 = R^3 = H$ **6**, $R^1 = H$, $R^2 = OCH_3$, $R^3 = Ac$
3, $R^1 = R^2 = H$, $R^3 = OCH_3$ **7**, $R^1 = OH$, $R^2 = H$, $R^3 = CH_3$, methiodide
4, $R^2 = R^3 = H$, $R^1 = OCH_3$

The analytical data supported assignment of the molecular formula $C_{18}H_{11}NO_4$. The compound's limited solubility, high melting point, fluorescence in solution, cherry-red coloration upon treatment with dilute mineral acid, and failure to show NH absorption in the infrared suggested that this highly conjugated ketone was a member of the oxoaporphine series. Comparison of the infrared and ultraviolet spectra of **1** with those reported for liriodenine (**2**)[7,8] showed them to be very similar and suggested that the new alkaloid also possessed a 1,2-methylenedioxy group.

The nmr spectrum of oxoxylopine showed signals for a methylenedioxy group at τ 3.35 (2 H, s), a methoxyl group at 5.88 (3 H, s), and six aromatic protons in the region of 1.22–2.47. A comparison of these data with the recorded nmr data for liriodenine (**2**) and atherospermidine (**3**)[9] (see Table I) suggested that C-3 is unsubstituted, since a one-proton singlet analogous to that found in liriodenine was observed in the spectrum of oxoxylopine at τ 2.47. The signals for the C-4 and C-5 protons appeared as doublets ($J_{4,5}$ = 6 Hz) at τ 1.55 and 1.22, respectively, indicating that the methoxyl group is not located in ring B. Analyses of the signals for the remaining free protons showed them to constitute a 1,2,4 aromatic hydrogen system. The signal for one proton at τ 1.22 (d, J = 9 Hz) showed *ortho* coupling to a second proton with a signal at 2.33 (dd, J = 3,9 Hz) which was *meta* coupled to the third proton with a signal at 1.93 (d, J = 3 Hz). The presence of a 1,2,4 pattern for the ring-D protons restricted placement of the methoxyl group to C-9 or C-10, and oxoxylopine could then be represented by either structure **1** or **4**.

The ultraviolet spectra of aporphines are known to vary with the location of oxygen substituents[10] and the specific ultraviolet spectra of the aporphines corresponding to **1** or **4** are sufficiently different to enable ready differentiation between these isomers. Oxoxylopine was therefore reduced with zinc–hydrochloric acid,[11] to afford a compound whose ultraviolet spectrum corresponded to that reported for the 1,2-methylenedioxy-9-methoxy isomer, xylopine (**5**).[12] Acetylation afforded (±)-N-acetylxylopine (**6**), with ultraviolet and infrared spectra and thin layer chromatographic properties indistinguishable from those of an authentic sample of (−)-N-acetylxylopine.[13] The cited facts established that oxoxylopine possesses structure **1**.

Recently another new oxoaporphine, lanuginosine,[14] has been isolated from *Michelia lanugionosa* Wall (*Magnoliaceae*) and structure **1** has also been assigned to this compound. However, a comparison of the melting point and infrared and nmr spectral data[14] with those of oxoxylopine clearly showed these compounds to be different. The assignment of structure **1** to lanuginosine was based largely upon nmr spectral arguments, and lanuginosine has yet to be interrelated with a known compound. The signals for the ring-D

(3) H. L. de Waal and E. Weideman, *Tydskr. Natuurwet.*, **2**, 12 (1962).
(4) H. L. de Waal, B. J. Prinsloo, and R. R. Arndt, *Tetrahedron Lett.*, 6169 (1966).
(5) M. Tomita, I. Ibuka, Y. Inubushi, and K. Takeda, *ibid.*, 3605 (1964).
(6) The authors acknowledge with thanks the receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U. S. Department of Agriculture by the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health.
(7) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, **25**, 1389 (1960).
(8) W. I. Taylor, *Tetrahedron*, **14**, 42 (1961).
(9) I. R. C. Bick and C. K. Douglas, *Tetrahedron Lett.*, 1629 (1964).
(10) M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, **64**, 59 (1964).
(11) T.-H. Yang, *J. Pharm. Soc. Jap.*, **82**, 804 (1962).
(12) J. Schmutz, *Helv. Chim. Acta*, **42**, 335 (1959).
(13) The authors cordially thank Dr. Jean Schmutz, Dr. A. Wander Research Institute, Bern, Switzerland, for the authentic sample of (−)-N-acetylxylopine.
(14) S. K. Talapatra, A. Patra, and B. Talapatra, *Chem. Ind.* (London), 1056 (1969).

protons in lanuginosine show a 1,2,4 pattern with the same coupling constants as those for oxoxylopine, although the chemical shifts are significantly different (see Table I). In view of the considerations discussed above, it appears likely that lanuginosine is the 10-methoxy isomer of xylopine and should be represented by structure **4** rather than structure **1**. It is noteworthy that michepressine iodide (**7**), an aporphine corresponding in substitution pattern to structure **4**, has been isolated from *Michelia compressa*.[15] Since oxoaporphine alkaloids are probably formed in the plant *via* oxidation of the corresponding aporphines,[16,17] the isolation of michepressine iodide from a *Michelia* species supports assignment of the revised structure **4** for lanuginosine.

Experimental Section

Melting points were determined on a Thomas–Hoover Unimelt apparatus and are corrected. Ir spectra were determined on a Beckman IR-9 double-beam recording spectrophotometer. Uv spectra were determined on a Beckman DK-2A recording spectrophotometer. Nmr spectra were determined on a Varian Associates A-60A spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Mass spectra were measured on a Hitachi RMU-6A spectrometer. We thank the Purdue Mass Spectrometry Center, supported under U. S. Public Health Service Grant FR-00354, for the mass spectral data.

Extraction and Preliminary Fractionation.—The dried ground roots and rhizomes (7 kg) of *Stephania abyssinica* were extracted continuously with ethanol until the extract returning to the pot was nearly colorless. Evaporation of the ethanolic extract gave a mobile semisolid residue (901 g) which was triturated three times with 1.6 *N* hydrochloric acid (3-l. total) to leave a gummy residue (143 g). The aqueous solution was partially basified with concentrated ammonium hydroxide solution to pH 5 and extracted with chloroform (four 1-l. portions) to yield, after evaporation, the weak base fraction (28.7 g). The remaining aqueous solution was decanted from insoluble residue (70 g), basified to pH 8 with concentrated ammonium hydroxide solution, and extracted with chloroform (four 1-l. portions) to give, after evaporation, the strong base fraction (10.4 g).

Oxoxylopine (1).—The weak base fraction was chromatographed over silicic acid (900 g), eluting with chloroform, 1% methanol–chloroform, 2.5% methanol–chloroform, and 5% methanol–chloroform. The fraction eluted with 2.5% methanol–chloroform (6 g) was rechromatographed over acid-washed alumina, eluting with benzene–chloroform mixtures. A fraction eluted with 2:1 benzene–chloroform (150 mg) crystallized on standing to give orange prisms (108 mg). Two recrystallizations from chloroform yielded oxoxylopine (**1**, 70 mg): mp 319–321° dec; $\lambda_{max}^{CHCl_3}$ 246 mμ (ε 28,650), 271 (21,800), 314 (5960); $\lambda_{max}^{0.1\,N\,HCl}$ 257 mμ (ε 20,570), 284 (15,500); λ_{max}^{KBr} 3.37, 6.02, 6.24, 6.36, 6.67, 6.86, 7.06, 7.66, 7.92, 8.17, 9.57, 9.84 μ; *m/e* 305 (M^+, 100%), 275 ($M^+ - CH_2O$, 15%).

Anal. Calcd for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.63; N, 4.59. Found: C, 70.88; H, 3.76; N, 4.63.

Oxoxylopine was found to be nearly insoluble in ethanol, methanol, benzene, ethyl acetate, ether, cyclohexane, and acetone, and only sparingly soluble in chloroform. Its chloroform solution exhibited a strong green-yellow fluorescence in visible light. Oxoxylopine showed a cherry-red coloration upon treatment with dilute hydrochloric or sulfuric acid, as observed earlier for other oxoaporphine alkaloids.

Conversion of Oxoxylopine (1) into (±)-N-Acetylxylopine (6).—A solution of oxoxylopine (22 mg) in acetic acid–water (2:1, 2 ml) was treated with powdered zinc (3 g) and 10 *N* hydochloric acid (6 ml). The reaction mixture was heated with stirring at 100° for 18 hr, after which time the zinc had been consumed and the reaction mixture turned red, indicating the presence of unreduced oxoaporphine. Additional zinc dust (1 g) and concentrated hydrochloric acid (3 ml) was added and the reaction was stirred at 100° for an additional 24 hr, after which time the zinc had again been consumed and the reaction mixture was colorless. The acidic solution was made strongly basic with a large excess of concentrated ammonium hydroxide solution and was extracted with chloroform (five 150-ml portions). The combined, dried (Na_2SO_4) chloroform extracts were evaporated to give crude (±)-xylopine (18 mg; λ_{max}^{MeOH} 217, 237, 280, 320 mμ) (*cf.* 12), which was acetylated without further purification. Treatment of the (±)-xylopine with acetic anhydride (1 ml) and pyridine (1 ml) at 70° for 0.5 hr, followed by standing at room temperature for an additional 3 hr and evaporation under reduced pressure, gave a light brown gummy residue. This material was dissolved in ether–chloroform (3:1, 50 ml) and washed successively with 50 ml of 0.5 *N* hydrochloric acid, 1 *N* sodium hydroxide, and water. The organic phase was dried (Na_2SO_4) and the solvent was evaporated to give a residue which was crystallized twice from acetone–ether to give colorless needles (9 mg), mp 216–218°. The product was chromatographed over silicic acid (5 g) in chloroform to give (±)-N-acetylxylopine (5 mg): λ_{max}^{EtOH} 216.5 mμ (ε 32,200), 283 (16,700); $\lambda_{max}^{CHCl_3}$ 3.32, 3.41, 3.45, 3.52, 6.12, 6.33 μ. The spectra were indistinguishable from those of an authentic sample.

Registry No.—**1**, 23740-25-2; **2**, 475-75-2; **3**, 3912-57-0; **6**, 23740-28-5.

(15) K. Ito, *J. Pharm. Soc. Jap.*, **81**, 703 (1961).

(16) J. Cohen, W. Von Langenthal, and W. I. Taylor, *J. Org. Chem.*, **26**, 4143 (1961).

(17) NOTE ADDED IN PROOF.—Subsequent to submission of the manuscript, Dr. A. J. Liepa has isolated and characterized xylopine from the weak base fraction from *S. abyssinica*.

Selective O-Demethylation of Papaverine[1]

A. BROSSI AND S. TEITEL

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received October 14, 1969

Prior art has shown that papaverine (**1**) can be O-demethylated partially to the diphenol **6** by refluxing concentrated HCl[2] and completely to the tetraphenol papaveroline (**8**) by refluxing 48% HBr.[3] In connection with our interest in the partial O demethylation of polymethoxylated alkaloids,[4] we investigated the acid-catalyzed ether cleavage of **1** in more detail.

Thin layer chromatography using authentic samples of the various phenols as standards provided an excellent tool for this purpose. The monophenols **2**–**5** and papaveroline (**8**) were prepared according to literature procedures,[3,5] whereas the diphenol **6** and the triphenol **7** were synthesized by the conventional methods outlined in Schemes I and II, respectively. Analysis of the reaction mixture obtained by refluxing papaverine (**1**) with concentrated HCl for several hours showed the presence of starting material and the five phenols **2**, **3**, **6**, **7**, and **8**. The two monophenols **4** and **5** were not detected. The major component in this reaction mixture proved to be the diphenol **6**, which could be isolated in good yield but whose physical properties differed considerably from those reported.[2]

The interrelationship of the cleavage products follows. Treatment of papaverine (**1**) with liquid HBr gave a 1:1 mixture of the two monophenols **2** and **3**, as

(1) Presented in part by A. Brossi at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, Sept 25–27, 1969, Symposium Papers, pp 177–186.

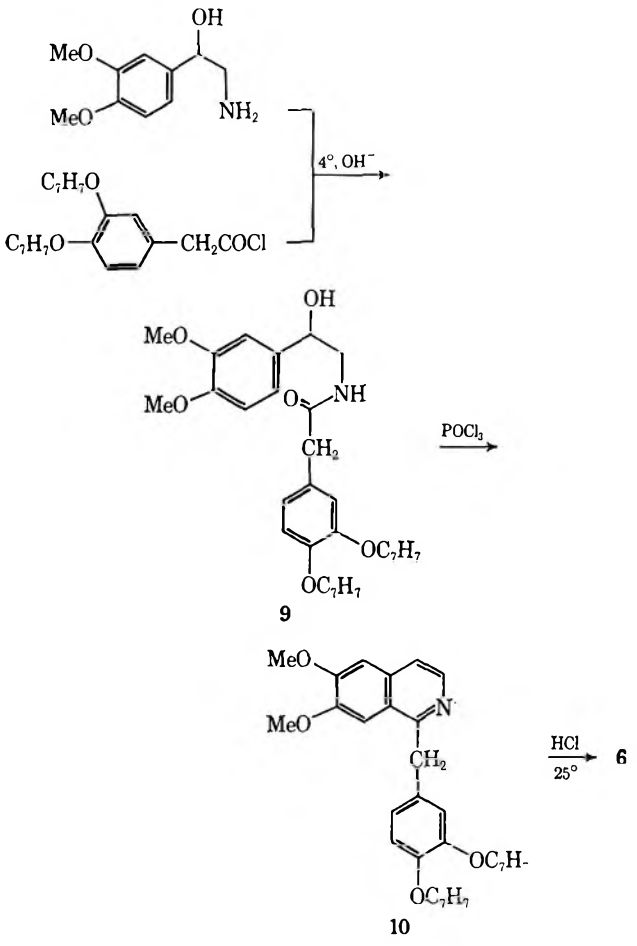
(2) A. Boucherle and J. Alary, *Bull. Soc. Chim. Fr.*, 1222 (1960).

(3) J. V. Burba and M. F. Murnaghan, *Biochem. Pharm.*, **14**, 823 (1965).

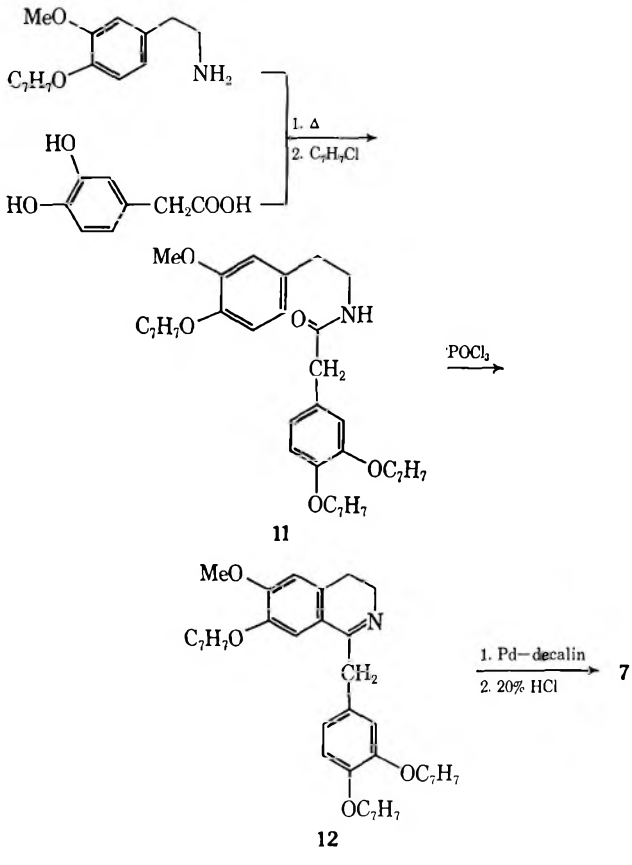
(4) A. Brossi and S. Teitel, *Helv. Chim. Acta*, **52**, 1228 (1969).

(5) E. Brochmann-Hanssen and K. Hirai, *J. Pharm. Sci.*, **57**, 940 (1968).

SCHEME I

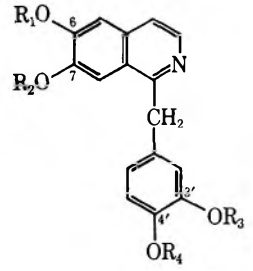


SCHEME II



shown by nmr and glpc. Short-time treatment of **1** with refluxing 48% HBr gave the diphenol **6** in more than 40% yield, whereas a longer reflux period provided the triphenol **7** in more than 80% yield. The mixture of the monophenols **2** and **3** was transformed stepwise with 48% HBr to afford the diphenol **6**, then the triphenol **7**, and finally the tetraphenol **8**.

Thus our studies show that the course of O-demethylation of papaverine (**1**) with mineral acid involves first the two methoxy groups in the benzylic side chain to provide the mixture of monophenols **2** and **3** and the diphenol **6**, then the methoxy group in the 7 position to form the triphenol **7**, and finally the 6-methoxyl[6] to give papaveroline (**8**). These cleavage conditions also provide a facile route to the preparation of these compounds.

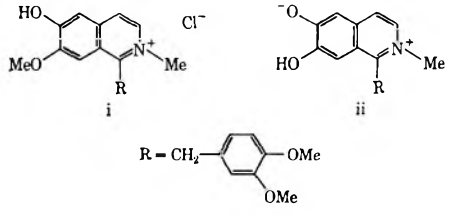


	R_1	R_2	R_3	R_4
1	Me	Me	Me	Me
2	Me	Me	Me	H
3	Me	Me	H	Me
4	Me	H	Me	Me
5	H	Me	Me	Me
6	Me	Me	H	H
7	Me	H	H	H
8	H	H	H	H

Experimental Section[7]

Mixture of 6,7-Dimethoxy-1-(4-hydroxy-3-methoxybenzyl)isoquinoline (2) and 6,7-Dimethoxy-1-(3-hydroxy-4-methoxybenzyl)-isoquinoline (3).—To 200 ml of liquid HBr at −78° was added a solution of 5 g (14.8 mmol) of papaverine (**1**) in 500 ml of CH_2Cl_2. The mixture was allowed to warm to room temperature and stored for 72 hr and the solvent was evaporated. The residue was dissolved in water, rendered alkaline with 5% NaOH, and extracted with EtOAc. The organic extract was evaporated to give 3.5 g (65%) of **1**. The alkaline aqueous layer was filtered free of solids, adjusted to pH 8 with 20% HCl, and extracted with $CHCl_3$. The extract was concentrated to a low volume and stored at 4° and the tan crystals were filtered to give 1.5 g (82% overall) of a 1:1 mixture of **2** and **3**: mp 160–162°, identical with the melting point of a 1:1 authentic mixture of **2**[5] and **3**;[5] R_f 0.74, identical with the R_f of authentic **2**[5] and **3**[5] (R_f of **4**[5] 0.66, R_f of **5**[5] 0.29); nmr ($CDCl_3$) δ 3.70, 3.82, 3.88, 3.99 (6 CH_3O), 4.50 (broad CH_2), 6.77,6.80 ($C_{2'}$,$C_{5'}$, $C_{6'}$), 7.04 (C_5 or C_8), 7.31 (multiplet, C_4 and C_5 or C_8), 8.16, 8.30 (C_3) [nmr of authentic

(6) The relative resistance of the 6- and 7-methoxyls in **1** to cleavage with mineral acid is in marked contrast to their lability on thermal fusion of **1** HCl which affords a mixture of the protopapaverines i and ii; see B. K. Cassels and V. Deulofeu, *Tetrahedron, Suppl.* **8**, part II, 485 (1966), and references cited therein.



(7) Melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Thin layer chromatography employed silica gel G plates developed for 10 cm with ethyl acetate–methanol–concentrated ammonium hydroxide (95:5:5) and detected with Dragendorff's reagent. The ir spectra were determined with either a Beckman IR-9 or a Perkin-Elmer 621 recording spectrophotometer and the uv spectra with a Cary 14 spectrophotometer using ethanol as solvent unless otherwise noted. The nmr spectra were obtained with either a Jeolco C-60H or a Varian HA-100 spectrometer using DMSO-d_6 as solvent except as noted and tetramethylsilane as internal standard. Gas–liquid partition chromatography (glpc) was done on a Barber–Colman Model 5000 instrument at 230° on a 200 cm × 2 mm i.d. glass column packed with Corning GLC 110 glass beads coated with 0.4% OV-101 (Applied Science Laboratories, Inc.). Extracts of products were washed with water and dried over anhydrous sodium sulfate prior to evaporation.

2—δ 3.70, 3.87, 3.96 (3 CH_3O), 4.49 (CH_2), 6.76, 6.79 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.02, 7.34 (C_5, C_8), 7.40 (C_4), 8.34 (C_3); nmr of authentic 3—δ 3.82, 3.89, 3.99 (3 CH_3O), 4.49 (CH_2), 6.78 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.04, 7.33 (C_5, C_8), 7.35 (C_4), 8.18 (C_3)]; glpc of TMS derivative of mixture of **2** and **3** gave Kovats Retention Indices of 2800 and 2830 corresponding to the values obtained from the TMS derivative of authentic **3** and **2**, respectively.

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89. Found: C, 69.79; H, 6.06.

6,7-Dimethoxy-1-(3,4-dihydroxybenzyl)isoquinoline (6). A. By Synthesis.—To a solution of 11.2 g (32 mmol) of 3,4-dibenzyloxyphenylacetic acid[8] in 150 ml of $CHCl_3$ was added 1.55 ml of $SOCl_2$. The mixture was stirred and refluxed for 2 hr and evaporated *in vacuo*. The residue was dissolved in 50 ml of CH_2Cl_2 and added over 30 min to a vigorously stirred mixture of 6.3 g (32 mmol) of 2-(3,4-dimethoxyphenyl)-2-hydroxyethylamine[9] in 50 ml of CH_2Cl_2 and 10 ml of water, maintained at 4° and slightly alkaline by the addition of 10% NaOH as needed. The mixture was stirred at 25° for 1 hr, the organic layer was separated and evaporated, and the residue was crystallized from Et_2O to give 13.6 g (80%) of N-(3,4-dimethoxy-β-hydroxyphenethyl)-2-(3,4-dibenzyloxyphenyl)acetamide (**9**): mp 116–117°; ir ($CHCl_3$) 3610, 3420, 1655, 1510, 1260 cm^{-1}.

Anal. Calcd for $C_{32}H_{33}NO_6$: C, 72.84; H, 6.30. Found: C, 72.72; H, 6.11.

A mixture of 10.6 g (20 mmol) of **9** and 20 ml of $POCl_3$ in 120 ml of toluene was refluxed for 2 hr and evaporated *in vacuo*. A solution of the residue in water was rendered alkaline with 10% NaOH and extracted with EtOAc. The extract was evaporated and the residue was crystallized from EtOAc to give 9.4 g (96%) of 1-(3,4-dibenzyloxybenzyl)-6,7-dimethoxyisoquinoline (**10**): mp 120–121°; uv max 240 mμ (ε 66,100), 269 (6600) (sh), 279 (7000), 290 (5250) (sh), 314 (3750), 327 (4500); nmr δ 3.83, 3.92 (2 CH_3O), 4.47 (CH_2), 5.04 (2 CH_2O), 6.8–7.7 (16 aromatics), 8.24 (C_3 or C_4).

Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95. Found: C, 78.23; H, 5.81.

A mixture of 2.45 g (5 mmol) of **10**, 20 ml of concentrated HCl and 20 ml of C_6H_6 was vigorously stirred at 25° for 17 hr and evaporated *in vacuo*. The residue was dissolved in water and rendered alkaline with 5 ml of concentrated NH_4OH. The precipitate that formed was filtered and crystallized from MeOH to give 1.2 g (78%) of **6**: mp 199–200°; R_f 0.52; uv max 236 mμ (ε 62,900), 267 (5800) (sh), 278 (6500), 280 (5400) (sh), 312 (3850), 325 (4470); nmr δ 3.88, 3.92 (2 CH_3O), 4.37 (CH_2), 6.63 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.28, 7.47 (C_5, C_8), 7.54 (C_4), 8.23 (C_3), 8.40, 8.64 (2 OH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.55; H, 5.70.

An aliquot of **6** was converted into the hydrochloride and crystallized from EtOH: mp 232–233°; ir (KBr) 3380, 3240–2600, 1640, 1615, 1520, 1290 cm^{-1}; uv max 227 mμ (ε 25,400) (sh), 253 (55,200), 288 (6800), 311 (8300), 327 (6600) (sh), 345 (5000) (sh); uv max (0.1 *N* KOH) 233 mμ (ε 41,700), 270 (16,500) (sh), 324 (9600), 390 (7500) (sh); nmr δ 3.97, 3.99 (2 CH_3O), 4.76 (CH_2), 6.6–6.8 ($C_{2'}$, $C_{5'}$, $C_{5'}$), 7.64, 7.77 (C_5, C_8), 8.18, 8.30 (C_3, C_4), 8.88 (broad, OH, NH^+).

Anal. Calcd for $C_{18}H_{17}NO_4 \cdot HCl$: C, 62.16; H, 5.22. Found: C, 62.27; H, 5.39.

An aliquot of **6** was converted into the picrate and crystallized from MeOH: mp 180–181°, uv max 238 mμ (ε 61,400), 254 (28,400) (sh), 281 (7600), 292 (7400) (sh), 314 (9500) (sh), 327 (12,750), 353 (15,600), 415 (8200) (sh); nmr δ 4.00, 4.03 (2 CH_3O), 4.70 (CH_2), 6.62 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.68, 7.80 (C_5, C_8), 8.15, 8.40 (C_3, C_4), 8.56 (picric acid aromatics).

Anal. Calcd for $C_{18}H_{17}NO_4 \cdot C_6H_3N_3O_7$: C, 53.34; H, 3.73. Found: C, 53.23; H, 3.88.

B. From 1 and Concentrated HCl.—A solution of 7 g (18.7 mmol) of **1** HCl in 30 ml of concentrated HCl was refluxed for 9 hr and cooled to 25°. The supernatent was decanted from the resulting oil and the latter was crystallized from Me_2CO to give 1 g of a mixture: mp 190–206°; R_f 0.85, 0.74, 0.52, 0.24, and 0.04 corresponding to values exhibited by **1**, **2** and **3**, **6**, **7**, and **8**. The Me_2CO mother liquors were evaporated; the residue was dissolved in 20 ml of water and rendered alkaline with 5 ml of concentrated NH_4OH. The precipitate that formed was filtered and crystallized from MeOH to give 3.7 g (64%) of **6**, mp 199–200°, identical in mixture melting point, tlc, and uv and nmr spectroscopy with **6** prepared *via* A. An aliquot was converted into the hydrochloride, mp 230–232° (lit.[2] mp 170°[10]), identical in melting point and tlc with **6** HCl prepared *via* A. An aliquot, when converted into the picrate, melted at 180–182° (lit.[11] mp 104°[10]) and caused no mixture melting point depression on admixture with the picrate of **6** prepared *via* A.

C. From 1 and 48% HBr.—A solution of 5 g (14.8 mmol) of papaverine (**1**) in 50 ml of 48% HBr was refluxed for 10 min, cooled, and diluted with 100 ml of water; the pH was adjusted to 8 with concentrated NH_4OH. The gum that precipitated solidified on standing and was filtered and washed with water. The solid was suspended in 40 ml of MeOH and refluxed for 1 hr. The resulting crystals were filtered and dried to give 2.16 g (47%) of **6**, mp 199–200°, identical in mixture melting point and tlc with **6** prepared *via* A.

D. From a Mixture of 2 and 3 and 48% HBr.—A solution of 1 g (3.1 mmol) of the 1:1 mixture of **2** and **3** in 10 ml of 48% HBr was refluxed for 6 min and worked up by the procedure given in C to yield 400 mg (42%) of **6**, mp 200–201°, identical in mixture melting point and tlc with **6** prepared *via* A.

1-(3,4-Dihydroxybenzyl)-7-hydroxy-6-methoxyisoquinoline (7). A. By Synthesis.—A mixture of 21 g (0.125 mol) of 3,4-dihydroxyphenylacetic acid and 32 g (0.125 mol) of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine[12] was heated under N_2 at 180–190° for 2 hr, cooled, and dissolved in 1 l. of EtOH. To the solution was added 84 g (0.665 mol) of benzyl chloride and 91 g (0.665 mol) of anhydrous K_2CO_3. The mixture was stirred and refluxed for 20 hr and filtered hot. The filtrate was cooled and the resulting crystals were filtered and recrystallized from EtOH to give 52 g (71%) of N-(4-benzyloxy-3-methoxyphenethyl)-2-(3,4-dibenzyloxyphenyl)acetamide (**11**): mp 125–126°; ir ($CHCl_3$) 3440, 1670, 1525, 1265 cm^{-1}.

Anal. Calcd for $C_{38}H_{37}NO_6$: C, 77.60; H, 6.35. Found: C, 77.35; H, 6.55.

A mixture of 30 g (0.051 mol) of **11** and 60 ml of $POCl_3$ in 600 ml of toluene was refluxed for 2 hr and evaporated *in vacuo*. The residue was dissolved in water, EtOAc was added, and the mixture was rendered alkaline with 20% NaOH. The organic extract was acidified with ethanolic HCl and evaporated. The residue was twice crystallized from a mixture of EtOH and Et_2O to give 22.4 g (73%) of 1-(3,4-dibenzyloxybenzyl)-7-benzyloxy-6-methoxy-3,5-dihydroisoquinoline hydrochloride (**12** HCl): mp 193–194°; ir (KBr) 3000–2400, 1650, 1610, 1520, 1270 cm^{-1}; uv max 236 mμ (ε 18,600) (sh), 246 (17,400) (sh), 253 (14,700) (sh), 277 (5300) (sh), 309 (8400), 362 (7500).

Anal. Calcd for $C_{38}H_{35}NO_4 \cdot HCl$: C, 75.30; H, 5.99. Found: C, 75.31; H, 6.26.

A solution of 6 g (0.01 mol) of **12** HCl was dissolved in water, rendered alkaline with 10% NaOH, and extracted with EtOAc and the extract was evaporated. The residue was dissolved in 150 ml of decalin, 3 g of 10% Pd-C was added, the mixture was stirred and refluxed for 3 hr and filtered, and the filtrate was evaporated. The residual oil (4.5 g) was dissolved in 170 ml of 20% HCl, refluxed for 2 hr, and evaporated *in vacuo*. The residue was crystallized from EtOH and recrystallized from a mixture of MeOH and Et_2O to give 1.5 g (51%) of **7** HCl: mp 250–251°; R_f (0.24); uv max 237 mμ (ε 37,250), 281 (4400), 290 (4000) (sh), 313 (4000), 328 (3500), 353 (2200) (sh); nmr δ 4.04 (CH_3O), 4.94 (CH_2), 7.2 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.67, 7.79 (C_5, C_8), 8.08, 8.28 (C_3, C_4), 8.80 (broad, OH), 10.94 (NH^+).

Anal. Calcd for $C_{17}H_{15}NO_4 \cdot HCl$: C, 60.99; H, 4.85. Found: C, 60.66; H, 5.18.

An aliquot of **7** HCl was dissolved in water and rendered alkaline with NH_4OH. The precipitate that formed was filtered (darkened on standing), dissolved immediately in EtOH, rendered acidic with ethanolic HBr, and evaporated. The residue was crystallized from EtOH to give **7** HBr, mp 245–246°.

Anal. Calcd for $C_{17}H_{15}NO_4 \cdot HBr$: C, 53.95; H, 4.28. Found: C, 53.88; H, 4.65.

B. From 1 and 48% HBr.—A solution of 1 g (2.96 mmol) of **1** in 10 ml of 48% HBr was refluxed for 1 hr and evaporated *in vacuo*. The residual solid was crystallized from a mixture of MeOH and Et_2O to give 900 mg (82%) of **7** HBr, mp 246–248°, identical in mixture melting point, tlc, and nmr spectroscopy with the **7** HBr prepared *via* A.

(8) T. Kametani and S. Kano, *J. Pharm. Soc. Jap.*, **85**, 256 (1965).

(9) N. A. Chaudhury and A. Chatterjee, *J. Indian Chem. Soc.*, **36**, 585 (1959).

(10) Obtained by cleavage of papaverine and probably contaminated.

(11) A. Pictet and G. H. Kramers, *Arch. Sci. Phys. Na. Genève*, **15**, 124 (1903) [*Chem. Zentr.*, **1**, 844 (1903)].

(12) J. M. Bobbitt and T-T. Chou, *J. Org. Chem.*, **24**, 1106 (1959).

C. From 6 and 48% HBr.—A solution of 1 g (3.22 mmol) of 6 in 10 ml of 48% HBr was refluxed for 30 min, diluted with 10 ml of water, and stored at 4°. The crystals that formed were filtered, washed with water, and dried to give 1 g (90%) of 7 HBr, mp 246–248°, identical in mixture melting point and tlc with the 7 HBr prepared *via* A.

1-(3,4-Dihydroxybenzyl)-6,7-dihydroxyisoquinoline Hydrobromide (8 HBr).—A solution of 2 g (5.9 mmol) of 7 HBr in 20 ml of 48% HBr was refluxed for 8 hr and evaporated *in vacuo*. The residue was crystallized from water to give 1.42 g (74%) of 8 HBr (identical in mixture melting point and tlc with the 8 HBr, obtained from 1 in 80% yield by the same procedure[4]): mp 257–259°; R_f 0.04; nmr δ 4.50 (CH_2), 6.60 ($C_{2'}$, $C_{5'}$, $C_{6'}$), 7.40, 7.65 (C_5, C_8), 8.00, 8.23 (C_3, C_4), 9.00 (broad, OH, NH^+). *Anal.* Calcd for $C_{16}H_{13}NO_4 \cdot HBr$: C, 52.75; H, 3.87. Found: C, 52.81; H, 4.01.

Registry No.—1, 58-74-2; 2, 18813-60-0; 3, 18694-10-5; 6, 16637-56-2; 6 HCl, 16637-68-6; 6 picrate, 23740-72-9; 7 HCl, 23829-46-1; 7 HBr, 23740-73-0; 8 HBr, 23740-74-1; 9, 23740-75-2; 10, 23740-76-3; 11, 4672-97-3; 12 HCl, 4761-17-5.

Acknowledgment.—We are indebted to our Physical Chemistry Department under the direction of Dr. P. Bommer for the spectral and microanalytical data. We are grateful to Mr. J. O'Brien for technical assistance and to Professor G. Büchi, Massachusetts Institute of Technology, for fruitful discussions.

Microbiological Hydroxylation of Allethrone

R. A. LEMAHIEU, B. TABENKIN, J. BERGER, AND R. W. KIERSTEAD

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

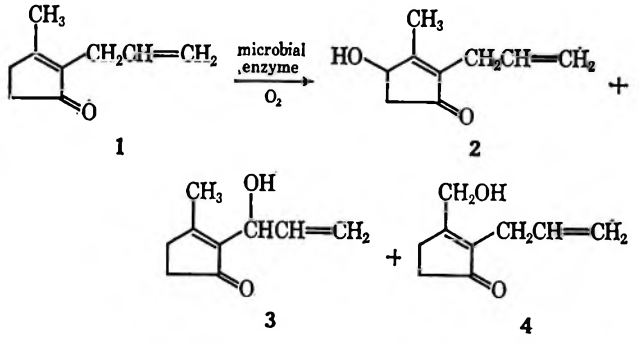
Received October 8, 1969

A number of synthetic analogs of the natural pyrethrins[1] exhibit high insecticidal activity. One of these, allethrin,[2] is prepared commercially by esterification of allethrolone (2) with chrysanthemic acid. We have recently investigated the microbiological conversion of cinerone into cinerolone[3] and now wish to report a similar conversion of allethrone (1) into allethrolone (2). Allethrone (1) was prepared by treatment of 2-N-pyrrolidmo-5-methyl-2-cyclopenten-1-one with allylmagnesium bromide followed by dehydration as described by Dahill.[4]

Incubation of 1 with *Aspergillus niger* NRRL 3228 for 12 days gave a crude product, which was shown by glpc analysis to contain three major components (retention times of 5.5, 6.6, and 11.6 min, respectively). Small amounts of the three pure components were separated by preparative glpc and their mass spectra showed them to be monohydroxylated isomers of allethrone. Based on allethrone consumed, the yield of the mixture was 22%. The major component (73% of the mixture) was identified as allethrolone (2) by comparison of its glpc retention time and spectra (ir, nmr, and mass) with those of the authentic compound.[5]

The component with the shortest retention time (5% of the mixture) gave an infrared spectrum with a carbonyl band at 5.95 μ, indicating hydrogen bonding to the ketone. The nmr spectrum revealed three vinyl protons, one ring methyl, and two ring methylenes. The nmr absorption of the side-chain methylene group was absent and was replaced by a broad peak at δ 5.06. These data are consistent with structure 3, which incorporates a side-chain hydroxyl group.

The component with the longest retention time (18% of the mixture) gave a normal cyclopentenone carbonyl band at 5.88 μ in the infrared spectrum. The nmr spectrum exhibited three vinyl protons, two ring methylenes, and a side-chain methylene. The nmr absorption of the ring methyl was absent and a two-proton singlet appeared at δ 4.50 consistent with structure 4, in which hydroxylation has occurred on the ring methyl group.



Experimental Section[6]

Thirty 500-ml erlenmeyer flasks containing 100-ml quantities of fermentation medium were inoculated with a heavy filamentous growth of *Aspergillus niger* NRRL 3228 and incubated at 28° on a rotary shaker. The shaker was operated at 280 rpm and described a 2-in. circular orbit. After 2 days, 50 mg of allethrone (1) dissolved in 2 ml of absolute ethanol was added to each flask. Incubation was continued for 12 days and the contents of the flasks were then pooled and filtered to remove the cells. The cells were washed with 300 ml of distilled water and the washing was added to the filtrate. The filtrate was extracted with three equal volume portions of methylene chloride. After drying (Na_2SO_4), the solvent was removed at reduced pressure and the residual oil was distilled. The low-boiling fraction [bp 35–47° (0.1 mm), 0.49 g] was shown by thin layer chromatography (tlc) to contain only unreacted allethrone. The high-boiling fraction [bp 47–110° (0.1 mm), 0.55 g] on tlc revealed a spot with an identical R_f as authentic allethrone along with a slower moving spot with an identical R_f as authentic allethrolone. The allethrone (0.13 g) was separated from the allethrolone fraction (0.24 g) by preparative tlc on silica gel. Evaporative distillation of the allethrolone fraction at 0.1 mm (bath temperature 120°) gave 0.22 g of a colorless oil, λ_{max}^{EtOH} 229 mμ (ε 11,300). Glpc on a 10% EPON column at 200° showed three major peaks: peak 1, structure 3 (5% of the total, retention time of 5.5 min); peak 2, structure 2 (73% of the total, retention time of 6.6 min, identical with the retention time of authentic allethrolone); and peak 3, structure 4 (18% of the total, retention time of 11.6 min). Mass spectra were obtained using a Finnigan mass spectrometer coupled to a gas chromatograph and showed the three components to be isomers of molecular weight 152. The mass spectrum of peak 2

(1) L. Crombie and M. Elliot, *Fortschr. Chem. Org. Naturstoffe*, **19**, 121 (1961).

(2) M. S. Schechter, N. Green, and F. B. La Forge, *J. Amer. Chem. Soc.*, **71**, 3165 (1949).

(3) B. Tabenkin, R. A. LeMahieu, J. Berger, and R. W. Kierstead, *Appl. Microbiol.*, **17**, 714 (1969).

(4) R. T. Dahill, *J. Org. Chem.*, **31**, 2694 (1966).

(5) Obtained from Benzol Products, Newark, N. J.

(6) The ir spectra were determined using a Beckman IR-9 spectrophotometer. The uv spectra were obtained with a Cary 14 spectrophotometer. The nmr spectra were determined using a Varian HA-100 spectrometer with a C-1024 time-averaging computer when necessary. The mass spectra were obtained using a Finnigan mass spectrometer coupled to a Perkin-Elmer gas chromatograph.

was identical with that of authentic allethrolone,[5] while those of the other two peaks exhibited similar fragmentation patterns. The bands at *m/e* 134 ($M^+ - H_2O$) and 121 ($M^+ - CH_2OH$) were much more intense in peak 3, structure **4**, than in the other two peaks.

Small amounts of the three pure components were separated by preparative glpc using the above column. Data for peak 1, structure **3**, follow: ir (neat) 2.92 (broad), 5.95, and 6.10 μ; nmr ($CDCl_3$, time averaged, 140 scans) δ 2.09 (s, 3, CH_3), 2.42 (m, 2, CH_2CH_2), 2.56 (m, 2, CH_2CH_2), 5.06 (m, 1, CHOH), 5.14 and 5.24 (m, 2, CH_2=), and 6.12 (m, 1, CH=). Peak 2 gave ir and nmr spectra identical with those of authentic allethrolone. Data for peak 3, structure **4**, follow: ir (neat) 2.92, 5.88, and 6.04 μ; nmr ($CDCl_3$) δ 2.36 (m, 2, CH_2CH_2), 2.61 (m, 2, CH_2CH_2), 2.94 (d, 2, J = 6 Hz, -CH_2CH=), 4.50 (s, 2, CH_2OH), 4.84 and 4.97 (m, 2, CH_2=), and 5.75 (m, 1, CH=).

Registry No.—**1**, 3569-36-6; **2**, 23680-22-0; **3**, 23680-23-1; **4**, 23680-24-2.

Acknowledgment.—We wish to thank the following members of our Physical Chemistry Department (Dr. P. Bommer, director): Dr. W. Benz, Dr. V. Toome, and Mr. S. Traiman, for the mass, ultraviolet, and infrared spectra, respectively. Special thanks are due to Dr. C. G. Scott for the separations by preparative glpc, and Mr. R. Pitcher for the nmr spectra, including the work with the time-averaging computer.

Conversion of 2′,3′-*O*-Isopropylidene Adenosine into Its 5′,5′-Di-*C*-Methyl Derivative[1]

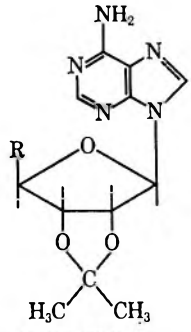
PETER J. HARPER AND ALEXANDER HAMPTON

The Institute for Cancer Research, Fox Chase, Philadelphia, Pennsylvania 19111

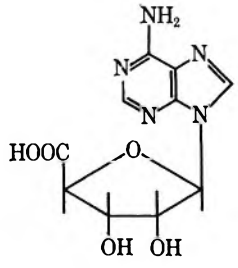
Received October 6, 1969

Direct chain extension and other carbon substitutions at the 5′ position of purine ribonucleosides have been restricted to oxidation of nucleosides to the 5′ aldehydes[2] followed by application of the Wittig reaction[3] or to conversion of a 5′-halogeno-5′-deoxy nucleoside into a 5′-cyano compound.[4] Syntheses of other 5′ carbon-substituted purine nucleosides, such as 5′-hydroxymethyl-5′-deoxyadenosine (homoadenosine)[5,6] and 5′,5′-di-*C*-methyladenosine,[7] have been effected by condensation of the respective blocked sugar derivatives with the adenine moiety. We now illustrate the practicability of a new approach which comprises conversion of a nucleoside, *via* its 5′-carboxylic acid, into the 5′-carbomethoxy derivative and application to the latter of the Grignard reaction.

Adenosine has been converted into the 5′-carboxylic acid **6** by oxidation with molecular oxygen in the presence of a platinum catalyst.[8] In our laboratory, this procedure, when applied to 2′,3′-*O*-isopropylidene adenosine (**1**), consistently gave low yields (2–5%) with reduced Adams catalyst from a variety of commerical preparations. Treatment of **1** with chromium trioxide in the presence of pyridine, acetic acid, or water yielded a complex mixture of products. Oxidation with potassium permanganate gave less complex mixtures, and after trials in the pH range of 2–12 and temperatures of 0–80°, a procedure was selected which employed 2 molar equiv of potassium permanganate at room temperature and pH 9–9.5. Although only *ca.* 30% conversion into the carboxylic acid **2** was obtained, the yield based on recovered isopropylidene adenosine was 90%. The product could be isolated directly in pure form and unreacted material could be readily recovered and recycled. When conversion of **1** into **2** was enhanced by the use of stronger oxidizing conditions, additional products were obtained and purification of **2** was rendered more tedious. The purification and properties of one such by-product (as yet of unassigned structure) is detailed in the Experimental Section. Two recently described alkaline potassium permanganate oxidations of **1**[9,10] were found to yield 50–60% homogeneous **2** and three by-products which amounted to 15% of the weight of **1** employed. Acidic treatment of **2** removed the isopropylidene group to furnish 9-(β-D-ribofuranosyluronic acid)adenine (**6**). Attempts to obtain **6** by direct oxidation of adenosine with potassium permanganate, chromium trioxide–acetic acid, or chromium trioxide–pyridine produced a complex mixture of products.



1, R = CH_2OH
2, R = COOH
3, R = $COOCH_3$
4, R = CH_2NH_2
5, R = $C(CH_3)_2CH$



6

Treatment of the carboxylic acid **2** with diazomethane produced the methyl ester **3** in 90% yield. The only other product detected was trace amounts of the amine **4**, the structure of which was deduced from nmr data and elemental analysis and confirmed by comparison with a specimen prepared by reduction of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene adenosine.[11]

(1) This work was supported by USPHS Grants CA-06927, FR-05539, and CA-11196, American Cancer Society Grant IN-49, an appropriation from the Commonwealth of Pennsylvania, and an award from The Pennsylvania Science and Engineering Fund.

(2) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).

(3) G. H. Jones and J. G. Moffatt, *ibid.*, **90**, 5337 (1968).

(4) G. Etzold, G. Kowollik, and P. Langen, *Chem. Commun.*, 422 (1968).

(5) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 2503 (1964).

(6) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **9**, 234 (1966).

(7) R. F. Nutt and E. Walton, *ibid.*, **11**, 151 (1968).

(8) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and A. Todd, *J. Chem. Soc.*, 1149 (1963).

(9) R. R. Schmidt, U. Schloz, and D. Schwille, *Chem. Ber.*, **101**, 590 (1968).

(10) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Chem. Ind.* (London), 1141 (1969).

(11) W. Jahn, *Chem. Ber.*, **98**, 1705 (1965).

Addition of a large excess of methylmagnesium iodide to a solution of **3** in dioxane–tetrahydrofuran resulted in the immediate precipitation of an intermediate product, which presumably resulted from reaction of the Grignard reagent with the 6-amino group of **3**. However, reaction at the 5′ position of **3** slowly proceeded to completion in the essentially heterogenous mixture and yielded 30% tertiary alcohol **5**. The yield of **5** was not enhanced by prior N-benzoylation of **3**. Reaction of a Grignard reagent with a nucleoside derivative has not hitherto been demonstrated to be a feasible synthetic procedure. Methyl Grignard reagents did not react with 2′,5′-di-*O*-trityl-3′-ketouridine,[12] owing possibly to steric interference by the 2′-*O*-trityl group.

The nmr spectrum of **5** showed nonequivalence of the protons of the two 5′-methyl groups, and a Corey–Pauling–Koltun molecular model indicated that restricted rotation about the 4′–5′ bond could result from a concerted steric interaction of the 3′ and 4′ hydrogens with the 5′ methyls.

Experimental Section

Melting points (uncorrected) were determined by the capillary method. Ultraviolet spectra were obtained in buffered aqueous solutions with a Cary Model 15 spectrophotometer and infrared spectra (in KBr disks) with a Perkin-Elmer 137 spectrophotometer. The nmr spectra were run in deuterated dimethyl sulfoxide with a Varian HA-100 instrument. Thin layer chromatograms were run on Eastman cellulose sheets in (A) 5% aqueous K_2HPO_4 overlaid with isoamyl alcohol and (B) 1-butanol saturated with water and on Eastman silica gel in (C) methanol–chloroform (6:94). Preparative tlc was carried out with Merck 2-mm silica gel plates in system C. Elemental analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich.

9-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyluronic acid)adenine (2).—2′,3′-*O*-Isopropylidene adenosine (**1**, 0.8 g) was dissolved in boiling water (200 ml), and potassium permanganate (1.2 g) and ammonia (30 ml, 15 *N*) were added to the cooled (25°) solution. After 12–15 hr at 25° the permanganate color had disappeared and ammonia (50 ml) was added to convert the colloidal manganese oxides into a readily filterable form. The filtrate was evaporated at 40° to *ca.* 15 ml and stored for 1 hr at 10°, when unreacted starting material (0.5–0.6 g) crystallized and was removed by filtration. The filtrate was evaporated to 15 ml, adjusted to pH 3–4 with acetic acid, and cooled to 10°. The precipitate which formed was filtered off, dried, and crystallized from methanol to give **2** (0.18–0.28 g, 90–95% yield based on unrecovered starting material) as fine needles: mp 300–305° dec; ir 3050, 1718, 1640, and 1520 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,400), (pH >7) 259 (14,700); R_f 0.75 (system A) and 0.47 (system B).

Another compound could be isolated in small amounts (2–5%) from the mother liquors by evaporation and preparative tlc. It was also produced in larger amounts by using more forcing conditions in the oxidation. Crystallization from chloroform–petroleum ether (bp 30–60°) gave the compound as prisms: mp 250–255° dec; ir 3050, 1695, 1602, 1555, 1125, and 1080 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,500), (pH >7) 259 (14,800); nmr δ 8.27 (s, 1, H-8), 8.10 (s, 1, H-2), 7.23 (s, 2, exchanges with D_2O, NH_2), 6.09 (d, 1, J = 3 Hz, H-1′), 5.30 (d of d, 1, J = 3 and 7 Hz, H-2′), 4.94 (d of d, 1, J = 2.5 and 7.0 Hz, H-3′), 4.20 (m, 1, H-4′), 3.50 (apparent d), 3.41 (exchanges with D_2O), and 1.52 and 1.30 (s, 3, isopropylidene methyls); R_f 0.68 (system C).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.76; H, 5.57; N, 22.77. Found: C, 51.03; H, 5.55; N, 22.87.

Oxidation of **1** according to Schmidt, *et al.*,[9] or Harmon, *et al.*,[10] gave 50–60% pure **2**, mp 300–305° dec (lit. mp 276° dec,[9] 277–279° [10]), after crystallization of the crude product from water. Preparative tlc of the mother liquors of crude **2** in solvents B and C gave the by-product described above together with two additional ultraviolet-absorbing solids in amounts of 6, 6, and 3%, respectively, of the weight of the starting material. All three by-products had higher R_f values than **2** in systems B and C.

9-(β-D-Ribofuranosyluronic acid)adenine (6).—Compound **2** (0.2 g) was dissolved in the minimum amount of boiling water, and acetic acid was added to give pH 2.3–2.4. The solution was heated on a steam bath until tlc (system B) showed that the reaction was complete (1–1.5 hr), then cooled and evaporated under vacuum to *ca.* 20 ml. The crystalline solid was filtered off and recrystallized twice from water to give **6** (0.19 g, 95%) as small plates: mp 285–295° dec; ir 3210, 1720, 1640, and 1525 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,300), (pH ≥7) 259 (14,600); R_f 0.08 (system A) and 0.12 (system B). A melting point of >320° has been reported[9,10] for **6**. Repetition of these procedures gave material, mp 288–297° dec and 290–296° dec, respectively.

Anal. Calcd for $C_{10}H_{11}N_5O_5$: C, 42.70; H, 3.97; N, 24.90. Found: C, 42.96; H, 4.06; N, 24.78.

9-(2′,3′-*O*-Isopropylidene-β-D-riburonic acid methyl ester)adenine (3).—Compound **2** (1 g) was dissolved in dioxane–methanol (1:1, 1600 ml) and cooled to 0°. Diazomethane (3 g) in diethyl ether (200 ml) was added and the mixture was held at 0° for 1 hr and then evaporated to dryness under vacuum. Recrystallization from methanol afforded **3** (0.9 g, 90%) as fine needles: mp 245–248° dec; ir 3120, 2950, 1728, 1670, 1600, 1080, and 840 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,800), (pH >7), 259 (15,000); nmr δ 8.15 (s, 1, H-8), 7.97 (s, 1, H-2), 7.38 (s, 2, exchanges with D_2O, NH_2), 6.31 (s, 1, H-1′), 5.55 (d of d, 1, J = 6.0 and 1.5 Hz, H-3′), 5.34 (d, 1, J = 6.0 Hz, H-2′), 4.75 (d, 1, J = 1.5 Hz, H-4′), 3.23 (s, 3, $CH_3OC{=}O$), and 1.51 and 1.26 (s, 3, isopropylidene methyls); R_f 0.72 (system C).

Anal. Calcd for $C_{14}H_{17}N_5O_5$: C, 50.26; H, 5.11; N, 20.89. Found: C, 50.49; H, 5.09; N, 20.96.

In some cases 3–6% yields of another compound (**4**) could be isolated by preparative tlc (system C) of the mother liquors. Recrystallization from methanol afforded needles: mp 215–217° (under vacuum); with authentic amine, mmp 214–217°; ir 3300 (sh), 3230, 3120, 3025, 1670, 1545, 1499, 1200, 1090, 1055, and 865 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,800), (pH >7) 259 (14,900); nmr δ 8.17 (s, 1, H-8), 8.00 (s, 1, H-2), 7.17 (s, 2, NH_2), 7.04 (s, 2, NH_2), 6.18 (d, 1, J = 1.5 Hz, H-1′), 5.23 (m, 2, H-2′ and H-3′), 4.42 (d, 1, J = 1.8 Hz, H-4′), 3.10 (d, 1, J = 4.0 Hz, CH_2NH_2), and 1.50 and 1.24 (s, 3, isopropylidene methyls); R_f 0.16 (system C).

Anal. Calcd for $C_{13}H_{18}N_6O_3$: C, 50.92; H, 5.91; N, 27.40. Found: C, 51.20; H, 5.80; N, 27.34.

5′,5′-Di-*C*-methyl-2′,3′-*O*-isopropylidene Adenosine (5).—Compound **3** (1.0 g) was dissolved in dioxane–tetrahydrofuran (1:1, 150 ml) and added with stirring to a solution of methylmagnesium iodide (prepared from 6.2 ml of methyl iodide and 2.4 g of magnesium in 50 ml of ether) at 20° in an atmosphere of nitrogen. A dense white precipitate formed immediately and stirring was continued for 7 days, at which time the ir spectrum of the product showed no absorption near 1728 cm^{-1}. The solution was treated with water dropwise until excess reagent was destroyed, and the precipitate of magnesium salts was removed by filtration. The filtrate was evaporated to dryness and the product was purified by preparative tlc (system C). The major component (R_f 0.82) was eluted with methanol and recrystallized from acetone and then from methanol to give **5** (0.24–0.35 g, 24–35%) as large prisms: mp 225–227°; ir 3380 (sh), 3140, 2980, 1685, 1601, 1225, and 1085 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,300), (pH >7) 259 (14,600); nmr δ 8.31 (s, 1, H-8), 8.09 (s, 1, H-2), 7.24 (s, 2, exchanges with D_2O, NH_2), 6.03 (d, 1, J = 4.2 Hz, H-1′), 5.09 (d of d, J = 4.2 and 6.3 Hz, H-2′), 4.91 (d of d, J = 2.7 and 6.3 Hz, H-3′), 3.90 (d, 1, J = 2.7 Hz, H-4′), 3.30 (s, *ca.* 2, exchanges with D_2O, H_2O, and OH), 1.53 and 1.28 (s, 3, isopropylidene methyls), and 1.1 [two peaks partly resolved, 6, $CH_3C(CH_3)O$–]; R_f 0.82 (system C).

Anal. Calcd for $C_{15}H_{21}N_5O_4 \cdot {}^1/_2H_2O$: C, 52.35; H, 6.43; N, 20.38. Found: C, 52.79; H, 5.95; H, 20.68.

Registry No.—**1**, 362-75-4; **2**, 19234-66-3; **3**, 23754-29-2; **4**, 21950-58-3; **5**, 23680-27-5; **6**, 3415-09-6.

Acknowledgment.—The authors are indebted to Dr. Michael Gross of Varian Associates, Springfield, N. J., for determination of nmr spectra.

(12) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967).

O-Benzyl-N-*t*-butyloxycarbonyl-L-serine[1]

VICTOR J. HRUBY AND KENNETH W. EHLER[2]

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

Received October 8, 1969

In solid-phase peptide synthesis, it is desirable to incorporate both serine and threonine as their O-benzyl-N-acyloxycarbonyl derivatives.[3] Recently, a simple method for preparing O-benzyl-N-*t*-butyloxycarbonyl-L-threonine was reported.[4] On the other hand, methods for preparing O-benzyl-N-*t*-butyloxycarbonyl-L-serine are very laborious.[5,6] The present study reports a simple two-step synthesis of O-benzyl-N-*t*-butyloxycarbonyl-L-serine from L-serine.

O-Benzyl-N-*t*-butyloxycarbonyl-L-serine was obtained directly from the readily available N-*t*-butyloxycarbonyl-L-serine[7] by treatment of the latter compound, in anhydrous liquid ammonia, first with sodium metal and then with benzyl bromide. No detectable racemization was observed. By use of column chromatography for purification, it was possible to recover optically pure N-*t*-butyloxycarbonyl-L-serine for subsequent preparations. No ester was detected in the reaction mixture.

When the same procedure was applied to the synthesis of O-benzyl-N-*t*-butyloxycarbonyl-L-threonine, the maximum yield of this substance from N-*t*-butyloxycarbonyl-L-threonine was 6%.

Experimental Section[8]

O-Benzyl-N-*t*-butyloxycarbonyl-L-serine.—Freshly cut sodium metal (920 mg, 40 mg-atoms) was added to freshly distilled anhydrous ammonia (120 ml) at −70°, and N-*t*-butyloxycarbonyl-L-serine[7] (4.2 g, 20 mmol) was added with stirring under nitrogen. The mixture was vigorously stirred until colorless and then sodium metal (*ca.* 5 mmol) was added, followed by benzyl bromide (3.72 ml, 31 mmol). The turbid solution was stirred for 30–60 min at −50 to −30° to give a clear solution. The ammonia was then removed by slow evaporation and lyophilized. The residue was dissolved in distilled water (20 ml), and the solution was extracted with ether (two 20-ml portions). The aqueous phase was chilled, acidified to pH 3.5 with solid citric acid, saturated with sodium chloride, and extracted with ethyl acetate (four 100-ml portions). The combined organic layers were washed with saturated sodium chloride solution (three 35-ml portions) and dried over anhydrous sodium sulfate. The ethyl acetate was removed *in vacuo* at room temperature to give a colorless oil. The oil was dissolved in chloroform (8 ml), placed on a 3 × 45 cm column of silicic acid (150 g, Baker Analyzed), and eluted with chloroform (800 ml). The chloroform was evaporated *in vacuo* to give O-benzyl-N-*t*-butyloxycarbonyl-L-serine as a clear oil (2.7 g, 45%). Further elutions with methanol yielded 2.7 g of a mixture of N-*t*-butyloxycarbonyl-L-serine and traces of O-benzyl-N-*t*-butyloxycarbonyl-L-serine as an oil. Thin layer chromatography of the oils on silica gel plates in solvent system A against standard reference samples indicated the above structural assignments. An analytical sample of the O-benzyl-N-*t*-butyloxycarbonyl-L-serine was prepared by crystallization of the oil from ether–petroleum ether (bp 30–60°) and a recrystallization from the same solvent mixture: mp 56–58°; $[\alpha]^{25}D$ +19.8° (*c* 2.0, 80% EtOH) [lit.[9] mp 54–63°; $[\alpha]^{25}D$ +20.3° (c 2, 80% EtOH)].

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.12; H, 7.19; N, 4.70.

Recrystallization of the oil from the methanol elution yielded optically pure starting material: mp 86–90°; $[\alpha]^{25}D$ −7.3° (*c* 2.29, 8% EtOH) [lit. mp 84°;[7] $[\alpha]^{25}D$ −7.7°[9] (c 2, 8% EtOH)].

Demonstration of Steric Purity.—An aliquot of O-benzyl-N-*t*-butyloxycarbonyl-L-serine prepared by the above procedure was dissolved in 5.4 *N* HBr–HOAc (2 ml). After 1 hr at room temperature, the reaction mixture was evaporated under water aspirator pressure at 20° to yield a residue which was then diluted to 5 ml with 1 *N* HCl for optical rotation determination. This sample showed the same optical rotation as a sample of L-serine similarly treated, $[\alpha]^{25}D$ +14° (*c* 2.1, 1 *N* HCl).

Registry No.—O-Benzyl-N-*t*-butyloxycarbonyl-L-serine, 23578-14-5.

(1) Supported in part by Grant AM-13411 from the U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow.

(3) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman and Co., San Francisco, Calif., 1969, p 22.

(4) T. Mizoguchi, G. Levin, D. W. Woolley, and J. M. Stewart, *J. Org. Chem.*, **33**, 903 (1968).

(5) K. Okawa, *Bull. Chem. Soc. Jap.*, **29**, 486 (1956); E. Wünsch and C. Fürst, *Z. Physiol. Chem.*, **329**, 109 (1962).

(6) H. Otsuka, K. Inouye, F. Shinozaki, and M. Kanayama, *Bull. Chem. Soc. Jap.*, **39**, 1171 (1966).

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

(8) All melting points were determined in capillaries on a Mel-Temp apparatus and are corrected. Microanalysis was by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography was performed on silica gel plates using chloroform–methanol–acetic acid (85:10:5)—system A.

(9) Schwarz BioResearch, Orangeburg, N. Y. 10962.

Preparation of 2-Acetamido-2-deoxy-α-glycopyranosides. II[1]

BERNARD WEISSMANN

Department of Biological Chemistry, University of Illinois College of Medicine, Chicago, Illinois 60612

Received October 23, 1969

Notwithstanding the marked influence of temperature on the anomeric equilibrium of glycosides of glucosamine and galactosamine,[2] a single product, phenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-mannopyranoside (**1**),[3] is found to predominate in condensation of mannosamine pentaacetate with phenol, at 150 or 125° with catalysis by zinc chloride, or at 100° with *p*-toluenesulfonic acid. The β anomer (**2**), not reported previously, is isolable in small amounts from all three reaction mixtures. A similar preference for formation of the α glycoside has been observed in analogous reactions of mannose derivatives.[4] Formulation of **1** as the α pyranoside[3] was confirmed by nmr studies.[5] The present formulation of **1** and **2** and the derived phenyl 2-acetamido-2-deoxy-α- and -β-D-mannopyranosides (**3** and **4**) as anomeric pairs of pyranosides is supported by their optical-rotation data and by their resistance to acid hydrolysis. For the glycosides **3** and **4**, the value of $2A$ ($\Delta[M]D$) is 43,800; for their tri-O-acetyl esters **1** and **2**, $2A$ is 60,500. For comparison, $2A$ is 47,400 for the phenyl α- and -β-D-mannopyranosides and 58,000 for their tetraacetyl esters.[4] A parallel correspondence has been noted for the glycosides of

(1) Supported by Research Grant AM-02479 from the National Institutes of Health.

(2) B. Weissmann, *J. Org. Chem.*, **31**, 2505 (1966).

(3) M. L. Wolfrom, P. Chakravarty, and D. Horton, *ibid.*, **30**, 2728 (1965).

(4) B. Helferich and S. Winkler, *Chem. Ber.*, **66**, 1553 (1933).

(5) M. L. Wolfrom, P. Chakravarty, and D. Horton, *J. Org. Chem.*, **31**, 2502 (1966).

glucose and 2-acetamido-2-deoxyglucose,[2] although the values of $2A$ for these differ appreciably from those found in the mannose series. The sensitivity to acid hydrolysis of **3** and **4** is of the correct order of magnitude for pyranosides (48 and 31% liberation of phenol from 0.01 *M* solutions in 0.05 *M* HCl, heated 20 min at 100°), as shown by comparisons with the behavior of the phenyl 2-acetamido-2-deoxy-α- and -β-D-glucopyranosides (15 and 30% liberation of phenol). As reported elsewhere,[6] **3** and **4** are inactive as substrates for α- or β-acetylglucosaminidase or for α-acetylgalactosaminidase.

The crystalline *o*- and *p*-nitrophenyl 2-acetamido-2-deoxy-α-D-galactopyranosides (**5** and **6**) are produced by O-deacetylation of the syrupy product from nitration of the previously characterized phenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranoside (**7**).[2] The two nitrophenyl glycosides, which are separable by adsorption chromatography on Dowex 50,[7] are valuable test substrates for α-acetylgalactosaminidase (to be published).

Experimental Section

Melting points are corrected. A Perkin-Elmer Model 141 polarimeter was used with 1-dm tubes. Microanalyses were done by Spang Microanalytical Laboratories, Ann Arbor, Mich. Acetate esters were O-deacetylated in warm methanol–chloroform with sodium methoxide catalysis.[2] The orientation of nitro groups in pure glycosides and mixtures was determined by acid hydrolysis and chromatography.[2] Phenol was estimated by the method of Folin and Ciocalteau.[6]

Phenyl 2-Acetamido-2-deoxy-α- and -β-D-mannopyranoside (3 and 4).—Pentaacetyl β-mannosamine, 2 g, was allowed to react with 5 g of phenol and 0.5 g of zinc chloride for 2.5 hr at 125° (50 mm).[2] The reaction product was crystallized from ethyl acetate, yielding 1.18 g of the pure tri-O-acetyl α-glycoside **1**, mp 198–198.5°, $[\alpha]^{23}D$ +72.6° (*c* 0.6, chloroform) [lit.[3] mp 192–193°, $[\alpha]^{30}D$ +74° (chloroform)].

A second crop, 0.63 g, mp 165–180°, $[\alpha]^{23}D$ +34.8°, and a third crop, 0.06 g, mp 156–176°, $[\alpha]^{23}D$ +44.6°, were obtained with the aid of ether and hexane. Systematic fractional crystallization of these materials from ethyl acetate–isopropyl ether and absolute ethanol yielded additional quantities of **1** and 59 mg (3%) of pure phenyl 2-acetamido-tri-O-acetyl-2-deoxy-β-D-mannopyranoside (**2**), mp 184.5–185°, $[\alpha]^{23}D$ −70.2° (*c* 0.6, chloroform).

Anal. Calcd for $C_{20}H_{25}NO_9$: C, 56.7; H, 5.95; N, 3.31. Found: C, 56.7; H, 5.96; N, 3.21.

O-Deacetylation of **1** and crystallization of the syrupy product from moist acetone gave the α glycoside **3**, mp 104°, which contained water of hydration not determined with precision. For the monohydrate, a loss of 5.7% was calculated and a loss of 4.1% was found at 110° (0.05 mm). The optical rotation, $[\alpha]^{26}D$ +49.1° (*c* 1.0, ethanol) and +42.8° (*c* 0.8, water), and analyses are reported for the dried substance.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.44; N, 4.71. Found: C, 56.6; H, 6.49; N, 4.57.

For anhydrous (?) **3**, the following values were reported: mp 98–99°, $[\alpha]D$ +50° (ethanol).[3]

O-Deacetylation of **2** gave a syrup, crystallized from methanol–ether and recrystallized from hot water to yield the pure β glycoside **4**, mp 184–185°, $[\alpha]^{26}D$ −104.4° (*c* 0.8, water).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.44; N, 4.71. Found: C, 56.6; H, 6.32; N, 4.58.

***o*- and *p*-Nitrophenyl 2-Acetamido-2-deoxy-α-D-galactopyranoside (5 and 6).**—A nitration mixture prepared from 2.25 ml of nitric acid (90%) and 7.5 ml of acetic anhydride was added at one time to a stirred solution of 10 g of **7** in 25 ml of acetic acid, and the reaction[2] was allowed to proceed for 2 hr at 37°. After dilution with 60 ml of ice-cold 2 *M* potassium acetate solution and storage for 3 hr at room temperature, the reaction mixture was extracted with chloroform. Washing of the extract with 2 *M* sodium carbonate and water, drying with sodium sulfate, clarification by passage through a small pad of silicic acid, and removal of solvent under reduced pressure left a syrupy mixture of *o*- and *p*-nitrophenyl derivatives, not successfully resolved. O-Deacetylation of the syrup yielded a solid product, recrystallized from absolute ethanol to give 6.1 g of colorless, seemingly homogeneous needles and a second crop, 0.6 g, both shown to be gross mixtures of the *o*- and *p*-nitrophenyl glycosides (**5** and **6**). These were not separated by repeated recrystallizations from absolute ethanol, acetone, or water. The mixture was applied as a 1% solution in 0.001 *M* acetic acid to a column of Dowex 50 × 4-H^+ (200–400 mesh) of bed volume 3.2 l. Development with the same solvent completely resolved two peaks (11.8 and 17.4 l.), as revealed by absorbance measurements at 265 mμ. Concentration *in vacuo* of the pooled fractions of the first peak and recrystallization of the solid residue from absolute ethanol gave the pure *o*-nitrophenyl glycoside **5**: yield 3.6 g; mp 208–209°; $[\alpha]^{25}D$ +244° (*c* 0.5, water); uv max (water) 265 mμ (ε 3640) and 322 (2000); solubility in water at 25°, 0.70%.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.1; H, 5.30; N, 8.19. Found: C, 49.0; H, 5.36; N, 8.07.

Similarly, the pooled fractions of the second chromatographic peak gave the pure *p*-nitrophenyl glycoside **6**: yield 2.2 g; mp 266° dec; $[\alpha]^{25}D$ +310° (*c* 0.2, water); uv max 222 mμ (ε 6930) and 305 (10,760); solubility in water at 25°, 0.23%.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.1; H, 5.30; N, 8.19. Found: C, 49.3; H, 5.29; N, 8.03.

Registry No.—**2**, 23646-65-3; **3**, 4366-43-2; **4**, 23646-66-4; **5**, 23646-67-5; **6**, 23646-68-6.

(6) B. Weissmann, G. Rowin, J. Marshall, and D. Friederici, *Biochemistry*, **6**, 207 (1967).

(7) R. Sargent and W. Rieman, III, *J. Phys. Chem.*, **61**, 354 (1957); *Anal. Chim. Acta*, **18**, 214 (1958).

Phosphonic Acids and Esters. XXI.[1] Dimerization and Diels–Alder Reactions of Dialkyl 1-(1,3-Butadienyl)phosphonates

C. E. GRIFFIN[2a] AND W. M. DANIEWSKI[2b]

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Received October 1, 1969

Previous studies have shown that vinylic[3] and acetylenic[4] phosphonates function as moderately reactive dienophiles in Diels–Alder reactions. Aromatization of the adducts provides a useful synthesis of substituted phenylphosphonates.[3,4] Pudovik and coworkers[5,6] have shown that diethyl 1-(1,3-butadienyl)phosphonate (**1a**) is a comparably effective diene. On heating, **1a** forms

$$CH_2{=}CHCH{=}CHP(O)(OR)_2$$
1a, R = C_2H_5
b, R = CH_3

a dimer, and the reaction of **1a** with acrylonitrile yields a Diels–Alder adduct.[6] Both reactions were apparently directionally specific to yield a single isomer; structures

(1) Part XX: C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, **34**, 1532 (1969).

(2) (a) Department of Chemistry, The University of Toledo, Toledo, Ohio 43606; (b) Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw.

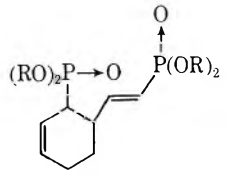
(3) W. M. Daniewski and C. E. Griffin, *J. Org. Chem.*, **31**, 3236 (1966).

(4) D. Seyferth and J. D. H. Paetsch, *ibid.*, **34**, 1483 (1969).

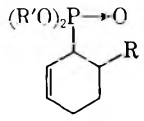
(5) A. N. Pudovik and I. V. Konovalova, *J. Gen. Chem. USSR*, **31**, 1580 (1961).

(6) A. N. Pudovik, I. V. Konovalova, and E. A. Ishmaeva, *ibid.*, **33**, 2446 (1963).

2a and 3a were proposed for these products, but the structures were not substantiated.[6] Since little or no



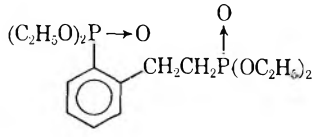
2a, R = C_2H_5
b, R = CH_3



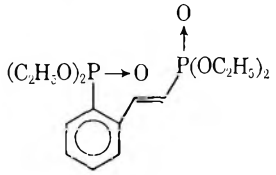
3a, R = CN; R′ = C_2H_5
b, R = $P(O)(OC_2H_5)_2$; R′ = C_2H_5
c, R = $COOC_2H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CN; R′ = CH_3

orientational selectivity was observed in reactions of vinylic phosphonates with unsymmetrically substituted dienes,[3] these observations suggested that the Diels–Alder reactions of 1 might provide a more effective and selective entry to substituted phenylphosphonates. Accordingly, we have investigated the dimerization of 1, as well as its Diels–Alder reactions with a number of simple dienophiles.

There are four possible orientations for the dimerization of 1. If the less highly substituted (3,4) vinyl group of 1 were the more dienophilic, dimer 2 or its 1,3 isomer 4 would result. Alternatively, a higher dienophilic reactivity for the 1,2 double bond would result in the formation of 5-vinyl-3,4-bis(diethoxyphosphono)-cyclohexene or the corresponding 4-vinyl-3,5-bisphosphono isomer. Dimerization of 1a by the published procedure[6] yielded a single (glpc, tlc) product. The integrated intensities of the vinylic protons of the product established it to be either 2a or 4, but the level of analysis of the pmr spectrum did not allow a differentiation between the two structures. However, structure 2a was confirmed for the adduct by an aromatization–oxidation sequence. Treatment of 2a with 1 equiv of N-bromosuccinimide gave a monobromide, which was dehydrobrominated with triethylamine to yield the phenethylbisphosphonate 5, while a similar sequence employing 2 equiv of N-bromosuccinimide gave the *trans*-stryrylbisphosphonate 6. The aromatic proton multiplets of 5 and 6 were similar in appearance



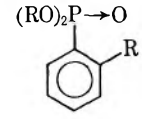
5



6

to those of other *ortho*-substituted phosphonobenzenes.[7,8] Confirmation of the *ortho* relationship of the substituents in 5 and 6 and, consequently, in 2a was provided by hydrolytic oxidation of both 5 and 6 to the known[9] *o*-carboxyphenylphosphonic acid (7a) with aqueous potassium permanganate. Similar results were obtained with the dimer 2b formed from the dimethyl ester 1b.

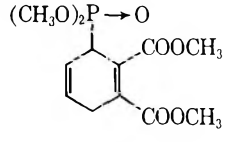
Reactions of 1a with diethyl vinylphosphonate,[3] ethyl acrylate, and acrolein, and of 1b with acrylonitrile, led to the formation of adducts 3b–3d and 3e, respectively. Both 3b and 3e were isolated in a pure state, but 3c and 3d could not be separated from the dimer 2a which is formed during the reaction.[10] Aromatization of 3b, 3c, and 3d to the phenylphosphonates 7b,[4,11] 7c,[9] and 7d[8] was achieved by Pd–C–nitrobenzene



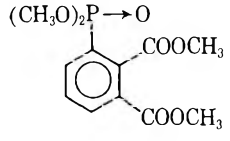
7a, R = COOH; R′ = H
b, R = $P(O)(OC_2H_5)_2$; R′ = C_2H_5
c, R = $COOC_2H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CN; R′ = CH_3

treatment. Separations of 7c and 7d from the contaminating 2a were readily achieved. Attempted aromatization of 3e with Pd–C–nitrobenzene was unsuccessful, but 7e was formed by the reaction sequence used in the preparation of 6. The cyanophenylphosphonate 7e could not be purified satisfactorily, but was identified by hydrolysis to 7a.[9] In all of these Diels–Alder reactions, orientation was specific. Glpc examinations of reaction mixtures indicated the absence of the 1,3 isomers of 3b–3e. However, the low yields (11–23%) of the adducts severely limits this approach for the synthesis of 7.

Adducts were also obtained from the reactions of 1b with two symmetrical dienophiles. Reaction of the diene with dimethyl acetylenedicarboxylate gave a 32% yield of a 1:1 adduct. The pmr spectrum of this adduct indicated structure 8, but integrated intensities indicated some degree of disproportionation or rearrangement to the conjugated cyclohexadiene. Aromatization of 8 with Pd–C–nitrobenzene gave 9. Similarly, reaction of 1b with dimethyl maleate gave a low yield of adduct,[10] which was not isolated but aromatized



8



9

directly to 9 with Pd–C–nitrobenzene. Attempted reactions of 1a with benzoquinone and maleic anhydride were unsuccessful.

Experimental Section[12]

Diethyl 1-(1,3-butadienyl)phosphonate (1a), bp 82–83° (0.5 mm) [lit.[5] bp 122–123° (13 mm)], and dimethyl 1-(1,3-butadienyl)phosphonate (1b), bp 60–63° (0.3 mm) [lit.[13] bp 77–78.5° (3 mm)], were prepared by the published[5] procedure.

Formation of Dimers 2a and 2b.—A mixture of 0.1 mol of the butadienylphosphonates 1a or 1b and 0.1 mol of anhydrous cuprous chloride was held under a nitrogen atmosphere with constant stirring at 120–130° for 12 hr. After cooling to room temperature, the reaction mixture was diluted with 200 ml of

(7) C. E. Griffin, *Tetrahedron*, **20**, 2399 (1964).
(8) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).
(9) M. Gordon, V. A. Notaro, and C. E. Griffin, *J. Amer. Chem. Soc.*, **86**, 1898 (1964).
(10) Pudovik and coworkers[6] reported successful Diels–Alder reactions of 1a with methyl methacrylate, acrolein, and dialkyl maleates, but were also unable to separate the dimer contaminant.
(11) R. Obrycki and C. E. Griffin, *Tetrahedron Lett.*, 5049 (1966).
(12) Details of experimental procedures are given in ref 3.
(13) K. N. Anisimov and N. E. Kolobova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 923 (1956).

carbon tetrachloride and filtered. The solvent was removed under reduced pressure to give an oil which was distilled to give **2a** (63%), bp 185–190° (0.05 mm) [lit.[6] bp 182° (0.04 mm)], and **2b** (57%), bp 195° (0.1 mm).

Aromatization of Dimers 2a and 2b.—N-Bromosuccinimide (2.6 g, 14.5 mmol) was added in portions to a refluxing solution of 5.0 g (13 mmol) of **2a** and 0.1 g of azoisobutyronitrile in 40 ml of carbon tetrachloride. When dissolution of N-bromosuccinimide was complete, the reaction mixture was refluxed for an additional 0.5 hr, cooled to room temperature, and kept at 5° overnight. Succinimide (1.2 g, 84%) separated, was removed by filtration, and was washed with carbon tetrachloride. The combined carbon tetrachloride solutions were concentrated under reduced pressure to yield an oil which was dissolved in 40 ml of benzene. A solution of 10.0 g (100 mmol) of triethylamine in 20 ml of benzene was added slowly with stirring to this solution. After the addition was completed, the reaction mixture was refluxed with stirring for 1 hr, cooled, and held at 5° overnight. Triethylammonium bromide (2.3 g, 96%) was removed by filtration and the filtrate was concentrated under reduced pressure to give an oil which was distilled to yield 2.5 g of an oil, bp 198–210° (0.08 mm). This product was further purified by chromatography on neutral alumina using successive elutions with hexane, benzene, and chloroform. The combined chloroform eluents were dried over sodium sulfate, concentrated, and distilled to give 2.0 g (40%) of **diethyl *o*-(2-diethoxyphosphonoethyl)-phenylphosphonate** (**5**), bp 181° (0.03 mm).

Anal. Calcd for $C_{16}H_{28}O_6P_2$: C, 50.80; H, 7.47; P, 16.37. Found: C, 50.99; H, 7.51; P, 16.51.

The reaction of **2a** with 2 equiv of N-bromosuccinimide was carried out in the same manner. The crude product was not distilled, but was purified by chromatography on neutral alumina. Two purifications gave analytically pure **diethyl *o*-(2-diethoxyphosphonovinyl)phenylphosphonate** (**6**, 13%).

Anal. Calcd for $C_{16}H_{26}O_6P_2$: C, 51.18; H, 6.88; P, 16.44. Found: C, 51.31; H, 7.08; P, 16.59.

The same procedure was employed for the aromatization of **2b**. A 30% yield of **dimethyl *o*-(2-dimethoxyphosphonovinyl)-phenylphosphonate** was obtained: pmr (CCl_4) τ 6.25 (d, J_{PH} = 11 Hz, CH_3), 3.78 [2 × 2, $J_{HH} \cong J_{PH} \cong 17$ Hz, H(P)C=], 2.0–3.0 (m, C_6H_4), and 1.88 ppm (2 × 2, $J_{HH} \cong J_{PH} \cong 17$ Hz).

Anal. Calcd for $C_{12}H_{18}O_6P_2$: C, 45.10; H, 5.64; P, 19.32. Found: C, 45.20; H, 5.74; P, 19.21.

Diels–Alder Reactions of Dienes 1a and 1b. A. With Diethyl Vinylphosphonate.—A mixture of 7.0 g (37 mmol) of **1a**, 30.0 g (183 mmol) of diethyl vinylphosphonate, and 0.1 g of hydroquinone was placed in an autoclave which was then evacuated and heated at 150° for 12 hr. Distillation of the reaction mixture gave 26.1 g of diethyl vinylphosphonate, bp 48–55° (0.1 mm), 1.0 g (11%) of **3,4-bis(diethoxyphosphono)cyclohexene** (**3b**), bp 200–205° (0.1 mm), and polymeric residue (7.1 g).

B. With Acrylonitrile.—A mixture of 16.0 g (100 mmol) of **1b**, 15.9 g (300 mmol) of acrylonitrile, and 0.1 g of hydroquinone was heated in an autoclave under an atmosphere of nitrogen at 125° for 12 hr. The reaction mixture was concentrated under reduced pressure in a rotary evaporator and the residue was distilled to give 4.5 g of **1b**, 4.5 g of crude **3e**, bp 130–137° (0.2 mm), 1.0 g of a mixture of **3e** and **2b**, bp 137–175° (0.2 mm), and 8 g of a rubbery residue. The two higher boiling fractions were combined and redistilled to give 3.5 g (23%) of **3-dimethoxyphosphono-4-cyanocyclohexene** (**3e**), bp 134–135° (0.2 mm). The same conditions were employed for the reactions of **1a** with ethyl acrylate and acrolein and of **1b** with dimethyl maleate. In each of these cases, the mixture of adduct and dimer could not be separated by distillation.

C. With Dimethyl Acetylenedicarboxylate.—A mixture of 5.0 g (31 mmol) of **1b**, 4.4 g (31 mmol) of dimethyl acetylenedicarboxylate, and 0.1 g of hydroquinone was heated under a nitrogen atmosphere for 12 hr at 100°. The reaction mixture was concentrated under reduced pressure in a rotary evaporator (bath temperature 130°) to give a 6.0-g residue, which was chromatographed on silicic acid (100 g). Elution with *n*-hexane gave small amounts of the acetylene dicarboxylate. **1,2-Dicarbomethoxy-3-dimethoxyphosphonocyclohexa-1,4-diene** (**8**, 3.0 g, 32%) was eluted with 1:1 benzene–*n*-hexane.

Aromatization of Diels–Alder Adducts.—The general procedure[3] is exemplified by the aromatization of **3b**. A mixture of 0.75 g (3 mmol) of **3b**, 1.0 g (8 mmol) of nitrobenzene, 1.5 g of 5% palladium on charcoal, and 80 ml of anhydrous ethanol was held at reflux temperature for 100 hr. The catalyst was removed by filtration and, after concentration under reduced pressure, the reaction mixture was distilled to give 0.4 g (80%) of **tetraethyl *o*-phenylenebisphosphonate** (**7b**), bp 180–185° (0.1 mm). The aromatizations of **3c** and **3d** to **7c** and **7d** were carried out in the same manner. Products **7b–7d** were identified by comparisons with authentic samples.[8,9,11]

Dimethyl 2,3-dicarbomethoxyphenylphosphonate (**9**) was prepared by refluxing a mixture of 3.0 g (10 mmol) of **8**, 6.0 g (49 mmol) of nitrobenzene, 3.0 g of 5% palladium on charcoal, and 60 ml of anhydrous methanol for 72 hr. The catalyst was removed by filtration and, after concentration under reduced pressure in a rotary evaporator (bath temperature 100°), the reaction mixture was chromatographed on silicic acid (100 g). Initial elution with *n*-hexane gave small amounts of nitrobenzene. Elution with benzene gave 1.5 g (50%) of **9**.

Anal. Calcd for $C_{12}H_{15}O_7P$: C, 47.71; H, 5.04; P, 10.25. Found: C, 47.33, 47.41; H, 4.87, 4.91; P, 10.03, 9.98.

Aromatization of the adduct of dimethyl maleate and **1b** and isolation of **9** was carried out in the same manner.

Adduct **3e** was aromatized by the bromination–elimination sequence used for the preparation of **6**. **Dimethyl *o*-cyanophenylphosphonate** (**7e**) was isolated by distillation, but was contaminated by **2b** and its aromatization products. Neither redistillation nor silicic acid chromatography achieved satisfactory purification, and the product was hydrolyzed with refluxing 2 *N* hydrochloric acid to yield **7a**. Identity was established by comparisons with an authentic sample.[9]

Registry No.—**1a**, 7158-35-2; **1b**, 4037-11-0; **5**, 23293-54-1; **6**, 23293-55-2; **9**, 23293-56-3; dimethyl *o*-(2-dimethoxyphosphonovinyl)phenylphosphonate, 23293-57-4.

Acknowledgment.—We are indebted to Dr. W. E. Byrne, Dr. M. Gordon, and Dr. M. P. Williamson for the determination of pmr spectra. This study was supported in part by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, under Grant AF-AFOSR-470-64.

A Novel Acylation of Amino Acids with S-Carboxymethyl Dialkyldithiocarbamates

WILLIAM J. GOTTSTEIN, ANN H. EACHUS, AND LEE C. CHENEY

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

Received October 27, 1969

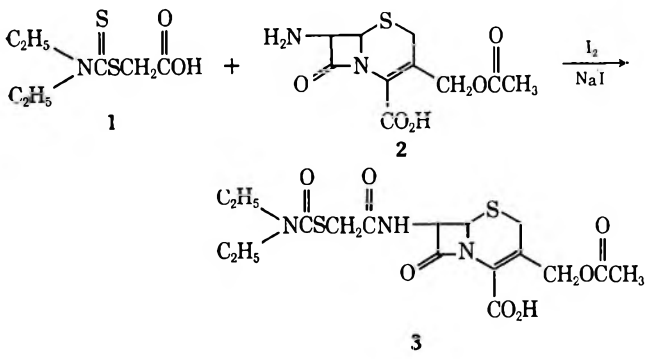
In an attempt to thioacylate[1,2] 7-aminocephalosporanic acid (**2**) with S-carboxymethyl N,N-diethyldithiocarbamate (**1**) in the presence of iodine–sodium iodide complex, we have unexpectedly isolated N,N-diethylcarbamoylmercaptomethylcephalosporin (**3**). This compound was identified by its ir and nmr spectra and by synthesis through the direct acylation of **2** with S-carboxymethyl N,N-diethylthiocarbamate mixed anhydride.

This acylation is not confined to **2**[3] but works equally well with other amino acids such as 6-aminopenicillanic acid and 2-phenylglycine. The reaction also proceeds readily with other S-carboxymethyl dialkyldithiocarbamates. However, in the absence of iodine, the reaction fails.

(1) J. F. W. McOmie, *Ann. Rep. Progr. Chem.*, **45**, 208 (1948).

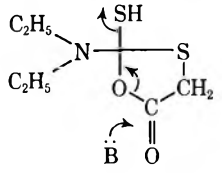
(2) R. H. Hall, H. D. Holingworth, D. P. Young, and R. Sherlock, British Patent 36,842,161 (1964); *Chem. Abstr.*, **60**, 15877*g* (1964).

(3) W. J. Gottstein and A. H. Eachus, U. S. Patent 3,391,141 (1968); *Chem. Abstr.*, **69**, 86992 (1968).



The acylating acids were prepared by condensation of carbon disulfide with aliphatic secondary amines in aqueous potassium hydroxide followed by treatment with chloroacetic acid.[4]

A mechanism for this reaction may be visualized as one proceeding through the cyclic 2-dialkylamino-2-mercapto-5-oxo-1,3-oxathiole intermediate as shown below, where B represents the attacking nucleophile.



Experimental Section[5]

Sodium 7-(N,N-Diethylcarbamoylmercaptoacetamido)cephalosporanate.—To a mixture of 1.4 g (0.005 mol) of **2** and 1.2 g (0.005 mol) of S-carboxymethyl-N,N-diethyldithiocarbamate[4] in 100 ml of pH 7 phosphate buffer was added 10% sodium hydroxide solution until the acids dissolved. A solution of 10 ml of 1 *N* sodium iodide–iodine solution was added with stirring at 5° over a 20-min period. The solution was maintained at pH 7 during this period by the addition of 10% sodium hydroxide. The reaction mixture was filtered to remove some insoluble impurities and acidified with dilute phosphoric acid to pH 2. The mixture was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and treated with sodium 2-ethylhexanoate. The salt was collected and recrystallized from dimethylformamide and acetone to yield 580 mg (24%) of white crystals: mp 152–155° dec; ir (KBr) 3340 (amide NH), 1770 (β-lactam C=O), 1745 (ester C=O), 1685 (amide C=O), and 1650–1610 cm^{-1} [N(C=O)S and (C=O)O]; nmr (D_2O) 5.65 (d, 1, J = 5 Hz, NCHCO), 5.08 (d, 1, J = 5 Hz, NCHS), 4.88 (m, 2, CH_2OAc), 3.67 (s, 2, SCH_2CO), 3.40 (m, 4, J = 7.5 cps, CH_2NCH_2), 2.05 (s, 3, CH_3CO), and 1.12 ppm (t, 6, J = 7.5 Hz, CH_3, CH_3). The C_2 protons are obscured in the 3.7–3.1-ppm region.

Anal. Calcd for $C_{17}H_{22}NaN_3O_7S_2 \cdot H_2O$: C, 41.64; H, 4.93; N, 8.57. Found: C, 41.91; H, 5.21; N, 8.60.

This same compound was also prepared from S-carboxymethyl N,N-diethylthiocarbamate.

S-Carboxymethyl N,N-Diethylthiocarbamate.—Carbonyl sulfide was bubbled into a solution of 14.6 g (0.2 mol) of diethylamine in 150 ml of ether at 5° until a total of 6 g (0.1 mol) had been added. The solution was stored for 15 hr at 30° and the solvent was removed under reduced pressure to a light yellow, crystalline solid which weighed 13.7 g. This was dissolved in 75 ml of water, and 7.7 g (0.06 mol) of sodium chloroacetate was added. The solution was stirred for 3 hr at 30° and for 50 min at 50–55°. The solution was acidified to pH 2 with concentrated hydrochloric acid and extracted with ether. The ether was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield a crystalline solid which weighed 6.5 g (34%), mp 36–38°.

Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85. Found: C, 44.00; H, 7.01.

Sodium 7-(N,N-Diethylcarbamoylmercaptoacetamido)cephalosporanate by Direct Acylation.—To a solution of 3.2 g (0.017 mol) of S-carboxymethyl N,N-diethylthiocarbamate and 1.8 g (0.018 mol) of triethylamine dissolved in 100 ml of tetrahydrofuran at 0° was added dropwise 2.1 g (0.018 mol) of isovaleryl chloride. The mixture was stirred for 20 min and a solution of 4.8 g of **2** dissolved in 50 ml of water and 5 ml of triethylamine was added all at once. After stirring for 25 min the solution was diluted with cold water, acidified to pH 2 with 1:1 phosphoric acid, and extracted with ethyl acetate. The organic layer was washed twice with water, filtered, and evaporated to an oil. The oil was dissolved in acetone and treated with 20% sodium 2-ethyl hexanoate in acetone until the turbidity ceased. The white, crystalline solid was collected and recrystallized from water–acetone to yield 2.5 g. The ir and nmr spectra were identical with the spectra obtained from the product prepared by the iodine–sodium iodide reaction.

Registry No.—S-Carboxymethyl-N,N-diethylthiocarbamate, 20708-46-7; sodium salt of **3**, 23740-36-5.

(4) G. Nachmias, *Ann. Chim.* (Paris), **7**, 584 (1954); *Chem. Abstr.*, **48**, 597 (1954).

(5) Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. The ir spectra were recorded on a Beckman IR-9 spectrometer. The nmr spectra were run on a Varian A-60 spectrometer at a sweep width of 500 cps using deuterium oxide as a solvent. The authors wish to thank Mr. R. M. Downing and Mr. D. F. Whitehead for the microanalytical and spectral data, respectively.

Palladium-Catalyzed Reactions of Formate Esters

JOSEPH S. MATTHEWS, DONALD C. KETTER, AND RALPH F. HALL

Gulf Research and Development Company, Pittsburgh, Pennsylvania 15230

Received October 8, 1969

The decarbonylation of aldehydes by palladium was first reported by Newman and Zahm,[1] and its application to syntheses with all types of aldehydes has been reported by various workers.[2] Recently,[3] evidence has been presented that this may be a free-radical process, although, if so, the radicals may exist only on the catalyst surface. That aldehydes can be decarbonylated *via* free radicals is already well known.[4]

Formates can be considered to have an aldehydic hydrogen and carbonyl, but the decarbonylation of formate esters by palladium has not been reported. In this case, if decarbonylation occurred, the expected intermediate would be an alkoxy radical, which could lead to the alcohol by abstraction of a hydrogen atom.

It was found that on refluxing *n*-octyl formate with palladium charcoal, carbon monoxide was eliminated and *n*-octyl alcohol was formed (Table I).

TABLE I
DECARBONYLATION PRODUCTS OF *n*-OCTYL FORMATE

Liquid	% by glc	Gas	Mol %
Octan-1-ol	95.71	CO	85.50
Octyl formate	1.70	H_2	12.27
Octanal	1.34	CO_2	1.58
High molecular weight	1.25	Hydrocarbons	0.65

(1) M. S. Newman and H. V. Zahm, *J. Amer. Chem. Soc.* **65**, 1097 (1943).

(2) See, *e.g.*, H. E. Eschinazi, *Bull. Soc. Chim. Fr.*, 967 (1962); M. S. Newman and N. Gill, *J. Org. Chem.*, **31**, 3860 (1966); J. O. Hawthorne and M. H. Wilt, *ibid.*, **25**, 2215 (1960); N. E. Hoffman, A. T. Kanakkanatt, and R. F. Schneider, *ibid.*, **27**, 2687 (1962).

(3) J. W. Wilt and V. P. Abegg, *ibid.*, **33**, 923 (1968).

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

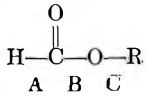
However, when benzyl formate was refluxed with palladium on charcoal, the major products were toluene and carbon dioxide (Table II).

TABLE II
DECARBOXYLATION PRODUCTS OF BENZYL FORMATE

Liquid	% by glc	Gas	Mol %
$C_6H_5CH_3$	96.7	CO_2	91.07
C_6H_6	1.3	CO	6.97
C_6H_5CHO	0.2	H_2	1.96
$C_6H_5CH_2OH$	0.2		
$(C_6H_5)_2CH_2$	0.4		
$(C_6H_5CH_2)_2$	0.9		
$(C_6H_5)_2CHCH_3$	0.2		

In both these cases, the products, and especially the by-products, can be explained on the basis of free-radical mechanisms, although these may occur only on the surface of the catalyst. (1,1-Diphenylethane appears to be a rearrangement product.)

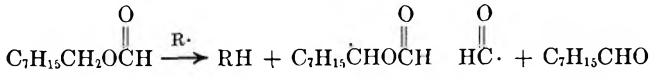
In the molecule shown, calculations of the homolytic bond dissociation energies (BDE) of bonds A, B,



and C by the method of Benson[5] indicate that benzyl formate and *n*-octyl formate should cleave at C to yield carbon dioxide, but only benzyl formate does this.

It appears that in octyl formate, the catalyst weakens bond B sufficiently to overcome the 11-kcal difference between bonds B and C (*ca.* 14 kcal), to induce cleavage at bond B. However, in benzyl formate, bond C is still weaker by *ca.* 10 kcal, and hence the pyrolysis of benzyl formate proceeds *via* rupture of this bond to yield carbon dioxide.

Examination of the by-products in Tables I and II tend to bear out that the reactions occurring, even if on the surface of the catalyst, are proceeding *via* radical intermediates. The occurrence of octanal (Table I) can arise from alkoxy radical *via* hydrogen abstraction or disproportionation. Another possibility is as follows.



This reaction would be followed by decarbonylation of the aldehyde to produce hydrocarbons or higher molecular weight products. This accounts in part for the formation of hydrogen. Octyl formate was unchanged on heating at 200° alone or with activated charcoal (Darco G60). Tests for aldehyde were negative on heating octyl alcohol with palladium on charcoal; so octanal cannot arise in this way.

More interesting by-products were obtained with benzyl formate, since the intermediate benzyl radical is more stable. This can explain the formation of bibenzyl and diphenylmethane. Overall, very little of the reaction (1.7%) proceeds *via* the alkoxy radical, which leads to benzyl alcohol, benzaldehyde, and benzene. Benzyl formate itself was recovered unchanged on prolonged heating at reflux without the catalyst or with added activated charcoal.

(5) S. W. Benson, "Thermochemical Kinetics," John Wiley & Sons, Inc., New York, N. Y., 1968.

Experimental Section

The octyl formate and benzyl formate used were at least 99% pure according to glpc. The 10% palladium-on-charcoal catalyst was purchased from E. H. Sargent & Co. Products were separated on an F & M 720 chromatograph using a 9 ft × 0.125 in. column of 30% Embaphase silicone on Chromosorb. Individual unknown peaks were identified by combined mass-glpc and ir-glpc analysis. Material balances were usually 90–95%.

Decarbonylation of *n*-Octyl Formate.—In a typical experiment, a 25-ml, two-neck flask was equipped with a serum cap on one neck. On the other neck a ground joint tube 8 in. long and bent at a right angle was attached to a plastic bag. Into the tared flask was weighed 9.0500 g of octyl formate and 0.1236 g of palladium on charcoal. The outlet tube was connected to the evacuated plastic bag and the flask was lowered into a heated bath at 200°. The flask contents were magnetically stirred. At intervals, 0.2-μl samples were removed through the serum cap for analysis until the reaction indicated *ca.* 97% completion. The reaction was cooled and filtered, and the gas and liquid products were identified as indicated above.

Glpc showed that there was a 98.3% conversion into the products listed in Table I. There was a total material balance of 92%.

Registry No.—Palladium, 16065- 88-6; *n*-octyl formate, 112-32-3; benzyl formate, 104-57-5.

Reaction of Terephthalic Acid with Formaldehyde in Sulfur Trioxide Media

LEROY S. FORNEY

Research and Development Laboratories,
Mobil Chemical Company,
Edison, New Jersey 08817

Received August 29, 1969

The aromatic ring of terephthalic acid is highly deactivated toward electrophilic substitution. However, scattered references are found in the literature for its reaction with inorganic species.[1] Nitration provides a route to nitroterephthalic acid, and, while terephthalic acid is remarkably stable to sulfonation in the absence of a catalyst, it reacts with sulfuric acid in the presence of mercuric salts to give sulfoterephthalic acid. Chlorination leads to the commercially important dimethyl tetrachloroterephthalate, "Dacthal." In spite of these references, no substitution of terephthalic acid with an electron-deficient carbon species has been observed.

The condensation of various methoxybenzoic acids with formaldehyde in concentrated hydrochloric acid has been reviewed by Charlesworth, *et al.*,[2] and phthalide formation was observed, frequently accompanied by chloromethylation. The action of formaldehyde on *m*-hydroxybenzoic acid in hydrochloric acid also yields phthalide derivatives exclusively.[3] It has been shown that 2-chloromethylbenzoic acids frequently react to produce phthalides in high yields.[4] Indeed, it may be expected that, whenever an aromatic methylol or potential methylol substituent is located *ortho* to a carboxyl

(1) "Encyclopedia of Chemical Technology," R. E. Kirk and D. F. Othmer, Ed., The Interscience Encyclopedia, Inc., New York, N. Y., 1953, Vol. X.

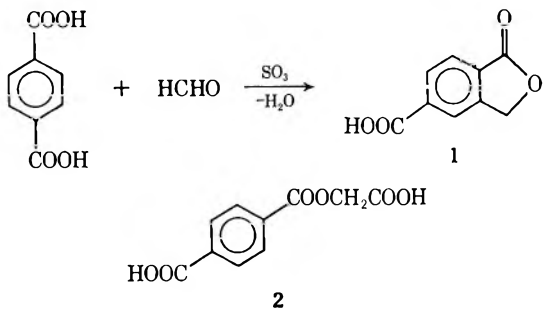
(2) E. H. Charlesworth, R. P. Rennie, J. E. Sinder, and M. M. Yan, *Can. J. Res*, **23B**, 17 (1945).

(3) (a) C. A. Buechler, T. A. Powers, and J. G. Michels, *J. Amer. Chem. Soc.*, **66**, 417 (1944); (b) C. A. Buechler, J. G. Harris, C. Shacklett, and B. P. Block, *ibid.*, **68**, 574 (1946).

(4) J. C. Overeem and G. J. M. Van Der Kerk, *Rec. Trav. Chim. Pays-Bas*, **83**, 1023 (1964).

group under dehydrating conditions, a rapid loss of water would occur to produce a phthalide moiety. However, in the few reported instances of negatively substituted benzoic acids or benzoic acid itself undergoing reaction with formaldehyde, more vigorous conditions were required and only intermolecular condensation products were isolated. Thus benzoic acid reacted with formaldehyde in sulfuric acid to give 3,3′-dicarboxydiphenylmethane,[5] and isophthalic acid provided 3,3′,5,5′-tetracarboxydiphenylmethane.[6]

We wish to report the condensation of terephthalic acid with formaldehyde in sulfur trioxide media, a process which produces 5-carboxyphthalide (1) cleanly and in excellent yield. The reaction is generally free of by-product formation over a fairly wide range of reaction conditions, although terephthaloyloxyacetic acid (2) has been identified (as its dimethyl ester) from reaction in the presence of excess formaldehyde and from reaction media containing <20% SO_3. Prior routes to 1 involved several-step processes or reduction of trimellitic anhydride, which provides a mixture of the 5- and 6-carboxyphthalides which are difficult to separate.[7] This synthesis of 1 is believed to represent the first reported substitution of terephthalic acid with an electron-deficient carbon species.



Experimental Section

A Beckman IR-5A infrared spectrophotometer, Varian A-60 nmr spectrometer and 21-110B Consolidated Electronics mass spectrometer were used for spectral determinations. Gravimetric analysis utilized a Du Pont 950 Thermogravimetric Analyser. Carbon–hydrogen analyses were done by Galbraith Laboratories, Knoxville, Tenn. An F & M 5750 research chromatograph was used with a 12 ft × 0.25 in. 10% UCW 98 on an acid-washed Chromosorb W DMCS-treated column for analysis of esters.

5-Carboxyphthalide (1).—Sulfur trioxide (180 ml, 4.3 mol of "Sulfan B") was slowly added to terephthalic acid (200 g, 1.2 mol), with stirring, and formaldehyde (48 g, 1.6 mol of "Trioxane") added (exothermic). The resultant slurry was heated to 120–130° for 2 hr. The reaction was accompanied by a color change after the excess sulfur trioxide distilled off. After cooling, the mixture was poured into ice water (4 l.) and crude product received by filtration. The filter cake was slurried with water, partially neutralized with NaOH to remove residual sulfuric acid, filtered, and washed again, to give 192.3 g of pink solids, mp 285–290°. Chloroform extraction of the filtrates gave an additional 6.0 g of product (93% yield). The acid can be recrystallized from acetic acid or 50% aqueous dimethyl sulfoxide to provide purified 5-carboxyphthalide, mp 290–294° (literature value,[8] 283–284°). Esterification with methanol–BF_3 gave 5-carbomethoxyphthalide, mp 166–167°, which exhibited ir bands at 5.70 (phthalide C=O) and 5.80 μ (carboxyl C=O); nmr ($CDCl_3$, 60 MHz) δ 8.08 (m, 3), 5.37 (s, 2, OCH_2), 3.98 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* 192 (parent peak). Both the ester and phthalide linkages were cleaved under basic conditions, in accord with the literature.[9]

Anal. Calcd for $C_{10}H_8O_4$: C, 62.48; H, 4.20. Found: C, 63.57; H, 4.21; sapon equiv 96.05.

Esterification with ethanol–BF_3 gave 5-carbethoxyphthalide, mp 147.5–148°.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.05; H, 4.89. Found: C, 64.11; H, 4.86.

2-Hydroxymethylterephthalic Acid.—Acidification of the solution received from saponification of 5-carbomethoxyphthalide gave 2-hydroxymethylterephthalic acid, isolated by filtration and drying [85° (20 mm)]. It gave no phthalide C=O absorption at 5.70 μ in the ir.

Anal. Calcd for $C_9H_8O_5$: C, 55.10; H, 4.08. Found: C, 54.70, 54.88; H, 4.15, 4.18. Differential gravimetric analysis indicated loss of water at 200° (Calcd weight loss for $-H_2O$: 9.20%. Found: 10.21%) and melting at 296° (5-carboxyphthalide).

Terephthaloyloxyacetic Acid Dimethyl Ester (2).—Terephthalic acid (0.83 g, 5 mmol), formaldehyde (0.90 g, 30 mmol, "Trioxane"), and 5.0 ml of 98% sulfuric acid were sealed in a glass tube and heated to 150° for 2 hr. The tube was chilled and opened; the contents were poured into methanol (100 ml), concentrated, poured into water (700 ml), and extracted into dichloromethane. In this way, 0.71 g of esters was received, shown by gas chromatography to contain 83.2% dimethyl terephthalate, 1.1% 5-carbomethoxyphthalide, and 15.7% a third component, by peak areas. The unknown was trapped from the eluent gases and identified as dimethyl terephthaloyloxyacetic acid: nmr (CCl_4, 60 MHz) δ 3.80 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 4.82 (s, 2, CH_2), 8.13 (s, 4).

Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 56.78; H, 4.76.

Registry No.—Terephthalic acid, 100-21-0; formaldehyde, 50-00-0; 2-hydroxymethylterephthalic acid, 23405-34-7; 1 methyl ester, 23405-32-5; 1 ethyl ester, 23405-31-4; 2 dimethyl ester, 23405-33-6.

(5) R. W. Beattie and R. H. Manske, *Can. J. Chem.*, **42**, 223 (1964).
(6) J. R. LeBlanc, D. B. Sharp, and J. G. Murray, *J. Org. Chem.*, **26**, 4731 (1961).
(7) O. O. Juveland, U. S. Patent 3,261,780 (1966).
(8) J. Thiele and O. Giese, *Ber.*, **36**, 842 (1903).
(9) W. H. Perkin, Jr., and J. F. S. Stone, *J. Chem. Soc.*, **127**, 2275 (1925).

Novel Fluorine-Containing β-Diketone Chelating Agents[1]

W. G. SCRIBNER

Monsanto Research Corporation, Dayton Laboratory, Dayton, Ohio 45407

B. H. SMITH, R. W. MOSHIER, AND R. E. SIEVERS

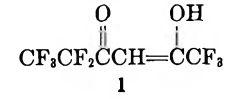
Aerospace Research Laboratories, ARC, Wright-Patterson Air Force Base, Ohio 45413

Received July 24, 1969

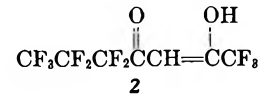
Increasing interest in volatile chelating agents[2] (or volatile metal chelates derived therefrom) for separations of metals by distillation or gas chromatography, for ultratrace analysis of metals or metal mixtures, for vapor deposition, for use as solvent extraction reagents, and for use as reagents that react directly with metals or oxides to form chelates has prompted the synthesis and examination of two new β-diketones. These ligands are 1,1,1,2,2,6,6,6-octafluoro-3,5-

(1) This work was supported in part by Aerospace Research Laboratory In-House Independent Laboratory Research Funds, and by Contract AF 33(615)-1093.
(2) R. W. Moshier and R. E. Sievers, "Gas Chromatography of Metal Chelates," Pergamon Press, Oxford, 1965, and references therein.

hexanedione (1) and 1,1,1,2,2,3,3,7,7,7-decafluoro-4,6-heptanedione (2), enol forms of which are shown below.

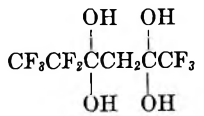


1



2

These compounds were prepared by Claisen condensation of trifluoroacetone with the required perfluoro ester using sodium methoxide.[3,4] Advantage was taken of the formation of a sparingly water-soluble hydrate of 1 (3) to effect its purification, which could



3

not be accomplished easily by distillation when ether or xylene was used as a solvent owing to azeotrope formation. The β-diketone was subsequently regenerated from 3 by treatment with phosphorus pentoxide and was distilled. The existence of a stable hydrate of 1 is not surprising since the analogous dihydrate of hexafluoroacetylacetone [H(hfa)] has been reported.[5] The infrared spectrum of 3 exhibits a strong OH absorption band at ~3 μ, no absorption in the carbonyl region at ~6 μ, and increased absorption at 11.0 μ. The spectrum of H(hfa) dihydrate possesses quite similar features.

Synthesis of 2 was effected conveniently in a hexane medium. After acidification of the reaction mixture and separation of the phases, the hexane phase was shaken with aqueous sodium acetate to remove the ligand from the hexane. The β-diketone was then purified in the usual manner[4] by precipitation of its copper chelate and regeneration of the β-diketone from the chelate with concentrated sulfuric acid.

A white solid appeared in 2 stored at −25°. This material was isolated and air-dried. Its infrared spectrum permits identification of the material as a hydrate of 2 (strong OH^- absorption band at ~3 μ, no carbonyl absorption band at ~6 μ, strong absorption band at 11 μ). When a mixture of 1 ml of 2 and 0.20 ml of water was cooled to −25°, all of the material solidified to a homogeneous white solid. An infrared spectrum of this solid material was identical with that of the solid material isolated from free β-diketone. On warming to room temperature, the solid melted with decomposition to 2 plus water. From these observations, then, it appears that 2 does indeed form a hydrate, but that the reaction occurs below room temperature, and that the hydrate is unstable at room temperature. The relatively poor tendency of 2 to form a hydrate as compared with H(hfa) and 1 may account, in part, for its greatly increased ability to extract divalent metals from aqueous solution as discussed below.

(3) J. C. Reid and M. Calvin, *J. Amer. Chem. Soc.*, **48**, 2928 (1950).

(4) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 111 (1954).

(5) B. G. Schultz and E. M. Larsen, *J. Amer. Chem. Soc.*, **71**, 3250 (1949).

Nmr data on the compounds indicated that both 1 and 2 exist essentially 100% in the enol form. There was no measurable peak in the δ 3.6–4.1 region where methylene protons of the keto form of β-diketones would be expected to appear.

Infrared spectra of both compounds exhibited carbonyl absorption bands at 5.95 (w) and 6.17 (m) μ, which are similar in position and intensity to those for H(hfa) [5.92 (w) and 6.15 (m) μ]. The spectra also contain broad, strong absorption bands in the 7–9-μ CF region, and medium intensity absorption bands at ~12.2 μ. The latter absorption band diminishes greatly upon hydrate formation, as is also the case with H(hfa).

The zirconium and hafnium chelates of 2 were prepared by direct reaction of the ligand with the anhydrous tetrachloride. It is interesting to note that despite molecular weights of 1319 and 1407, respectively, both chelates are liquids and can be distilled (Zr, 65–70°, 0.001–0.05 mm; Hf, 70°, 0.01 mm). The chromium(III) chelates of 1 and 2, and the iron(III) chelate of 2 are also liquids at room temperature.

The solvent extraction properties of 1 and 2 have been examined and compared with 1,1,1-trifluoro-2,4-pentanedione [H(tfa)] and H(hfa).[6] In benzene or chloroform 2 (~0.1 *M*) was able to extract 97% zinc or 98.7% cobalt(II) in 10 min from an equal volume of water at pH 5–6 provided the initial metal ion concentration was 0.001 *M* or less. The order of effectiveness of the reagents for the extraction of zinc or cobalt was found to be 2 > 1 ≫ H(tfa) > H(hfa). Increasing ability of these ligands to extract divalent metals with increasing fluorocarbon chain length may be related to the decreasing tendency of the ligands toward hydrate formation. Ligand hydrate formation would be expected to result in decreased solvent extraction ability because the metal ion would be in competition with water for the ligand.

Ultraviolet absorption measurements on 10^{-4} *M* aqueous solutions of 2 at pH 4.7 and 8.0 after 0, 1, 2, 5, and 7 days revealed logarithmically decreasing absorbance values at 308 nm (enolate ion) with time. The rate of decrease was faster at pH 4.7 than at pH 8.0. The half-life values were 45.6 and 67.2 hr, respectively.

Increasing instability of 2 with decreasing pH is opposite to the behavior of H(tfa) observed by Stokely.[7] Aqueous solutions of this ligand were stable at pH 7 and below, but decomposed rapidly at pH 9 or 10 with half-lives of ~3 and 2 hr, respectively.

Compounds 1 and 2 possess extremely irritating odors. Inhalation of small quantities is followed by a persistent bitter taste. Consequently, these compounds should be handled only in a hood.

Experimental Section

1,1,1,2,2,6,6,6-Octafluoro-3,5-hexanedione (1).—Ethyl pentafluoropropionate (Pierce Chemical Co., 250 g, 1.30 mol) was added dropwise with good stirring to a slurry of xylene (500 ml) and sodium methoxide (78 g, 1.45 mol) in a 2-l. flask fitted with a Dry Ice condenser. Trifluoroacetone (Pierce Chemical Co., 141 g, 1.25 mol) was added to the vigorously stirred solution; the temperature was maintained at 35–40° with an ice bath. The

(6) W. G. Scribner and R. E. Sievers, "Proceedings of the Fifth International Conference on Solvent Extraction Chemistry, Jerusalem, Sept 1968," Y. S. Marcus and A. S. Kertes, Ed., John Wiley & Sons, New York, N. Y., in press.

(7) J. R. Stokely, Ph.D. Dissertation, Clemson University, Clemson, S. C., 1966.

solution was allowed to stand overnight at room temperature. Dilute H_2SO_4 (650 ml, 6 *N*) was added slowly with stirring to the reaction mixture; the temperature was maintained at 20° or below with an ice bath. During the addition of the acid the color changed from amber to bright yellow to white. The mixture appeared to be an emulsion. By adding 5 ml of concentrated H_2SO_4 and shaking, the emulsion was broken and a white solid was observed. The solid was removed by vacuum filtration yielding 166 g of crude material (mp 84–87.5°).

The two phases in the filtrate were separated; the aqueous one was xylene extracted three times (150 ml each). These extracts were combined with the organic layer. The combined extracts were washed first with 200 ml of water and then with 200 ml of saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and distilled on a Todd 42-in. Vigreux column, yielding 73 g of material boiling at 68–125°. Water (25 ml) was added to the distillate and the mixture was allowed to stand overnight. The resulting crystals were filtered and dried: yield, 40 g. The total yield of **3** was 206 g (56%). A small portion of the compound was purified by sublimation at 85°, mp 60–61°.

Anal. Calcd for $C_6H_6O_4F_8$: C, 24.50; H, 2.06; F, 51.68. Found: C, 24.31; H, 1.94; F, 51.49.

A portion (50 g) of **3** was placed in a 500-ml erlenmeyer flask and ~50 g of P_4O_{10} was added with stirring in 10–15-g portions. Gummy semisolids resulted and liquid **1** was released. The remaining **3** was dehydrated. All liquid product was decanted, combined, and twice distilled, yielding 77.5 g (53%) of **1**: bp 85–86° (atm); $n^{25}D$ 1.3260; d^{23}_4 1.538; nmr (downfield from tetramethylsilane, internal) δ 12.9 (s, 1, enol OH), 6.49 (s, 1, CH=C); nmr (fluorine resonance upfield from trifluoroacetic acid, external) δ +48.4 (m, 2, J = 1 Hz, CF_3CF_2), +6.9 (t, 3, J = 1 Hz, CF_3CF_2), +0.9 (s, 3, CCF_3).

Anal. Calcd for $C_6H_2O_2F_8$: C, 27.92; H, 0.78; F, 58.90. Found: C, 27.71; H, 0.78; F, 59.06.

1,1,1,2,2,3,3,7,7,7-Decafluoro-4,6-heptanedione (2).—Sodium methoxide (78 g, 1.45 mol) was suspended in 478 ml of hexane with vigorous stirring. Ethyl heptafluorobutyrate (Pierce Chemical Co., 323 g, 1.33 mol) was added to the flask from a dropping funnel over a 30-min period with vigorous stirring. After an additional 30-min stirring almost all of the sodium methoxide was dissolved. Following the addition of the ester, 172 g, 1.53 mol, of trifluoroacetone was added dropwise over a 1-hr period. The solution was allowed to stand overnight. During addition of the ester and the ketone, a Dry Ice condenser was connected to the flask to prevent the escape of volatile materials.

Two phases were apparent after standing overnight. The mixture was acidified with 500 ml of 6 *N* H_2SO_4 with vigorous swirling in an ice bath. The two phases were separated in a 2-l. separatory funnel. The aqueous phase was washed twice with 100-ml portions of hexane, and the hexane extracts were added to the original hexane phase. The hexane phase was extracted five times with 200-ml portions of aqueous sodium acetate (260 g/l.). The third extraction produced a third phase (on the bottom) of a dark yellow–orange color. The first three aqueous extracts were added with vigorous stirring to a solution of 126 g of $CuSO_4 \cdot 5H_2O$ dissolved in 750 ml of water. A green precipitate formed as the extracts were added to the copper sulfate solution. This precipitate was collected on a Büchner funnel, washed sparingly with ice–water, and air-dried overnight.

The solid (331 g) was powdered and placed in a 2-l. flask and cooled in an ice bath. Cold concentrated H_2SO_4 was added in three 50-ml portions to the copper chelate, resulting in a green liquid with white solids. The liquid was distilled through a glass helices-packed column. The forecut (cloudy) consisted of material(s) boiling up to 100°. After the forecut was taken, the distillation was stopped, and the condenser was rinsed with acetone to remove white solids and was air-dried. The distillation was then continued. The principal cut (214 g) boiled between 100 and 104°.

After storage for 5 days at −25°, white solid material was observed in the product. This was removed by filtration. The filtrate was redistilled yielding 166 g (40%) of **2**: bp 103–104° (atm); $n^{25}D$ 1.3243; d^{23}_4 1.592; nmr (downfield from tetramethylsilane, internal) δ 13.3 (s, 1, enol), 6.50 (s, 1, CH=C); nmr (fluorine resonance upfield from trifluoroacetic acid, external) δ +50.8 (m, 2, $J \cong 1$ Hz, $CF_3CF_2CF_2$), +45.8 (m, 2, J = 9 Hz, $CF_3CF_2CF_2$), +4.6 (t, 3, J = 9 Hz, $CF_3CF_2CF_2$), +0.7 (s, 3, CCF_3).

Anal. Calcd for $C_7H_2O_2F_{10}$: C, 27.29; H, 0.65; F, 61.67. Found: C, 27.07; H, 0.70; F, 61.78.

Registry No.—**1** (keto form), 20825-07-4; **2** (keto form), 20583-66-8; **3**, 23405-28-9.

Carbanions in Dimethyl Sulfoxide. II.[1] Dimerization During the Base-Catalyzed Disproportionation of 1,4-Dihydronaphthalene

LAWSON G. WIDEMAN

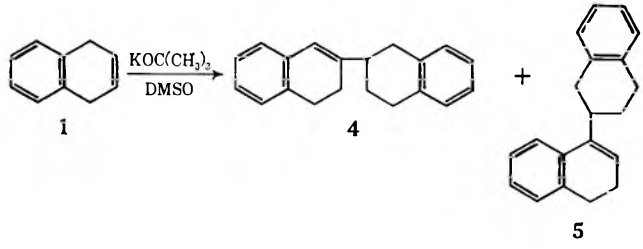
Contribution No. 434 from The Goodyear Tire and Rubber Company, Research Division, Akron, Ohio 44316

Received June 4, 1969

Recently the base-catalyzed disproportionation of cyclohexadiene to give benzene and cyclohexene was reported.[2] Disproportionation was effected with potassium *t*-butoxide in dimethyl sulfoxide (DMSO) and went equally well for the 1,3- or 1,4-dienes, which readily isomerize in base.[2,3]

In our investigation of DMSO and 1,4-dihydronaphthalene, we observed a similar disproportionation that gave naphthalene and tetralin (**3**) in the $KOC(CH_3)_3$–DMSO system at 25°. In contrast, however, the disproportionation accounted for only 37% of the reaction product. The main reaction was a dihydronaphthalene–anion addition to afford a 58% yield of a crystalline dimer **4** (Scheme I) that analyzed for $C_{20}H_{20}$

SCHEME I



1 4 5

with a molecular ion at *m/e* 260.1565 (theory 260.1565). The nmr spectrum showed the presence of eight aromatic protons (singlet at δ 7.00), eleven aliphatic protons in a broad multiplet at δ 1.60–3.00, and one unsplit olefinic proton that is assigned as being conjugated at δ 6.22. Evidence that the two ring systems are joined at the 2,2′ positions is obtained from the dehydrogenation product. When **4** is heated in the presence of palladium on charcoal, 2,2′-binaphthyl is obtained as the only product.

Two other dimers (**5** and **6**), isomeric with **4** ($C_{20}H_{20}$), were also found but in much smaller amounts. Compound **5** (5% yield) has an nmr spectrum showing an unsymmetrical aromatic multiplet at δ 6.75–7.38 within which is a sharp singlet at δ 6.96 (8 H), an olefinic triplet (1 H) centered at δ 5.81 (J = 4.3 Hz), and a

(1) Part I: S. B. Hanna and L. G. Wideman, *Chem. Ind.* (London), 486 (1968).

(2) J. E. Hofmann, P. A. Argabright, and A. Schriesheim, *Tetrahedron Lett.*, No. 17, 1005 (1964).

(3) A. T. Bottini and W. Schear, *J. Org. Chem.*, **30**, 3205 (1965); D. P. Wyman and I. H. Song, *ibid.*, **32**, 4139 (1967).

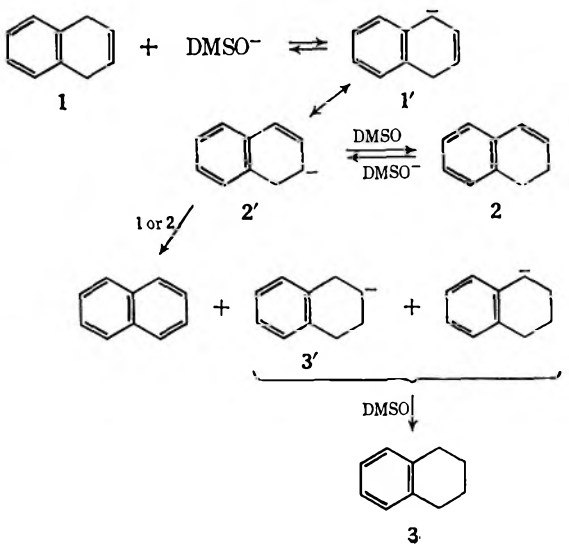
broad poorly resolved multiplet ranging from δ 0.70 to 3.34 (11 H). Ultraviolet analysis shows a system of extended conjugation similar to that of **4**.

The third dimer (**6**) in 1% yield appears to be a 1,2-bisdialin. Its nmr spectrum shows no protons in the olefinic region, and its uv spectrum shows no extended conjugation.

There was little effect on the products when the reaction mixture was heated at 100°. However, no disproportionation or addition products resulted when *t*-butyl alcohol was used as the solvent even upon heating.

The proposed reaction mechanism for disproportionation is shown in Scheme II and based on the formation

SCHEME II



of carbanions **1′** and **2′**. The isomerization of 1,4- to 1,2-dihydronaphthalene in the presence of base is quite facile.[4] Carbanion **2′** may then accept a proton from DMSO[5] and form **2**, or liberate a hydride ion to **1** or **2** to effect the disproportionation. Dimer **4** may form by the attack of **2′** on **1** or **2** followed by protonation and double bond isomerization. The favored reaction mechanism, however, is the attack of **3′** on **2** followed by liberation of a hydride ion, which may also account for **5**. In order to account for the formation of more product from the addition reaction than disproportionation it is also necessary to assume that **3′** is a better nucleophile than proton acceptor. Similar nucleophilic additions of anions have been observed in other systems.[6]

Experimental Section

DMSO was obtained from Eastman Organics and was dried over Linde 13X Molecular Sieves, filtered, and then distilled through more 13X Molecular Sieves at reduced pressure. Potassium *t*-butoxide was sublimed material of reagent grade purchased from Alpha Inorganics.

The melting points were determined on a Fisher-Johns apparatus and are uncorrected. The elemental analyses were performed by the Goodyear Research Analytical Section. The analytical and preparative glpc were carried out on an F & M (Model 500) chromatograph using a 12-ft column packed with 10% SE-30 on Diatoport W at 150 and 300°. Infrared spectra, obtained on a Perkin-Elmer (Model 137) spectrometer with a polystyrene reference, are reported as KBr pellets and melts for the solids and as films for the liquids. The nmr spectra (CCl_4) were obtained on a Varian A-60 spectrometer (TMS reference), and the mass spectra on an AEI MS-9 spectrometer.

1,4-Dihydronaphthalene (**1**).—Naphthalene was reduced with sodium metal in *t*-butyl alcohol and toluene by the method of Hansley.[7] The product is free of the 1,2 isomer and analyzed 99+% pure by glpc after fractional distillation (bp 58° at 2.8 mm, *m/e* 130). The ir spectrum was identical with that of redistilled authentic 1,4-dihydronaphthalene.[8]

1,2,3,3′,4,4′-Hexahydro-2,2′-binaphthyl (**4**).—A flask containing 11.2 g (0.1 mol) of potassium *t*-butoxide (under nitrogen) in 200 ml of DMSO was charged with 13.0 g (0.1 mol) of 1,4-dihydronaphthalene in 100 ml of DMSO which gave an instantaneous orange-red carbanion that turned green within a few minutes. The reaction mixture was periodically shaken during the 24-hr reaction time and held at 25° with a water bath. The reaction mixture was then poured into 300 ml of H_2O and the resulting mixture was extracted three times with ether. The ether portion was removed and back extracted with water to remove DMSO. After drying ($CaCl_2$) and removal of the solvent (steam bath), the thick oil was chromatographed (1 × 24 in. column) over neutral alumina (dry-column technique[9]) obtained from Matheson Coleman and Bell, activity I. Naphthalene (*m/e* 128, mp 79–80°) and tetralin (*m/e* 132, bp 206–207°) were eluted first with petroleum ether (bp 36–47°) and were further purified by preparative glpc. The ir spectra and glpc retention times were identical with those of reagent samples. Continued elution with petroleum ether afforded *ca.* 8.0 g of a white crystalline solid. The solid was recrystallized several times from methanol to give a constant melting compound (**4**) at 77–78° (99+% pure by glpc): $\lambda_{max}^{cyclohexane}$ 218 mμ (ε 33,480), 226 (22,925), 263 (15,715), and 273 (15,030); ir (melt) ν_{max} 3070, 2990, 2910, 2860, 1620, 1490, 1450, 1430, and 785 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}$: C, 92.31; H, 7.69. Found: C, 92.09; H, 7.83.

2,2′-Binaphthyl.—Compound **4** (1.0 g) and 5% Pd–C (0.1 g) were heated to 200° in a 50-ml 1-neck round-bottom flask. The pressure inside the flask was 0.40 mm. White crystals begin to condense at the top of the flask and heating was continued until no more solid formed. After cooling, the flask was washed with boiling benzene. The hot benzene was filtered and the clear solution taken to dryness. Recrystallization from hexane gave white crystals (0.9 g): mp 185–187° (authentic material, mp 185–187°[8]); mmp 185–187°; ir (KBr): ν_{max} 3090, 1600, 1390, 1370, 1275, 884, 855, 812, and 736 cm^{-1}; nmr (50° in CCl_4) broad singlet at δ 7.43 (2 H), multiplet at 7.18 (8 H), and multiplet at 6.76 (4 H).

Anal. Calcd for $C_{20}H_{14}$: C, 94.48; H, 5.51. Found: C, 94.15; H, 5.85.

1,2,3,3′,4,4′-Hexahydro-1′,2-binaphthyl (**5**) **and Compound** (**6**).—The methanolic mother liquor, from which compound **4** was recrystallized, was shown by glpc analysis to contain two other compounds. When the solution was concentrated and acetone added (50 ml), **6** precipitated and was recrystallized from acetone: mp 179–180°; ir (KBr) ν_{max} 3090, 3050, 2970, 2910, 1480, 1445, 1420, 753, and 739 cm^{-1}; nmr (CCl_4) singlet at δ 7.00 (8 H), multiplet from 3.50 to 2.59 (6 H), and multiplet from 2.30 to 1.12 (6 H); *m/e* 260.1569; $\lambda_{max}^{cyclohexane}$ 260 mμ (ε 1010), 266 (1565), and 273 (1790).

Concentration of the remaining solution and separation by preparative glpc gave a thick liquid: bp 175–180° at 1–2 mm; $\lambda_{max}^{cyclohexane}$ 214 mμ (ε 28,800), 219 (26,780), 226 (15,750), and 262 (9315); ir (film) ν_{max} 3090, 3050, 2940, 2900, 2860, 1630, 1494, 1445, 1425, 808, 770, and 740 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}$: C, 92.31; H, 7.69. Found: C, 92.03; H, 7.81.

Registry No.—**1**, 612-17-9; **4**, 23405-30-3; **5**, 23439-78-3.

Acknowledgment.—The author is grateful to W. John Layton for furnishing and discussing the nmr spectra.

(4) R. C. Fuson, "Reactions of Organic Compounds," John Wiley & Sons, Inc., New York, 1966, p 469; F. Straus and L. Lemmel, *Ber.*, **54**, 25 (1921).
(5) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).
(6) P. R. Stapp and R. F. Kleinschmidt, *J. Org. Chem.*, **30**, 3006 (1965).
(7) V. L. Hansley, U. S. Patent 2,473,997 (1949).
(8) Obtained from K & K Laboratories.
(9) B. Loev and M. M. Goodman, *Chem. Ind.* (London), 2026 (1967).

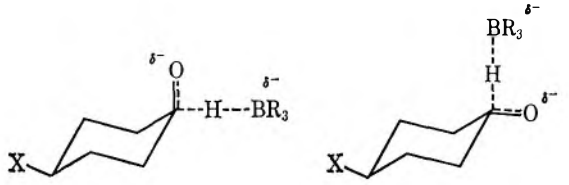
Sodium Borohydride Reduction of Substituted *trans*-Decalones

RICHARD S. MONSON,[1] DENNIS PRZYBYCIEN, AND ADINA BARAZE

Department of Chemistry, California State College, Hayward, California 94542

Received June 16, 1969

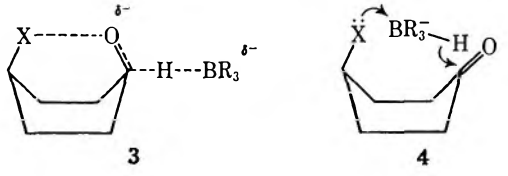
There has been considerable interest for some time in evaluating the effects of remote polar substituents on the course of ionic reactions. One such group of studies has been directed to the question of the stereochemical influence that a remote polar substituent can exert on the outcome of the sodium borohydride reduction of cyclohexanones.[2-5] In general, two visualizations of the mechanism by which such effects may operate have been proposed. The first describes the effect as purely electrostatic. The transition state is pictured in **1** and **2**, leading, respectively, to *cis* and *trans* product. When X is an electron-withdrawing group, the cisoid form (**1**) is electrostatically more



1 **2**

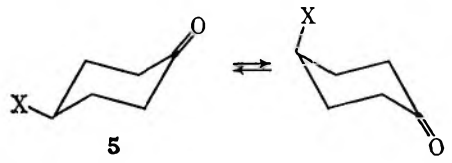
stable than the transoid form (**2**) because the negative oxygen is closer to the electron-deficient carbon at C_4 in form **1** than it is in form **2**.[6]

The second mechanistic proposal requires the direct participation of the remote substituent with either the keto group[3] (as in **3**) or with the borohydride moiety[4] (as in **4**). As is apparent from the representation, this second mechanism requires that the cyclohexane ring be capable of passing through a boat form.



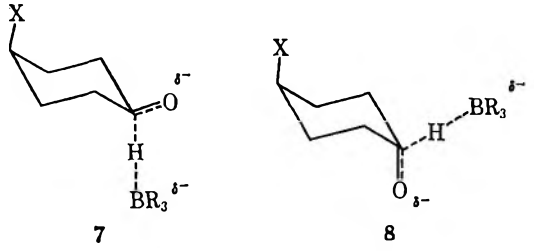
3 **4**

We view the first mechanistic proposal as an oversimplification for the following reasons. As has been amply demonstrated,[7,8] cyclohexane compounds with two polar substituents may show conformational abnormalities that are wholly unpredictable on steric grounds alone. For example,[3] 4-hydroxycyclohexanone-2,2,6,6-d_4 has been found to exist in the conformation analogous to **6** (*i.e.*, with an axial substituent) to the extent of 39% in D_2O, 53% in pyridine,



5 **6**

and 54% in chloroform. There is no reason why the factors influencing the conformational equilibrium in the case of the 4-hydroxy compound cannot be reasonably extended to any relatively unbulky polar substituent including chloro or carboxy, since it has been shown that intramolecular hydrogen bonding (which might be mentioned to explain the hydroxy case) is relatively minor in 4-hydroxycyclohexanone.[9] If the foregoing argument is valid, then one is not justified in considering electrostatic influences in only the two forms **1** and **2**, but one must also consider the likely existence of two additional forms **7** and **8**. If it is further noted that forms **1** and **7** both lead to *cis* product while forms **2** and **8** both lead to *trans* product,



7 **8**

it should be apparent that drawing conclusions as to the nature of electrostatic interactions in the transition state based only on analyses of the products of the reaction may be seriously misleading.

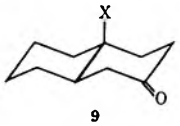
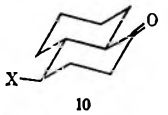
Our approach to the problem of evaluating the directing effects of remote polar substituents has been to employ as model substrates *trans*-1- and *trans*-2-decalones appropriately substituted. Since, of the possible conformations in the *trans*-decalin system, there is only a single chair–chair conformation, the question of conformational equilibrium of the type **5** $\rightleftarrows$ **6** does not enter. Our data are summarized in Table I.

The differences in the two sets of substrates are obvious: the compounds of type **9** are *trans*-2-decalones while those of type **10** are *trans*-1-decalones; the substituents in the case of **9** are axial while those in the case of **10** are equatorial. Despite these differences, the presence of a polar substituent in the (relatively speaking) 4 position was in all cases accompanied by an increase in the proportion of product oriented *cis* to the substituent, regardless of whether the resultant hydroxyl is itself oriented axially or equatorially.

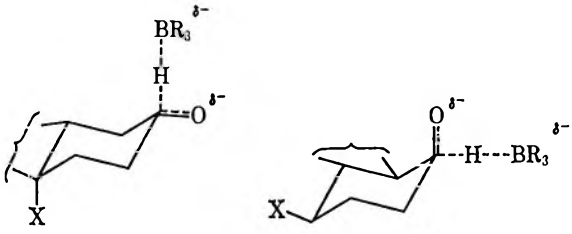
There are two likely mechanistic pictures that will account for the increased proportion of *cis*-oriented products in the presence of the polar substituent. The first suggests that the most favored transition states in the cases of type **9** and type **10** systems should

(1) To whom inquiries should be addressed.
(2) M. G. Combe and H. B. Henbest, *Tetrahedron Lett.*, 404 (1961).
(3) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, **84**, 2833 (1962).
(4) H. O. House, *et al.*, *J. Org. Chem.*, **27**, 4141 (1962).
(5) D. M. S. Wheeler and M. M. Wheeler, *ibid.*, **27**, 3796 (1962).
(6) Combe and Henbest (*cf.* ref 2) calculate the distances for **1** and **2** to be 3.40 and 4.12 Å, respectively.
(7) (a) K. Kozina and T. Yoshino, *J. Amer. Chem. Soc.*, **75** 166 (1953); (b) P. Groth and O. Hassel, *Acta Chem. Scand.*, **19**, 1709 (1965).
(8) W. F. Trager, B. J. Nist, and A. C. Huitric, *Tetrahedron Lett.*, 2931 (1965).
(9) R. D. Stolow, *J. Amer. Chem. Soc.*, **84**, 686 (1962).

TABLE I
RATIOS OF EQUATORIAL/AXIAL ALCOHOLS ARISING FROM THE SODIUM BOROHYDRIDE REDUCTION (METHANOL) OF *trans*-DECALONES

	Equatorial/axial hydroxyl orientation
 9	
a, X = H	76:24
b, X = COOH	92:8
c, X = $COOCH_3$	100:0
 10	
a, X = H	68:32
b, X = COOH	36:64
c, X = $COOCH_3$	56:44

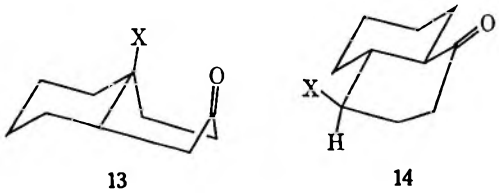
be represented as in **11** and **12**, respectively. In these representations, the negative oxygen achieves its



11 **12**

closest proximity to the *substituent* (which in the present cases has a markedly electron-deficient center adjacent to the ring) rather than to the electron-deficient carbon at C_4.

The second mechanistic picture that accounts for *cis*-oriented product requires intramolecular participation and is essentially that shown in **3**. Its relevance for the present case depends on the fact that the decalones **9** and **10** are capable of existing in half-boat conformations as in **13** and **14**, respectively. Compound



13 **14**

9 (in the form **13**) clearly satisfies the geometrical requirements necessary for intramolecular participation. Our examination of models suggests, however, that compound **10** (in the form **14**) cannot achieve suitable geometry for intramolecular participation.

In order to resolve the "electrostatic effect" *vs.* "participation effect" uncertainty, we are presently preparing for reduction additional decalones in which, it is hoped, the polar substituent is not capable of participation.

Experimental Section[10]

***trans*-1-Decalone (10a).**—Pure *trans-trans*-1-decalol was prepared according to the published procedure.[11] The product was recrystallized from pentane, mp 59–60° (lit.[11] mp 59.5°). The alcohol (5.0 g, 0.032 mol) was dissolved in acetone (10 ml) and treated with Jones reagent (6.8 ml, prepared from 27 g of chromium trioxide, 23 ml of concentrated sulfuric acid, and 100 ml of water). The oxidation proceeded at room temperature for 0.5 hr. The reaction mixture was then extracted four times with ether; the ether extracts were washed with water and then dried over anhydrous sodium sulfate. Distillation afforded *trans*-1-decalone, bp 80–85° (3 mm) [lit.[11] bp 80–85° (3 mm)], yield 3.6 g (72%).

***trans-anti*-4-Carboxy-1-decalone (10b).**—The compound was prepared according to the procedure of Nazarov, Kucherov, and Segal,[12] mp 154–155° (lit.[12] mp 156°).

***trans-anti*-4-Carbomethoxy-1-decalone (10c).**—*trans-anti*-4-Carboxy-1-decalone (**10b**) was dissolved in absolute methanol containing 2% concentrated sulfuric acid. The solution was refluxed for 3 hr. Methanol was distilled away and the residue was dissolved in ether. The ethereal solution was washed with water, bicarbonate solution, and water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the required ester, which was recrystallized from petroleum ether (bp 60–90°). It had mp 66–67° (lit.[12] mp 68°).

***trans-cis*-2-Decalol.**—$\Delta^{1,9}$-2-Octalone[13] was reduced according to the procedure of Van Tamelen and Proost[14] by lithium in anhydrous ammonia. Further reduction of this product by sodium borohydride in methanol followed by recrystallization from hexane gave the desired alcohol, mp 74° (lit.[11] mp 72.1–74.8°).

***trans*-2-Decalone (9a).**—*trans-cis*-2-Decalol (5.0 g, 0.032 mol) was oxidized with Jones reagent as before. Distillation of the product afforded the alcohol-free ketone, bp 78–80° (3.2 mm) [lit.[14] bp 106° (12 mm)], yield 3.9 g (78%).

***trans-cis*-2-Hydroxy-10-decalincarboxylic Acid.**—*trans-cis*-2-Hydroxy-10-decalincarboxylic acid lactone[15] (42 g, 0.23 mol) was mixed with aqueous sodium hydroxide (40 g of NaOH in 200 ml of water) and the mixture was refluxed for several hours. The homogeneous solution was cooled, acidified (concentrated HCl), and then continuously extracted with ether. Evaporation of the ether and recrystallization from hexane–ethanol gave the desired carboxy alcohol, mp 162–163° (lit.[16] mp 160–161°), yield 40 g (86%).

***trans*-10-Carboxy-2-decalone (9b).**—*trans-cis*-2-Hydroxy-10-decalincarboxylic acid (3.5 g, 0.018 mol) was oxidized with Jones reagent as before. Recrystallization of the product from ether–petroleum ether afforded the desired carboxy ketone, mp 90–91° (lit.[16] mp 91.5–93°), yield 1.9 g (54%).

Methyl *trans-cis*-2-Hydroxy-10-decalincarboxylate.—*trans-cis*-2-Hydroxy-10-decalincarboxylic acid (1.0 g, 0.005 mol) was methylated with ethereal diazomethane. The ether was allowed to evaporate and the product was recrystallized from petroleum ether (bp 60–90°), mp 82–84° (lit.[16] mp 82–83°), yield 0.96 g (89%).

***trans*-10-Carbomethoxy-2-decalone (9c).**—Methyl *trans-cis*-2-hydroxy-10-decalincarboxylate (0.67 g, 0.0031 mol) was oxidized with Jones reagent as before. The product, which could not be crystallized, was shown by its infrared spectrum to be free of alcohol and was therefore used in the subsequent reduction without further purification. The authenticity of the product was verified by comparison with the published[16] infrared spectrum.

Borohydride Reduction of *trans*-Decalones (9a and 10a).—The ketone (0.178 mol) was added to a stirred solution of sodium borohydride (0.178 mol) in methanol at room temperature. The reaction was continued for 24 hr. Sodium hydroxide solution (150 ml, 2 *N*) was added and the solution was refluxed for 2 hr. The resulting solution was continuously extracted with ether overnight. The ether extract was dried (anhydrous so-

(10) All melting points and boiling points are uncorrected. Melting points were determined on a Fisher-John apparatus. The infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer.

(11) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(12) I. N. Nazarov, V. F. Kucherov, and G. M. Segal, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1215 (1956).

(13) G. Stork, *et al.*, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(14) E. E. Van Tamelen and W. C. Proost, Jr., *ibid.*, **76**, 3632 (1954).

(15) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *ibid.*, **77**, 48 (1955).

(16) A. S. Dreiding and A. J. Tomasewski, *ibid.*, **77**, 411 (1955).

dium sulfate) and the ether was removed. The residual mixed alcohols were directly subjected to glpc analysis or were acetylated with a 30% molar excess of acetyl chloride in benzene solution, and the undistilled acetates were subjected to glpc analysis.

Borohydride Reduction of Substituted Decalones (9b, 9c, 10b, and 10c).—The ketone (0.012 mol) was added to a stirred solution of sodium borohydride (0.012 mol) in methanol at 0°. The reaction was continued for 4 hr, whereupon dilute hydrichloric acid was added to bring the solution to pH 4. Methanol was evaporated and the residue was continuously extracted with ether. After drying and evaporation of the ether, the mixed alcohols were methylated with ethereal diazomethane if appropriate (*i.e.*, in the case of **9b** and **10b**). The mixed ester–alcohols were acetylated as before with acetyl chloride and the analysis was carried out on the undistilled acetates.

Analysis.—Analyses were performed on an Aerograph Model 600 HyFi with flame ionization detector. The columns were either 15 ft by $^1/_8$ in. stainless steel packed with 10% Carbowax 20M on acid-washed Chromosorb, 80–100 mesh, or 20 ft by $^1/_8$ in. stainless steel packed with FFAP on acid-washed Chromosorb, 80–100 mesh. The oven was operated at constant temperatures varying from 180 to 230° ± 2°.

The composition of the product mixtures was compared before and after acetylation only for *trans*-1-decalone (**10a**) and *trans*-2-decalone (**9a**). In these cases, agreement was ±2%—within experimental error—and thereafter only the acetates were determined. The calibration of the column was carried out using authentic samples of *trans-trans*-1-decalyl acetate, *trans-cis*-2-decalyl acetate, and the acetate of methyl *trans-cis*-2-hydroxy-10-decalincarboxylate. In cases where authentic samples were not available, the identifications of equatorial hydroxyl (as acetate) and axial hydroxyl (as acetate) was made by relative retention times.

No attempt was made to isolate the products of the reductions. Reductions of all ketones were essentially complete as shown by the absence of other than trace amounts of unreduced ketone in the infrared spectra. The percentages reported in all cases are relative percentages of reduced materials.

Registry No.—Sodium borohydride, 16940-66-2; **9a**, 23646-48-2; **9b**, 23595-68-8; **9c**, 23595-69-9; **10a**, 21370-71-8; **10b**, 23595-70-2; **10c**, 23595-71-3.

Acknowledgment.—The authors wish to express their gratitude to the Research Foundation of California State College, Hayward, for financial assistance.

A Simple and Quantitative Method of Preparation of *cis*-Stilbene and Its Deuterated Analog, Ph—CD=CD—Ph

G. LEVIN, J. JAGUR-GRODZINSKI, AND M. SZWARC

Department of Chemistry, State University College of Forestry at Syracuse University, Syracuse, New York 13210

Received June 30, 1969

In the course of studies of the chemistry of radical ions and dianions of diphenylacetylene, we discovered a simple and quantitative method for synthesis of *cis*-stilbene and of its deuterated analog, Ph—CD=CD—Ph. To our knowledge, no method which yields quantitatively pure *cis* isomer, without admixture of the *trans*-stilbene, has been yet described in the literature.[1]

Ten milliliters of 10^{-2} *M* solution of diphenylacetylene in tetrahydrofuran is treated with metallic lithium at −78°. The chunks of lithium metal used for the reduction are previously washed with a cold (−78°) solution of diphenylacetylene which is subsequently decanted in a high-vacuum system. The reaction is over in *ca.* 1–2 hr and yields a slurry which is removed from the excess of metal by pouring it through a narrow tube into another container. Thereafter a solution of methanol, or deuterated methanol, is added and the protonated products are allowed to warm to room temperature. It should be stressed that all the operations, including the protonation, have to be performed at −78°, preferentially on a high-vacuum line. Whenever the reacting mixture is allowed to warm, even to −60°, other products, including *trans*-stilbene, are formed.

The alkali is extracted with water and the organic layer is extracted with carbon tetrachloride. The alkali-free layer is then dried with anhydrous $MgSO_4$, the solvent is evaporated, and the residual *cis*-stilbene (or deuterated *cis*-stilbene) is then isolated. The yield is quantitative. No difficulties are expected in scaling up this preparation.

The product was identified by its uv spectrum, a single sharp peak at 280 mμ characteristic of the *cis* isomer (the *trans* isomer gives a double peak at 298 and 310 mμ and a shoulder at 322 mμ). Its identity was also proved by vpc using a silicone column which separates the isomers (checked with original samples). Finally, the nmr spectrum gives two sharp peaks, one at 393.5 cps, the other at 428 cps, intensities being in the expected ratio 1:5. The deuterated product gives only one peak at 428 cps with no other peaks visible in the spectrum. The nmr spectrum of the *trans* isomer is much more complex, with seven peaks in the range 430–447 cps and the olefinic peak at 421 cps.

It is interesting to point out that the reduction with sodium under similar conditions gives several products, including the *trans* isomer, but none of the *cis* isomer. Apparently, the alkali salts of the dianions of diphenylacetylene have well-defined geometry, namely, the lithium salts being *cis* while the sodium salt appears to be of *trans* form.

The addition of LiCl to the cold (−80°) solution of the sodium salt in THF precipitates the red lithium salt which, on protonation, gives pure *cis*-stilbene.

The organolithium salts often are dimeric,[2] and we tentatively suggest that this tendency of forming quadrupoles may be responsible for the *cis* structure of the dilithium salt. Thus the two lithium cations could be located one above and the other below the plane of the hydrocarbon framework, each interacting with *both* lone electron pairs of the carbanions and with one half of the π-electron cloud. Of course, this geometry requires a *cis* form of the salt.

Registry No.—*cis*-Stilbene, 645-49-8; deuterated *cis*-stilbene, 3947-91-9.

Acknowledgment.—We gratefully acknowledge the support of this investigation by the National Science Foundation and by the Petroleum Research Fund, administered by the American Chemical Society.

(1) (a) O. H. Wheeler and H. N. Battle de Pabon, *J. Org. Chem.*, **30**, 1473 (1965). (b) K. N. Campbell and E. E. Young, *J. Amer. Chem. Soc.*, **65**, 965 (1943). Electrolytic reduction of tolane on spongy Ni cathode yields 80% *cis* isomer. (c) It is claimed that hydrogenation of acetylene on 5% palladium on $BaSO_4$ gives excellent yields of *cis* olefins: R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, p 69. However, this reaction was not checked for the tolane reduction.

(2) M. Szwarc, "Carbanions, Living Polymers and Electron-Transfer Processes," Interscience Publishers, New York. N. Y., 1968, Chapter VIII.

The Addition of Bromine Monofluoride to Acetylenes

R. E. A. DEAR

Allied Chemical Corporation, Morristown, New Jersey 07960

Received October 9, 1969

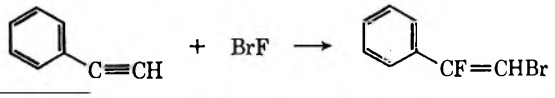
The addition of the elements of bromine monofluoride to a variety of olefinic substrates has been achieved in several different ways. Schrader[1] claimed the production of 1-bromo-2-fluoroethane by the reaction of a mixture of bromine and fluorine with ethylene. Bowers[2-4] showed that it was more convenient to use a mixture of anhydrous hydrogen fluoride and N-bromoacetamide in an ether solvent. In this manner additions of BrF to cyclohexene and unsaturated steroidal molecules were attained in good yields. Subsequently, Pattison and coworkers extended the reaction to the production of vicinal fluorobromides from aliphatic alkenes.[5]

To date, no reactions have been reported between acetylenes and BrF. Although there is a structural relationship between carbon–carbon double bonds and triple bonds, the reactivities of the two systems are quite different. Thus a triple bond is much less reactive than a comparably situated double bond toward electrophilic reagents such as halogens. This difference is probably due to respective electron distributions within the linkages.[6] In view of these considerations it was not certain that BrF would add to acetylenic compounds at all. Therefore a brief study was undertaken to establish this point.

It was found, using the anhydrous hydrogen fluoride–N-bromoacetamide (HF–NBA) system, that BrF could be added to several simple acetylenic molecules, giving bromofluoro olefins. In no case was the addition of a second molecule of BrF observed. This undoubtedly is due to the deactivation of the double bond caused by the α halogens. There may also be a slight steric effect, since it is known that under the appropriate conditions two molecules of chlorine can be added to triple bonds, whereas only one molecule of bromine or iodine will react under similar conditions.[6a]

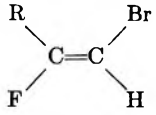
The HF–NBA procedure worked moderately well for 1-hexyne, 3-hexyne, 1,4-dichloro-2-butyne, and phenylacetylene, confirming the lower reactivity of triple bonds over double bonds. In the case of terminal alkynes the addition followed the Markovnikov rule;

$$CH_3(CH_2)_3C{\equiv}CH + BrF \longrightarrow CH_3(CH_2)_3CF{=}CHBr$$

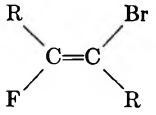


the magnitude of the H–F coupling constants (Table II) clearly indicate that hydrogen and fluorine cannot be attached to the same carbon atom.[7] When the triple bond was deactivated by electron-withdrawing groups, no reaction occurred. For example, $CH_3OC(CF_3)_2C{\equiv}CH$ and $CH_3OC(CF_3)_2C{\equiv}CCl$[8] were recovered unchanged and the parent alcohols[9] added bromine only slowly at 25°, in contrast to the vigorous reaction normally observed between acetylenes and bromine. Dimethylacetylene dicarboxylate and diphenylacetylene gave intractable products.

From a study of the products isolated, the principal mode of addition appeared to be *trans*, *i.e.*, F^- entering from the least hindered side. Use of the terminal acetylenes resulted in initial orientations of the type



1-Hexyne produced 95% *trans* and 5% *cis* isomer. The composition of the mixture was observed to change slowly over a period of months, from 95:5 to 40:60 (*trans* to *cis* ratios), indicating the former to be a kinetically produced mixture and the latter to be a thermodynamically produced composition. These changes were reflected in the change in intensities of the proton nmr signals. The product ratios were determined by measurement of the areas of the olefinic proton peaks. The styrene example was relatively unstable and no examination could be made for composition changes. 1,4-Dichloro-2-butyne and 3-hexyne both gave isomers of the type



as the principal product. In the case of 3-hexyne 22% of the alternate structure was formed. No isomerization was observed in these examples over a 15-month period.

The sensitivity of the reaction to the structure of the acetylenes indicates that the process is initiated by attack of a weakly electrophilic species at the triple bond. In view of the stereospecificity observed in the products it is probable that the intermediate species has more of the character of an oriented π complex, and should be distinguished from a discrete carbonium ion, where less selectivity would be anticipated. The reaction is completed by fluoride addition from HF. When the presence of electron-withdrawing groups prevents the first step from occurring, the reaction cannot take place.

One anomalous reaction was noted in this series of experiments. Methyl propiolate, $HC{\equiv}CCOOCH_3$, did not participate in the addition reaction. Instead, $BrC{\equiv}CCOOCH_3$ was formed in 36% yield, indicating that initial addition of Br^+ had taken place followed by collapse of the intermediate to the observed product. A less likely explanation is that BrF addition was followed by spontaneous dehydrofluorination.

Recently a new method, involving the use of a silver

(1) G. Schrader, British Intelligence Objectives Subcommittee, Report No. 1808.

(2) A. Bowers, *J. Amer. Chem. Soc.*, **81**, 4107 (1959).

(3) A. Bowers, L. C. Ibanez, E. Denot, and R. Becerra, *ibid.*, **82**, 4001 (1960).

(4) A. Bowers, E. Denot, and R. Becerra, *ibid.*, **82**, 4007 (1960).

(5) F. L. M. Pattison, D. A. V. Peters, and F. H. Dean, *Can. J. Chem.*, **43**, 1689 (1965).

(6) (a) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworth and Co. Ltd., London, 1955, pp 21, 35; (b) T. F. Rutledge, "Acetylenic Compounds," Reinhold Publishing Corp., New York, N. Y., 1968, p 2.

(7) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1966, pp 910, 911.

(8) R. E. A. Dear and E. E. Gilbert, U. S. Patent 3,450,773 (1969).

(9) R. E. A. Dear and E. E. Gilbert, *J. Org. Chem.*, **33** 819 (1968).

TABLE I
PROPERTIES OF NEW COMPOUNDS

Compd	Registry no.	Bp (mm), °C	$n^{25}D$	Calcd, %		Found, %	
		A. BrF Additions					
$CH_3(CH_2)_3CF{=}CHBr$	*cis*-, 23680-35-5; *trans*-, 23680-34-4	34 (12)	1.4361	C	39.80	C	39.67
				H	5.57	H	5.74
				Br	44.13	Br	43.96
$ClCH_2CF{=}CBrCH_2Cl$	*trans*-, 23680-36-6	49 (1.5)	1.5123	H	1.82	H	2.16
				Br	36.19	Br	35.86
				Cl	31.96	Cl	31.82
$CH_3CH_2CF{=}CBrCH_2CH_3$	*cis*-, 23680-38-8; *trans*-, 23680-37-7	37 (30)	1.4372	C	39.79	C	39.92
				H	5.57	H	5.60
$C_6H_5CF{=}CHBr$	*trans*-, 23680-39-9	48–50 (0.1)	1.5699	C	47.79	C	48.06
				H	3.01	H	3.13
		B. Br_2 Additions					
$HOC(CF_3)_2CBr{=}CHBr$	23754-52-1	56.6–57 (12)	1.4328	C	17.04	C	17.32
				H	0.57	H	0.71
				Br	45.42	Br	45.26
$HOC(CF_3)_2CBr{=}CClBr$	23668-74-8	90–92 (30)	1.4514	C	15.45	C	15.64
				H	0.26	H	0.33
				Br	41.37	Br	41.08

fluoride–halogen system, was reported.[10] Since it is operative at ambient temperatures, gives high yields, and does not employ corrosive materials, such as hydrogen fluoride, it would appear to be the method of choice for many BrF additions. However, in experiments using AgF–Br_2 in acetonitrile, only a trace of the BrF addition product of 1-hexyne was obtained. The major product was $CH_3(CH_2)_3C{\equiv}CBr$, probably formed *via* the silver salt and its subsequent reaction with bromine. Under similar conditions 3-hexyne gave only 3,4-dibromo-3-hexene.

In many cases the structure of the products was deduced from spectral data. The conformation assigned to the terminal hexenes, based on the position and magnitude of their nmr signals, is in full accord with analogies described in the literature.[7] In the styrene derivative the order of magnitude of the coupling constant J_{HCCF} (15.8 Hz) suggests a *cis* relationship between F and H. In the absence of the other isomer this conclusion can be only tentative, although formation of the molecule by approach of fluoride from the least hindered side also leads to the proposed structure in preference to the alternate. The structure of the isomers formed from 3-hexyne may be designated with some confidence, since it is known[7] that a fluorine located *trans* to another halogen and *cis* to an alkyl group generally has a larger chemical shift than one positioned conversely. The structure proposed for the 1,4-dichlorobutene is that anticipated from the addition of fluoride to the least hindered side. Since the *cis* isomer was not detected in this product, no definite conclusions can be drawn from the nmr assignments.

Experimental Section

Physical constants and analytical data for the new compounds are presented in Table I. Significant infrared bands and nmr data are reported in Table II. The nonfluorinated acetylenic chemicals were purchased from Farchan Research Laboratories. Nmr spectra were recorded on Varian A-60 and DP-56 instruments. The ^{19}F spectra were calibrated by generating side bands of Cl_3CF. All elemental analyses were made by Schwarzkopf Microanalytical Laboratory.

(10) L. D. Hall, D. L. Jones, and J. F. Manville, *Chem. Ind.* (London), 1787 (1967).

TABLE II
SPECTROSCOPIC PROPERTIES OF THE PRODUCTS[a]

A. $CH_3(CH_2)_2CF{=}CHBr$ [1667 cm^{-1} (s, C=C)][b]

	trans (95%)	*cis* (5%)
δ_{CF}	100	96.3
δ_{CH}	5.8	5.23
δ_{CH_2CF}	2.42	*c*
$\delta_{CH_2CH_2}$	1.4–1.6	
δ_{CH_3}	0.9	
$J_{FC=CH}$	13	27.5
J_{FCCH}	21	16.5
$J_{HC=CCH}$	1.0	
J_{HCCH}	7.0	

B. $ClCH_2CF{=}CBrCH_2Cl$ [1669 cm^{-1} (s, C=C)]

	trans (100%)
δ_{CF}	104
δ_{CH_2CF}	4.33
δ_{CH_2CBr}	4.39
J_{FCCH}	21
J_{FCCCH}	3.5

C. $CH_3CH_2CF{=}CBrCH_2CH_3$ [1689 cm^{-1} (s, C=C)]

	trans (78%)	*cis* (22%)
δ_{CF}	110	96.3
δ_{CF_2}	2.45	2.45
δ_{CH_3}	1.05	1.07
J_{FCCH}	23	21
J_{HCCH}	7.6	7.6

D. $C_6H_5CF{=}CHBr$ [1689–1587 cm^{-1} (s, C=C)[d]]

	trans (100%)
δ_{CH}	6.11
δ_{CH} (phenyl)	7.3, 7.8
J_{HCCF}	15.8

E. $HOC(CF_3)_2CBr{=}CHBr$ [1593 cm^{-1} (s, C=C)][e]

F. $HOC(CF_3)_2CBr{=}CClBr$ [1550 cm^{-1} (s, C=C)][e]

G. $BrC{\equiv}CCOOCH_3$ [2252 cm^{-1} (s, C=C)]

[a] Chemical shifts expressed as parts per million (δ) from Cl_3CF and $(CH_3)_4Si$ as internal references; coupling constants expressed in hertz. [b] C—F stretching bands also present at 1144 and 1079 cm^{-1}. The expected range for $RCF{=}CR_1R_2$ is 1700–1630 cm^{-1}: J. K. Brown and K. J. Morgan, *Advan. Fluorine Chem.*, **4**, 253 (1965). [c] Peaks for this isomer masked. [d] Includes aromatic C=C bands. [e] Analogous chlorinated materials absorb in the 1570–1600-cm^{-1} range (Brown and Morgan); so the frequencies observed are to be expected when the heavier bromine atoms are substituted for chlorine.

Typical experimental procedures are described below. No differences in product yield or composition were observed when diethyl ether was replaced by tetrahydrofuran. Similarly, it did not matter if the reagents were added alternately in small portions or consecutively in one portion each. An attempt to improve the yield by making fluoride ion more readily available as pyridine hydrofluoride was unsuccessful.

1-Bromo-2-fluoro-1-hexene.—Anhydrous hydrofluoric acid (50 g, 2.5 mol) was condensed into a 500-ml polyethylene bottle and the bottle was cooled to −78°. To the cooled acid was added ether (120 ml), N-bromoacetamide (34.5 g, 0.25 mol), and 1-hexyne (20.5 g, 0.25 mol). The pale yelow slurry so produced was stirred at −78° for 3 hr; then, after overnight storage at −20°, it was poured slowly into a mixture of sodium carbonate (250 g), water (200 ml), ice (200 g), and ether (60 ml). The ether layer was separated and the residue was extracted with ether (three 50-ml portions). The combined ether extracts were washed with nitrous acid solution to destroy any residual acetamide, washed with sodium carbonate solution and then with water, dried, and distilled. There was obtained 10.8 g (47.9%) of 1-bromo-2-fluoro-1-hexene, bp 34° (12 mm), n^{26}D 1.4361. The product was characterized by elemental analysis (Table I), a C=C stretching frequency in the infrared spectrum (Table II), and by nmr spectroscopy. Infrared spectroscopy also revealed the presence of C—F stretching frequencies at 1144 and 1079 cm^{-1}. The original 1-hexyne does not have any bands in this region.

3-Bromo-4-fluoro-3-hexene.—Anhydrous hydrogen fluoride (80 g, 4.0 mol) was condensed into a 500-ml polyethylene bottle cooled to −78°. Cold tetrahydrofuran (200 ml) was added together with pyridine (2 ml). N-bromoacetamide (70 g, 0.508 mol) and 3-hexyne (32.8 g, 0.4 mol) were added alternately in small portions over a 20–30-min period. The mixture was stirred at −78° for 2 hr, then at 0° for 3 hr. The pale yellow solution was poured onto a mixture of sodium carbonate (300 g, 2.8 mol), water (300 ml), ice (300 g), and methylene chloride (100 ml). The aqueous layer was extracted with a further 100 ml of methylene chloride. The organic extracts were washed with water, nitrous acid, and finally with water, After drying and distillation, 20.2 g (27.9%) of 3-bromo-4-fluoro-3-hexene was obtained. The product was characterized as described above.

Silver Fluoride–Bromine Procedure.—Silver fluoride (14 g, 0.11 mol) was finely ground and added to dry acetonitrile (25 ml) in a 100-ml, three-necked flask. 1-Hexyne (8.29 g, 0.1 mol) was added in one portion. Some heat was evolved. Bromine (16 g, 0.1 mol) in acetonitrile (20 ml) was added very slowly, with stirring, through a dropping funnel. Complete addition required 1.5 hr. The solution was pale yellow and contained a yellow-gray sludge. The solid was removed by filtration and the acetonitrile was removed from the product by water washing. The residue was dried and distilled. Unreacted 1-hexyne (2.5 g) was recovered together with a fraction boiling at 52–53° (29 mm). Nmr examination showed that there was a trace of the BrF addition product, but that the major product was 1-bromo-1-hexyne. A similar reaction with 3-hexyne gave only 3,4-dibromo-3-hexene.

Registry No.—BrC≡CCOOCH$_3$, 23680-40-2; bromine monofluoride, 13863-59-7.

Acknowledgement.—It is a pleasure to acknowledge the helpful discussion of these results with Dr. E. E. Gilbert and the assistance of Dr. B. B. Stewart with the nmr spectra.

Mesomorphic Properties of Alkoxybenzylideneaminoacetophenones

SARDARI L. ARORA, TED R. TAYLOR, AND JAMES L. FERGASON

Liquid Crystal Institute, Kent State University, Kent, Ohio 44240

Received September 19, 1969

Compounds of the alkoxybenzylideneaminoacetophenone series are of special interest, as many of them have a wide range of smectic phase A below 130°. Four homologs of this series with C_1, C_2, C_4, and C_8 in the *n*-alkoxy chain length have been reported by Castellano, *et al.*[1]

Their observation of a nematic phase in 4-*n*-octyloxybenzylidene-4′-aminoacetophenone we believe to be in error. The only phase we observe between the melt and the isotropic liquid is a smectic phase. The possibility of a nematic phase in the aforementioned compound is, further, ruled out because no nematic phase is observed in the lower homolog with C_7 in the chain length. The absence of the nematic phase in these two compounds is further confirmed by our optical and differential thermal analysis studies.

Of the 11 compounds synthesized by us in this series, the lowest homolog with C_1 in the alkyl chain shows no liquid crystalline phase. A nematic phase is observed in compounds with *n*-alkoxy chain lengths of C_3, C_4, C_5, and C_6 only. All other compounds from C_3 to C_{10}, C_{12}, and C_{14} show an enantiotropic smectic 1 phase. Monotropic smectic 2 is observed in compounds with chain lengths of C_3–C_9. A plot of phase transition temperatures *vs.* the number of carbon atoms in the alkyl chain is shown in Figure 1. For comparison, the data of Castellano, *et al.*,[1] is shown by dotted lines.

Smectic 1 shows the focal-conic texture typical of smectic A of Sackmann and Demus.[2] Monotropic smectic 2 appears to be identical with smectic 1, and it is not possible to distinguish this phase from smectic 1 by optical methods.

In Figure 1, one observes an unusually marked alternation of the nematic–isotropic transition temperatures for odd and even numbers of carbon atoms in the alkyl chain of this homolog's series. The plot for even carbon chain homologs lies above that for odd carbon chain members. Further, this extent of alternation decreases as the chain length increases. The alternation of nematic–isotropic transition temperatures in such a series is similar to that found by Gray[3] in alkoxybenzoic acids and alkoxy Schiff bases.

The nematic–isotropic transition curve (Figure 1) for both odd and even alkyl chain homologs appears to merge with the rising smectic–nematic transition curve at a point which lies below the point for the homolog with C_7 in the alkyl chain. When such a merging of the nematic–isotropic and smectic–nematic curves takes place, then it is well known that all other higher homologs above the merger do not show a nematic phase. This behavior is indeed observed in 4-*n*-heptyloxybenzylidene-4′-aminoacetophenone which does not exhibit a nematic phase but has only one enantiotropic smectic mesophase which passes directly into the isotropic liquid. Hence, on this basis, it is unlikely for C_8 to have a nematic phase when its predecessor homolog does not show such a phase.

The absence of a nematic phase in C_8 is further confirmed by our differential thermal analysis (DTA) of this compound. In Figure 2, the thermograms of homologs with alkyl chain length of C_6, C_7, and C_8 are shown. An examination of these establishes one enantiotropic liquid crystal phase between the melt and

(1) J. A. Castellano, J. E. Goldmacher, L. A. Barton, and J. S. Kane, *J. Org. Chem.*, **33**, 3501 (1968).

(2) H. Sackmann and D. Demus, *Mol. Cryst.*, **2**, 81 (1966).

(3) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, London and New York, 1962, p 197.

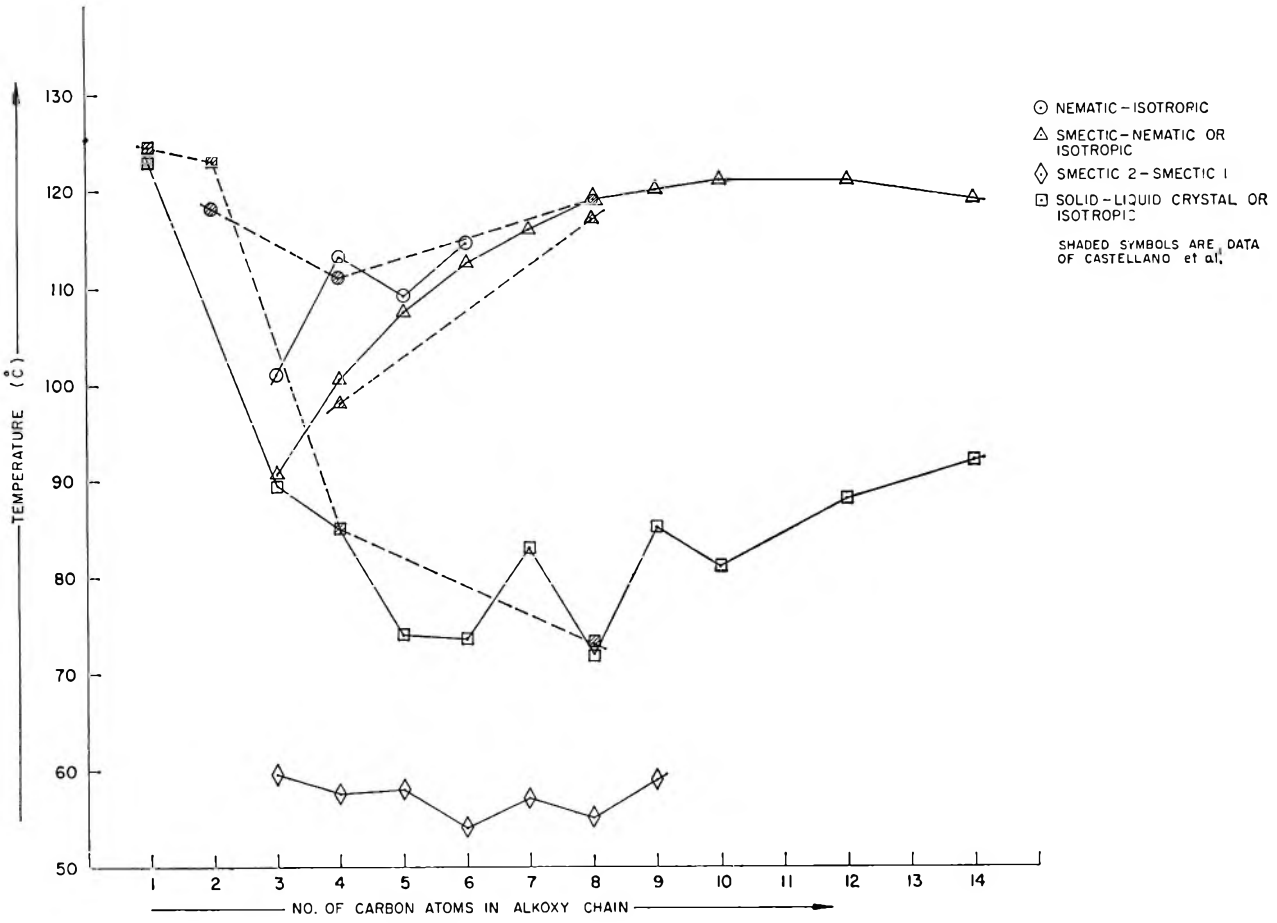


Figure 1.

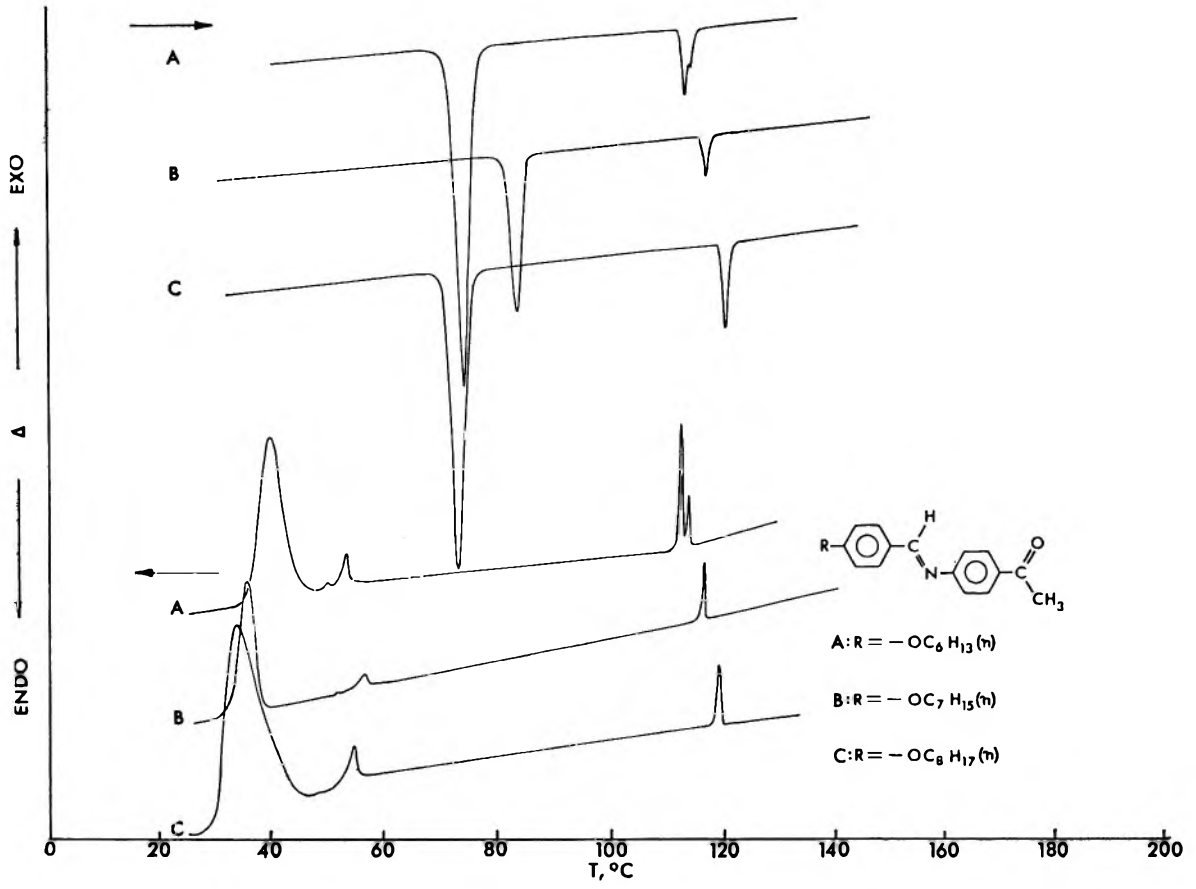
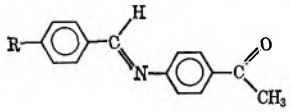


Figure 2.

TABLE I
4-*n*-ALKOXYBENZYLIDENE-4′-AMINOACETOPHENONES



Compd	Substitutents, R	Transition temperatures, °C, from solid or preceding liquid crystal state to— Smectic 1	Nematic	Isotropic	Calcd, % C	H	N	Found, % C	H	N
1	H_3CO[d]			123	75.87	5.97	5.53	75.65	5.93	5.50
				124.5[a]						
2	H_5C_2O			123[a]						
				(118)[a]						
3	H_7C_3O	89.5	90.5	101	76.84	6.81	4.98	76.81	6.80	5.01
		59.5[b]								
4	H_9C_4O	85	100.5	113	77.26	7.17	4.74	77.17	7.12	4.47
		85[a]	98[a]	111[a]						
		57.5[b]								
5	$H_{11}C_5O$	74	107.5	109	77.64	7.49	4.53	77.97	7.70	4.61
		58[b]								
6	$H_{13}C_6O$	73.5	112.5	114.5	77.99	7.79	4.33	78.32	7.55	4.43
		54[b]								
7	$H_{15}C_7O$	83		116	78.30	8.06	4.15	78.43	8.07	4.20
		57[b]								
8	$H_{17}C_8O$	72		119	78.60	8.32	3.98	78.49	8.51	4.08
		73[a]	117[a,c]	119[a]						
		55[b]								
9	$H_{19}C_9O$	85		120	78.87	8.55	3.83	78.83	8.53	3.77
		59[b]								
10	$H_{21}C_{10}O$	81		121	79.11	8.76	3.70	79.04	8.77	3.63
11	$H_{25}C_{12}O$	88		121	79.56	9.15	3.44	79.71	9.25	3.38
12	$H_{29}C_{14}O$	92		119	79.95	9.49	3.22	80.04	9.49	3.14

[a] Transition temperatures reported by Castellano, *et al.*[1] Value in parentheses is the monotropic nematic. [b] Transition from monotropic smectic 2. [c] Transition temperature for smectic 1-nematic by Castellano, *et al.*,[1] and is wrong because no nematic phase is observed in this compound. [d] DTA shows an apparent monotropic nematic phase at 98° but this phase is not observable microscopically.

isotropic liquid for C_7 and C_8. However, two enantiotropic mesophases are evident for C_6. Optical studies of these two mesophases indicate that the lower temperature phase is smectic and the higher temperature phase, nematic. Further, these two liquid crystal phases are separated from one another by a very narrow range. Optical studies of the single enantiotropic mesophase observed for C_7 and C_8 show this phase to be smectic A as defined by Sackmann and Demus.[2] In sum, our observations do not show a nematic phase for C_8 as reported by Castellano, *et al.*[1]

In compounds with alkyl chain length C_3–C_9, a previously unobserved[1] monotropic smectic 2 phase is observed. This phase is observed in cooling DTA thermograms as shown in Figure 2 for C_6, C_7, and C_8. Since smectic 2 is a supercooled state, it must be carefully distinguished from a transition to a solid. If the transition does represent a mesophase, the transition should be completely reversible. We, therefore, did make thermograms in which, after the smectic 1–smectic 2 transition occurred on cooling, the DTA was reversed and the transition ran through on the heating cycle. In all cases, the transition was still present on heating, confirming our supposition that the transition did not represent crystallization.

Optically, monotropic smectic 2 appears to be identical with smectic 1, that is, smectic A. Within the limits of our optical measuring techniques, we can observe no change at the smectic 1–smectic 2 transition temperature. There does appear to be a difference in viscosity between smectic 1 and smectic 2. If the relatively viscous smectic 2 is distorted by moving the cover slip, then on reheating there is flow near the smectic 1–smectic 2 transition temperature.

It is interesting to note that smectic 1 and smectic 2 cannot be classified according to the miscibility method of Sackmann and Demus.[2] Since both phases have identical optical textures, there would be no phase boundary owing to miscibility. We recently encountered a similar situation during our studies on the smectic phases of the homologs of 4-*n*-alkoxybenzylidene-4′-aminopropiophenones[4] where an explanation is given for the unusual behavior of these apparently identical smectic phases.

Experimental Section

Determination of Transition Temperatures.—The phase transition temperatures were determined both by differential thermal analysis (Du Pont DTA 900) and with a Leitz Panphot polarizing microscope using a Mettler FP-2 heating stage. Melting points (solid–liquid or solid–liquid crystal transition) have been regarded as the transitions with the highest transition energy. These are also always the transitions that can most easily be supercooled, whereas supercooling in the case of liquid crystal transitions is negligible.

Monotropic liquid crystal transition temperatures observed below the melting points during the cooling operation of DTA thermograms were confirmed by reheating of the samples before crystallization. The assignments of the transition temperatures were confirmed by the polarizing microscope, except for the monotropic smectic 2–smectic 1 transitions. The highest tem-

(4) S. L. Arora, T. R. Taylor, and J. L. Fergason, "Symposium on Ordered Fluids and Liquid Crystals, Sept 1969," American Chemical Society, Washington, D.C., in press.

perature smectic phase is always called smectic 1, the next lower one smectic 2, and so on. The transition temperatures for the various liquid crystal phases are listed in Table I. The error of the temperature measurements is estimated to be smaller than ±2°.

Preparation of Materials.—4-aminoacetophenone was recrystallized from commmercially available material.

4-*n*-Alkoxybenzaldehydes were prepared from *p*-hydroxybenzaldehyde and various alkyl bromides either according to the method of our earlier publication[5] or by that of Weygand and Gabler.[6]

Alkoxybenzylideneaminoacetophenones were prepared by refluxing equimolecular quantities of the 4-aminoacetophenone and the appropriate 4-*n*-alkoxybenzaldehyde in absolute alcohol for 5–6 hr. The product after isolation was recrystallized several times from appropriate solvents until the transition temperature remained constant.

The liquid crystal–liquid crystal transitions with the purified compounds were sharp and reversible. Differential thermal analysis gave on heating and on cooling, within a fraction of a degree, equal temperatures for these transitions.

Registry No.—**1,** 23596-02-3; **2,** 17224-17-8; **3,** 23596-04-5; **4,** 17224-18-9; **5,** 23596-06-7; **6,** 23596-07-8; **7,** 23596-08-9; **8,** 17224-19-0; **9,** 23596-10-3; **10,** 23596-11-4; **11,** 23596-12-5; **12,** 23596-13-6.

Acknowledgment.—The research reported in this paper was sponsored by the National Aeronautics and Space Administration, Washington, D. C., under Contract No. NGR-36-007-025, with Kent State University. One of the authors, Dr. T. R. Taylor, is grateful to the Advance Research Projects Agency, Contract No. F-44620-67-C-0103.

(5) S. L. Arora, J. L. Fergason, and A. Saupe, *Mol. Cryst. Liq. Cryst.*, in press.

(6) C. Weygand and R. Gabler, *J. Prakt. Chem.*, **155**, 338 (1940).

Quantitative Studies in Stereochemistry. XIII. The Peroxide-Induced Pinacolization of Acetophenone. The Thermal Stability of the Acetophenone Pinacols

JACK H. STOCKER AND DAVID H. KERN

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

Received September 2, 1969

The *t*-butyl peroxide induced pinacolization of aryl ketones has been reported to involve a dimerization of ketyl radicals as the final step in the reaction sequence.[1] Similar ketyl radicals are known to be intermediates in electro- and photopinacolization processes. Where the starting ketone (or aldehyde) is unsymmetrical, both *dl* and *meso* forms of the pinacol may be produced. Previous studies involving actophenone in neutral or acidic media have demonstrated that essentially identical *dl/meso* ratios of diastereomers are produced by both the electrochemical and photochemical techniques.[2–4] It would be anticipated that a stereochemical study of the peroxide-induced pinacolization should yield this same *dl/meso* ratio of products. Preliminary studies gave wildly erratic results; it was subsequently realized that the thermal stability of the acetophenone pinacols was an important factor. Tables I and II summarize the pertinent data.

(1) E. S. Huyser and D. C. Neckers, *J. Amer. Chem. Soc.*, **85**, 3641 (1963).
(2) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966).
(3) J. H. Stocker and R. M. Jenevein, *ibid.*, **33**, 294 (1968).
(4) J. H. Stocker, R. M. Jenevein, and D. H. Kern, *ibid.*, **34**, 2810 (1969).

TABLE I
THE PEROXIDE-INDUCED PINACOLIZATION OF ACETOPHENONE

Expt	*t*-Butyl peroxide, ml	Solvent, ml[a]	Time, hr	Temp, °C	Recovered ketone, %[b]	Pinacols, %[b]	Ratio *dl/meso*
1	1	4	16	120	8	88	0.89
2	2	4	1	120	32	65	1.05
3	1	4	0.5	160	7	92	1.01
4	1	4	2	160		100	1.00
5	0.5	4	0.5	160	3	95	0.98
6	0.1	4	0.5	160	80	16	0.94
7	0.5	2	5	160		100	0.92
8	0.5	2	24	160	33	58	0.78
9	0.5	2	48	160	18	80	0.79
10	0.5	2	120	160		85	0.50
11	None	4	360	160	70		

[a] 2-Pentanol. [b] Based on 500 mg of acetophenone starting material used in all runs.

Results and Discussion

From Table I it may be observed that the highest *dl/meso* ratios correspond to the largest amount of peroxide, the lower temperature, and the shortest periods of time. If peroxide stability is considered,[5–7] these data, taken collectively, may conveniently be interpreted as reflecting rapid utilization of the peroxide, rapid formation of the pinacols, and a slower interconversion of the pinacols *via* a thermal process. On this basis, expt 2 in Table I would best reflect the nonthermal process, *i.e.*, maximum amount of peroxide at the lower temperature for a period of time short of complete reaction. It will be noted that these conditions gave rise to a *dl/meso* ratio (1.05) which is virtually identical with those observed in the earlier photochemical studies (1.09 ± 0.03)[2] at room temperature, identical with those observed in the same study at the boiling point of 2-pentanol (1.03–1.05), and the highest ratio observed in the present study.

This excellent correspondence lends additional weight to the general mechanism proposed by Huyser and Neckers[1] and further supports the stereochemical arguments in the related photochemical studies.[2,4]

The subsequently carried out thermal studies reported in Table II verify and extend this interpretation. Previous studies of the thermal stability of pinacols[8] have dealt with those derived from symmetrical ketones, and no stereoisomerism would be observed. The present study would appear to constitute the first

(5) *t*-Butyl peroxide has been reported to have a half-life of 19.8 min at 160° in dilute benzene solution, although the decomposition is said to be practically unaffected by its chemical environment. See Lucidol Product Bulletin 7.101. Other selected figures from this source of $t_{1/2}$ include 34.0 hr (115°), 6.4 hr (130°), and 1.38 hr (145°).

(6) W. A. Pryor ("Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 84) reports half-lives of 11 years (60°) and 35 sec (180°).

(7) C. S. Huyser and A. A. Kahl [*Chem. Commun.*, 1238 (1969)] describe the accelerated decay of *t*-butyl peroxide in the presence of α-hydroxyalkyl radicals. Since such a condition would prevail in the present studies, the half-lives reported in ref 5 and 6 are correspondingly too long.

(8) D. C. Neckers and D. P. Colenbrander, *Tetrahedron Lett.*, 5045 (1968), and references cited therein.

TABLE II

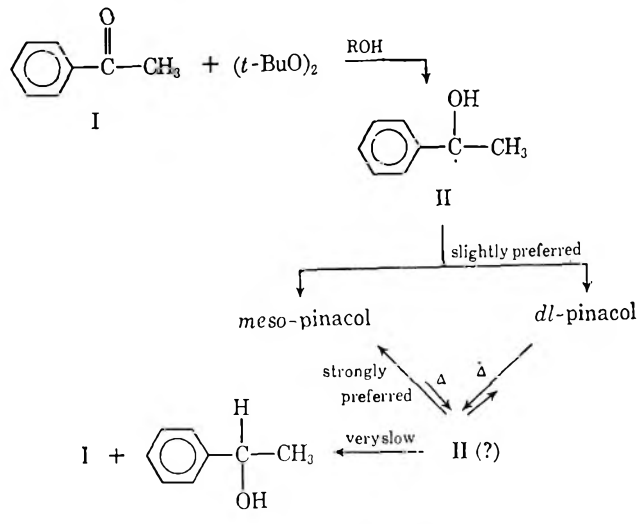
THERMAL STABILITY OF ACETOPHENONE PINACOLS[a] AT 160°

Expt	Pinacol, mg (form)	Solvent (ml)	Time, days	Product analysis[b] meso, %	dl, %	Other, % (product)
12	256 (*meso*) 257 (*dl*)	2-Pentanol (4)	4	54	46	None
13	250 (*dl*)	2-Pentanol (2)	2	17	83	None
14	250 (*dl*)	2-Pentanol[c] (2)	2	9	91	None
15	250 (*dl*)	2-Pentanol[c] (2)	5	14	86	None
16	200 (*dl*)	None	14	15	12	20 (methyl phenyl carbinol), 31 (acetophenone)
17	25 (*dl*)	2-Pentanol (4)	7	90	10	None
18	10 (*meso*) 10 (*dl*)	2-Pentanol (4)	7	95	5	None
19	25 (*meso*)	2-Pentanol (4)	7	100	0	None

[a] *meso*- and *dl*-2,3-diphenyl-2,3-butanediol. [b] Based on starting pinacol(s) as evaluated by proton integration of aromatic region (nmr) constituting 100% of invested aromatic protons; see J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968). [c] *t*-Butyl peroxide (0.5 ml) present.

report of simple *thermal* interconversion.[9] The *meso* form clearly predominates to a degree that observation of an equilibrium situation was not practical; *i.e.*, for very small samples a net conversion of 90% of the *dl* into the *meso* form, from a 50:50 mixture of the two forms, took place in 7 days (expt 18), while a net change of zero occurred for the *meso* form in a like period of time (expt 19). It may be noted that the presence of peroxide did not produce an appreciable change in results, the change, if real, being in a decelerative direction. Interconversion also took place in the absence of solvent (expt 16) but appreciably more slowly; cleavage by-products were observed. It would not be obvious, *a priori*, whether preferential cleavage of the *dl* form, or preferred recombination of the resultant ketyl radicals from both forms, or some combination of these two possibilities, would be responsible for this extreme dominance of the *meso* form over a period of time; if one makes the reasonable assumption that recombination of radicals is stereochemically unchanged from combination, preferential cleavage of the *dl* form must be invoked. A speculative alternative might consider the recombination to be from a tight pair rather than the initial freer combination.

The interrelationships involved are most simply rationalized as follows.



(9) A mechanism proposed by Neckers and Colenbrander[8] for the thermal breakdown of benzpinacol involved scission into benzhydrol radicals; these disproportionate[10] at temperatures above 100° (see ref 1, footnote 9). Interconversion of diastereomers would be implicit in this mechanism where radical stability permitted.

(10) The absence of disproportionation in the present studies (excepting only expt 16) is admittedly surprising. The products from this process—acetophenone and methyl phenyl carbinol—are readily observable in nmr analysis and were specifically sought. It may be suggested that in the related benzophenone studies, the more stable benzhydrol radical (compared with its acetophenone counterpart radical) is accordingly more readily formed and lingers longer, permitting the (slower) disproportionation reaction to become more important than recombination.

(11) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968).

The results reported suggest that stereochemical studies involving peroxides in this area may carry an important thermal component, and, further, that such interconversion may be exploited to enrich a mixture of diastereomers in the more favored isomer.

Experimental Section

Acetophenone, *t*-butyl peroxide, and 2-pentanol were the highest grade commercial products available and were used as received. *meso*- and *dl*-acetophenone pinacols were prepared by photochemical or organometallic techniques.[2]

General Procedure.—Acetophenone, *t*-butyl peroxide (if present), and 2-pentanol were placed in a 3-oz aerosol compatibility tube (Fisher and Porter) subsequently sealed with a stainless steel cap fitted with a pressure valve and neoprene gasket. Exact amount of all reaction components are given in Tables I and II. Temperatures were controlled by use of an oil bath and variable-temperature hot plate and were held to ±2° of the reported values. Following the reaction period, the pressure was released and the sample was prepared for nmr analysis as previously reported in the related photochemical studies.[11]

Registry No.—Acetophenone, 98-86-2; *meso*-acetophenone pinacol, 4217-65-6; *dl*-acetophenone pinacol, 22985-90-6.

Preparation of 2-Heteroalkyl Substituted 2-Cyclohexen-1-ones

M. A. TOBIAS, J. G. STRONG, AND R. P. NAPIER

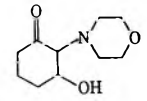
Mobil Chemical Company, Edison, New Jersey 08817

Received October 3, 1969

Because of our general interest in the chemistry of 2-cyclohexen-1-one (1), we wished to prepare and examine previously unreported 2-substituted derivatives

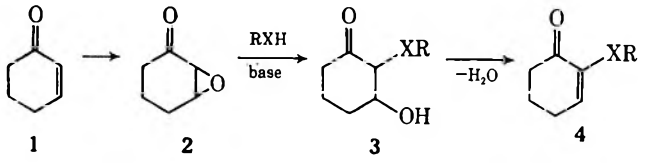
TABLE I

2-HETEROALKYL 2-CYCLOHEXEN-1-ONES (4)

XR	Registry no.	Yield, %	Mp or bp, °C (mm)	Calcd, % C	H	N	S	Found, % C	H	N	S	δ for C-3 proton
OCH_3	23740-37-6	25	117–119 (18)	52.46[a]	6.63	22.95	...	52.57	6.93	22.70	...	5.74
$SCH_2CH(CH_3)_2$	23740-38-7	72	122–125 (3)	65.21	8.69	...	17.39	65.33	8.83	...	17.30	6.73
$SCH(CH_3)_2$	23704-39-8	81	109–112 (3)	63.53	8.23	...	18.82	63.70	8.84	...	18.63	6.90
$SC(CH_3)_3$	23704-40-1	62	105–106 (3)	65.21	8.69	...	17.39	65.43	8.77	...	17.32	7.41
	23740-61-6	47	54–55	56.31[b]	5.45	15.16	...	56.53	5.60	15.00	...	6.40
	18543-93-6	75	83 (3)									5.37[c]
	23740-63-8	72	90 (3)	73.74	9.50	7.82	...	73.88	9.67	7.76	...	5.88
	23740-64-9	83	53–54	66.30	8.29	7.73	...	66.29	8.02	7.66	...	5.94
$N(CH_3)_2$	23740-65-0	86	55 (0.1)	69.03	9.41	...	...	69.05	9.51	...	...	5.78
$N(CH_2CH_3)_2$	13120-89-3	76	58 (0.1)	71.81	10.25	...	...	71.74	10.15	...	...	5.90
	23740-67-2	43	94–96	60.30	8.54	7.04	...	60.31	8.55	7.01	...	

[a] Analysis on semicarbazone, mp 211–212°. [b] Analysis on thiosemicarbazone, mp 186–187°. [c] Reported[4] at δ 5.44 for neat compound.

(4) of this material. Thus the following preparative scheme was adopted.



1 2 3 4

Epoxidation of 1 with either alkaline hydrogen peroxide[1] or *t*-butyl hydroperoxide[2] afforded 2,3-epoxycyclohexanone (2) in high yield. Base-catalyzed reaction of 2 with varied nucleophilic substrates (RXH) yielded 2-substituted 3-hydroxycyclohexanones (3), which generally dehydrated *in situ* or during isolation to afford the desired 2-substituted 2-cyclohexen-1-one (4).

The utility of this procedure is, however, highly dependent upon both the nucleophilicity of RXH and the stability of 2, 3, and 4 to the basicity of the reaction medium. Thus species which are both good nucleophiles and strong bases were not effective in preparing compounds of type 4, whereas strongly nucleophilic but weakly basic substrates gave very good yields of the desired products 4. For example, sodium methoxide in methanol reacted with 2 to afford a 25% yield of 2-methoxy-2-cyclohexen-1-one,[3] while both sodium isopropoxide and *t*-butoxide yielded only resinous reaction mixtures. On the other hand, primary, secondary, and tertiary alkyl mercaptans, aryl mercaptans, and both aliphatic and alicyclic secondary amines provided high yields of the 2-substituted derivatives of 1 (Table I).

The structure of these new cyclohexenones (4) were assigned on the basis of (A) the chemical shifts and splitting patterns of the C-3 vinyl proton, which appears as a triplet (J = 4–6 Hz) at 5.37–7.41 ppm; (B) the stretching frequencies of the α,β-unsaturated carbonyl at *ca.* 5.9 and 6.2 μ; and (C) satisfactory elemental analysis. An additional proof of structure for 2-methoxy-2-cyclohexen-1-one and 2-N-pyrrolidino-2-cyclohexen-1-one was obtained by converting the former into *o*-methoxyphenol and by comparing the spectral properties of the latter with those of an authentic sample prepared from pyrrolidine and 1,2-cyclohexanedione.[4]

Experimental Section[5]

The following examples are representeative of the synthetic method used. Homologous compounds were prepared by similar procedures.

2-N,N-Dimethylamino-2-cyclohexen-1-one.—Gaseous dimethylamine was introduced through a glass frit into a solution of 5.6 g (0.05 mol) of 2, 15 ml of methanol, and 5 ml of water. The exothermic reaction was controlled by regulating the flow of amine. After the exotherm had subsided (0.5 hr), the amine addition was stopped and the solvent was removed. The residue was taken up in chloroform, and the organic layer was dried ($MgSO_4$), concentrated, and distilled, giving 6.2 g of product, bp 55° (0.1 mm).

2-N-Morpholino-2-cyclohexen-1-one.—A solution of 5.6 g (0.05 mol) of 2, 5.3 g (0.06 mol) of morpholine, 15 ml of methanol, and 5 ml of water was refluxed for 3 hr. After cooling, the solvent was removed and the residue was placed in 100 ml of saturated brine solution. Extraction with ether, drying ($MgSO_4$), and removal of the solvent yielded 7.5 g of oil which solidified slowly. Several crystallizations from hexane afforded an analytically pure sample, mp 53–54°.

2-N-Morpholino-3-hydroxycyclohexanone.—When the temperature of the exothermic reaction resulting from the combination of 2 and morpholine was kept below 40° and an identical work-up procedure with that described above used, 4.3 g of the 2,3-disubstituted cyclohexanone was isolated, mp 94–96° after several crystallizations from hexane.

2-Thioisopropyl-2-cyclohexen-1-one.—Isopropyl mercaptan, 15.7 g (0.2 mol), was dissolved in 25 ml of ethanol and added during 1.5 hr to a solution of 22.4 g (0.2 mol) of 2, 75 ml of ethanol, and 1.25 ml of 15% sodium hydroxide. The temperature of the exothermic reaction was maintained at 35–40°. After the solution had stood for 12 hr at ambient temperature, the solvent was removed and the residue was distilled, giving 27.5 g of product, bp 109–112° (3 mm).

(1) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 552.

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

(3) Direct methylation of 1,2-cyclohexanedione has been reported to produce an 11% yield of impure material: M. S. Gibson, *J. Chem. Soc.*, 681 (1962).

(4) S. Danishefsky and R. Cavanaugh, *Chem. Ind.* (London), 2171 (1967).

(5) Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected. Nuclear magnetic resonance spectra were determined with a Varian Model A-60; pertinent chemical shifts are expressed in parts per million downfield from internal tetramethylsilane.

2-Methoxy-2-cyclohexen-1-one.—A solution of 11.2 g (0.1 mol) of 2 in 50 ml of 0.1 *M* sodium methoxide was allowed to stand at 20–25° for 40 hr. Neutralization of the reaction mixture, removal of excess solvent, and distillation yielded 3.1 g (25%) of product, bp 116–119° (18 mm).

The Synthesis of Amino-Substituted α,α,α-Trifluoroacetophenones

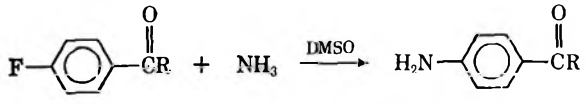
KENNETH J. KLABUNDE AND DONALD J. BURTON

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52240

Received July 17, 1969

In connection with other work in our laboratory, we were in need of a series of *meta*- and *para*-substituted perfluoroacyl ketones—especially substituted trifluoroacetophenones. Normal procedures for the preparation of substituted trifluoroacetophenones involve reaction of the appropriate Grignard reagents with trifluoroacetic acid,[1,2] or bromination, nitration, etc., of the appropriate perfluoroacyl ketone to give some *meta* derivatives not available by the Grignard procedure. However, these procedures fail when substituents such as amino, dimethylamino, cyano, iodo, or bromo are present in the Grignard reagent.[3] Consequently, substituents of this type cannot be introduced into the *para* position by these normal procedures.

Therefore, we have devised a new method for the introduction of such substituents. This procedure introduces a *p*-amino group into the appropriately substituted *p*-fluoro perfluoroacyl ketone (available *via* the Grignard method[1]). The introduction of the amino group allows the preparation of other *para* substituents (such as CN, I, Br, etc.) *via* diazotization followed by a Sandmeyer reaction. Since all of the synthetic reactions of the amino-substituted ketones are carried out in acid solution, no haloform-type reaction of the ketones are observed. Similar substituents can be introduced into the *meta* position *via* diazotization of the *meta*-amino ketone (available *via* nitration of the parent ketones). For the sake of completeness these substituted ketones are also included.



R = CF_3, CF_3CF_2, $CF_3CF_2CF_2$

Aryl carbon–fluorine bonds are significantly activated by the introduction of an electron-withdrawing group into the aromatic nucleus. In addition, fluorine atoms are relatively susceptible to displacement by nucleophilic species, much more so than other halogens.[4] Bader and coworkers[5] have found that dimethylamine displaces activated aryl fluorine atoms in both dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF) solvents. Therefore, we considered the displacement of activated fluorine by ammonia feasible. Indeed, it was found that in DMSO the conversion of *p*-fluorotrifluoroacetophenone (I)[2] into *p*-aminotrifluoroacetophenone (II) could be carried out by bubbling ammonia into the hot, well-stirred solution. The trifluoroacetyl group creates an activated aryl carbon–fluorine bond.[6] The *p*-chloro ketone did not react under the same conditions. In addition, the conversion did not occur in other solvents such as dimethoxyethane, formamide, or DMF.

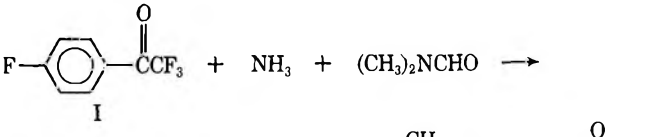
TABLE I

SUBSTITUTED TRIFLUOROACETOPHENONES *via* THE REACTIONS OF *m*- AND *p*-AMINOTRIFLUOROACETOPHENONE[a]

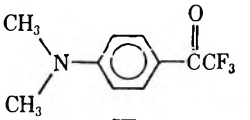
Starting trifluoroacetophenone	Product trifluoroacetophenone	Yield, %	Reagents[b]
p-NH_2	*p*-Cl	50	CuCl, HCl
p-NH_2	*p*-Br	70	CuBr, HBr
p-NH_2	*p*-I	74	KI, I_2
p-NH_2	*p*-CN	59	CuCN, KCN
m-NH_2	*m*-I	71	KI, I_2
m-NH_2	*m*-CN	62	CuCN, KCN

[a] Normal diazotization procedures which have been described in a general manner by Vogel[9] were employed. [b] The cuprous salts used were freshly prepared. Best results were obtained if dilute sulfuric acid was used as the diazotization medium.

The use of DMF as solvent, ammonia, and I enabled the preparation of *p*-dimethylaminotrifluoroacetophenone (III). Apparently, when ammonia is bubbled into DMF, dimethylamine is produced. Dimethylamine is a stronger base than ammonia and must react much more rapidly to displace the aryl fluorine. Thus, as dimethylamine is consumed more is produced, and good yields of III are obtained.



I



III

(1) K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, **78**, 2268 (1956).

(2) F. E. Herkes and D. J. Burton, *J. Org. Chem.*, **32**, 1311 (1967).

(3) F. E. Herkes, Ph.D. Thesis, University of Iowa, 1966.

(4) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benajmin, Inc., New York, N. Y., 1965, p 847.

(5) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

(6) The trifluoroacetyl group is not a specific activator for this reaction, and the same aryl fluorine displacement by ammonia has been carried out with 1-(*p*-fluorophenyl)pentafluoropropanone and 1-(*p*-fluorophenyl)heptafluorobutanone (these ketones were prepared by the method of Dishart and Levine[1] using *p*-fluorophenylmagnesium bromide with pentafluoropropionic acid and heptafluorobutyric acid, respectively). The *p*-amino ketones produced (V and VI, respectively) showed ir, ^1H nmr, and ^{19}F nmr spectra consistent with the expected structures. Data for V follow: ir 5.93 μ (C=O); ^1H nmr δ 4.40 (broad singlet, 2 H) and 6.67 and 7.95 (doublets, 4 H); ^{19}F nmr 82.1 (singlet, 3 F) and 115.2 ppm (singlet, 2 F). Data for VI follow: ir 5.94 μ (C=O); ^1H nmr δ 4.38 (broad singlet, 2 H) and 6.67 and 7.92 (doublets, 4 H); ^{19}F nmr 80.0 (3 F), 112.6 (2 F), and 125.1 ppm (2 F).

TABLE II
PHYSICAL PROPERTIES OF SUBSTITUTED TRIFLUOROACETOPHENONES[a]

Substituent	Registry no.	Bp, °C (mm)	Mp,[b] °C	Ir, μ (C=O)	$n^{20}D$	^1H nmr[c]	^{19}F nmr[d]
p-NH_2	23516-79-2	113 (0.5)	94.5–95.5	5.93		7.9, 6.6 (d, 4 H) 4.50 (br s, 2 H)	71.03
m-NH_2	23516-80-5	82 (0.5)		5.85		7.3 (m, 4 H) 3.90 (s, 2 H)	71.54
p-$N(CH_3)_2$	2396-05-6		74–75[e]	5.94		7.9, 6.6 (d, 4 H) 3.04 (s, 6 H)	70.84
p-Cl[f]	321-37-9	84 (23)		5.80	1.4901	7.78 (A_2B_2, 4 H)	72.03
p-Br	16184-89-7	95 (4)		5.80	1.5141	7.77 (A_2B_2, 4 H)	72.02
p-I	23516-84-9	89 (1)		5.80	1.5589	7.80 (A_2B_2, 4 H)	72.01
p-CN	23516-85-0	71 (0.2)	53–55	5.80		8.08 (A_2B_2, 4 H)	72.19
m-I	23516-86-1	89 (3)		5.81	1.5431	8.1, 7.3 (m, 4 H)	72.04
m-CN	23568-85-6	71 (0.2)		5.79		7.95 (m, 4 H)[g]	72.07[g]

[a] All compounds gave satisfactory C, H, N analyses with the exception of *m*-NH_2 (slightly impure). [b] All melting points are corrected. [c] In δ, parts per million, downfield from TMS; $CDCl_3$ solvent. [d] In parts per million upfield from $CFCl_3$; $CDCl_3$ solvent. The three fluorines appeared as a singlet in all cases. [e] Lit.[7] mp 74.5–75.5°. [f] Also identified by comparison of ir spectra with an authentic sample.[2] [g] A small amount of DMSO-d_6 was added to dissolve all of the material.

This preparation of III is superior to the one reported,[7] since pure material can be obtained with a minimum of experimental difficulty.

The preparation of *m*-aminotrifluoroacetophenone (IV) was carried out by conventional means. That is, trifluoroacetophenone[2] was nitrated in the *meta* position according to the method of Stewart and Vander Linden,[8] and reduced to the amine with tin and hydrochloric acid.

Both II and IV were readily diazotized and used to prepare other substituted ketones. General procedures for such diazotization reactions (Sandmeyer reactions) have been described.[9] Table I indicates the ketones which were prepared from II or IV, the isolated yields, and reagents used. Table II lists the physical properties of all materials prepared.

Experimental Section

p-Aminotrifluoroacetophenone.—Into a 1-l., three-necked flask equipped with a reflux condenser and gas inlet tube extending to the bottom of the flask were placed 61.6 g (0.32 mol) of *p*-fluorotrifluoroacetophenone (I)[2] and 200 ml of DMSO. The solution was stirred vigorously with a magnetic stirrer and heated to 135°. A large trap was inserted between the gas inlet tube and a tank of anhydrous ammonia, and ammonia was bubbled into the solution at a moderate rate for 24 hr. (The gas inlet tube had to be cleaned of solid formations several times during the reaction.) After cooling, the solution was poured into 1 l. of ice–water and stirred for several hours, and the dark precipitate was collected on a suction filter. The solid was air-dried and then melted and distilled under reduced pressure to yield 25.3 g (42%) of *p*-aminotrifluoroacetophenone (II).

p-Dimethylaminotrifluoroacetophenone.—In the manner described previously, ammonia gas was bubbled into 57.5 g (0.30 mol) of *p*-fluorotrifluoroacetophenone (I) and 200 ml of DMF. The addition of ammonia continued for 12 hr while the reaction temperature was held at 150°. The mixture was cooled, poured over 1200 ml of water, and stirred overnight, and the precipitate was collected on a suction filter. The light green solid was recrystallized from a water–ethanol mixture. The crystals were dried over $CaSO_4$ at *ca.* 1-mm pressure. The yield was 36.2 g (55%).

m-Aminotrifluoroacetophenone.—Into a 1-l., three-necked flask equipped with a reflux condenser and magnetic stirrer were placed 36.0 g (0.30 g-atom) of tin granules and 34.0 g (0.16 mol) of *m*-nitrotrifluoroacetophenone,[8] bp 131° (10 mm) [lit. bp 113° (12 mm)]. The mixture was stirred vigorously while 350 ml of concentrated hydrochloric acid was added in three portions. The reaction was moderated with a water bath. After the addition was completed, the solution was refluxed for 1 hr, cooled, and neutralized with aqueous sodium bicarbonate. The mixture was extracted twice with 200-ml portions of ether, and the extracts were washed with water. The ether was evaporated and the residue was distilled under reduced pressure to yield 11.5 g (39%) of *m*-aminotrifluoroacetophenone. Glpc analysis indicated 95% purity.

Acknowledgment.—K. J. K. would like to thank the National Science Foundation and Phillips Petroleum Co. for financial support during the course of this work. This work was also partially supported by research grants from the Public Health Service (GM 11809 and CA 10745).

(7) W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965).
(8) R. Stewart and R. Vander Linden, *Can. J. Chem.*, **38**, 399 (1960).
(9) A. I. Vogel, "Elementary Practical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1958.

Base-Catalyzed Reactions. XXXVIII.[1] Selected Lithium-Catalyzed Reactions of 4-Alkylpyridines with Olefins

WAYNE M. STALICK[2] AND HERMAN PINES

Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

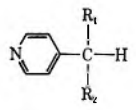
Received September 28, 1969

In previous papers of this series it was reported that sodium and potassium are catalysts for the side-chain alkylation,[3] aralkylation,[4] and alkenylation[5] of alkyl aromatics. It was also reported that potassium cat-

(1) (a) For paper XXXVII, see W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970). (b) Paper IX of the series Alkylation of Heteroaromatics. (c) For part VIII see ref 1a.
(2) Taken in part from the Ph.D. thesis of W. M. Stalick, Northwestern University, Aug 1969.
(3) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).
(4) (a) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **80**, 6001 (1958); (b) H. Pines and J. Shabtai, *J. Org. Chem.*, **26**, 4220 (1961); (c) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2618 (1962).
(5) H. Pines and N. C. Sih, *ibid.*, **30**, 280 (1965).

TABLE I

EFFECT OF CHANGING CATALYST ON PRODUCT RATIO AND CONVERSION



Expt no.	R_1	R_2	Catalyst	Temp, °C	Reaction time, hr	% conversion[a]	Products, % — Monoaddition — I[b]	II[c]	Diaddition — I[d]	II[e]	III[f]
1	CH_3	CH_3	K	20–25	2.5	75	58	42			
2	CH_3	CH_3	Na	20–25	2.0	84	77	23			
3	CH_3	CH_3	Li	20–25	>12.0	60	91	9			
4	H	CH_3	K	0–25	2.5	100[g]	39	32	14	15	Trace
5	H	CH_3	Na	20–25	2.5	96[h]	44	21	20	14	1
6	H	CH_3	Li	20–25	>15.0	98	75	18	5	2	Trace
7	H	H	K	20–25	1.5	51	13	9	38	32	8
8	H	H	Na	20–25	2.0	56	35	22	43		
9	H	H	Li	70	3.0	54	32	18	50		
10	H	H	*n*-BuLi	20–25	5.0	~95[i]	44	27	39		

[a] Per cent conversion is based on alkylpyridine reacted. [b] Tail addition compound. [c] Head addition compound. [d] Di-tail addition compound. [e] Head and tail addition compound. [f] Di-head addition compound. [g] After 1 hr at 0° the conversion was 70% and after 2 hr 93%. [h] After 1 hr at 23° the conversion was 66%. [i] Per cent conversion is based on isoprene for this experiment.

TABLE II

SIDE-CHAIN ETHYLATION OF 4-ETHYLPYRIDINE

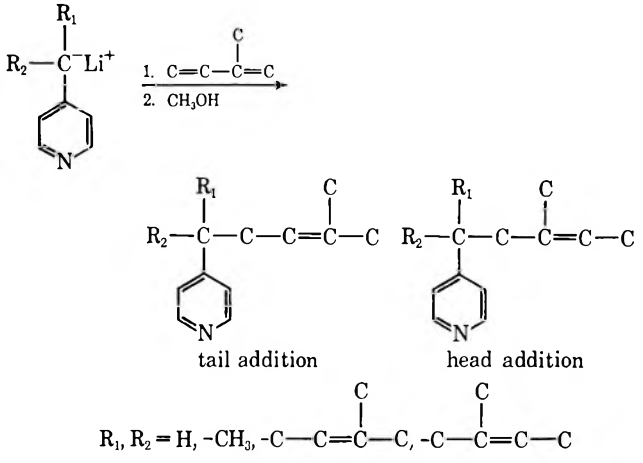
Expt no.	Catalyst	Temp, °C	Reaction time, hr	Max[a] *P*, atm	Min[a] *P*, atm	% yield	Mono-addition	Di-addition
1[b]	Na	150	5	28	10	58	100	
2	Li	150	15	45	45	0		
3	Li	185	12	105	74	49	86	14

[a] Maximum and minimum pressures at the reaction temperature. [b] Results taken from previous work; see footnote 15.

alyzed the cyclization of alkenylbenzenes while sodium gave only double-bond isomerization and lithium was inert,[6] indicating a marked difference in the catalysts. A similar trend was noticed in the cyclialkylation reaction of alkylbenzenes with olefins.[7] The use of lithium as a catalyst for the side-chain alkylation of toluene with ethylene[8] and propylene[9] has been reported, but the reactions had to be made at temperatures of 230–320°, and the yields of the side-chain alkylated products were very low. Owing to low yields and relatively high temperature, the products from the side-chain alkylation could be ascribed to a thermal[10] rather than to a catalytic reaction.

Since 2- and 4-alkylpyridines are more reactive than the corresponding alkylbenzenes, it was possible to carry out side-chain alkenylation and aralkylation reactions using conjugated dienes or styrenes[11] as olefins at room temperature or lower in the presence of sodium or potassium catalysts. The possible use of lithium as a catalyst for addition of 4-alkylpyridines to olefins was thus reinvestigated.

As in the case of potassium and sodium we now report that a catalytic amount of lithium metal can be dispersed in a 4-alkylpyridine medium to give the corresponding anions of 4-picoline, 4-ethylpyridine, and 4-isopropylpyridine. The reaction of 4-alkylpyridine with isoprene proceeds as follows.



The rates of addition for the lithium-catalyzed reactions are slower than for sodium and potassium (Table I). Previous studies indicated that sodium-catalyzed reactions were more selective, giving a larger amount of tail-addition product, than reactions catalyzed by potassium.[12] Table I reveals that the trend is continued, with lithium being the most selective of the three catalysts. This is best illustrated in expt 1–3 using 4-isopropylpyridine as the alkylpyridine, because in these experiments the absence of diaddition products permits a more quantitative estimation of the stereospecificity of the addition reaction.

The reaction was also tried using an *n*-butyllithium catalyst without any solvent, and expt 10 (Table I) shows that this reaction proceeds in a manner compara-

(6) H. Pines, N. C. Sih, and E. Lewicki, *J. Org. Chem.*, **30**, 1457 (1965).
(7) L. Schaap and H. Pines, *J. Amer. Chem. Soc.*, **79**, 4967 (1957).
(8) S. E. Voltz, *J. Org. Chem.*, **22**, 48 (1957).
(9) R. M. Schramm and G. E. Langlois, *J. Amer. Chem. Soc.*, **82**, 4912 (1960).
(10) H. Pines and J. T. Arrigo, *ibid.*, **79**, 4958 (1957).
(11) H. Pines and N. E. Sartoris, *J. Org. Chem.*, **34**, 2113 (1969).
(12) (a) H. Pines and J. Oszczapowicz, *ibid.*, **32**, 3183 (1967); (b) W. M. Stalick and H. Pines, *ibid.*, **35**, 415 (1970).

ble with the others. This is in contrast to the ring alkylation noted by other workers when *n*-butyllithium was used to metalate 4-picoline in ether.[13] The side-chain alkenylation of 4-alkylpyridines with isoprene in the presence of lithium gave no indication of polymerization, although lithium was reported to be highly stereoselective when used to polymerize isoprene in hydrocarbon solvents.[14]

The sodium-catalyzed addition of 4-ethylpyridine to ethylene has been studied in these laboratories.[15] Lithium-catalyzed reactions required longer reaction times and higher temperatures to get yields comparable with those obtained with sodium (Table II). In expt 2, under conditions for which sodium is known to catalyze the addition of ethylene, a lithium catalyst failed to yield any product.

Experimental Section[16]

Reagents.—4-Picoline and 4-ethylpyridine were obtained from Reilly Tar and Chemical Co. 4-Isopropylpyridine was purchased from Pfaltz and Bauer, Inc. The alkylpyridines were distilled, dried over Linde 5A Molecular Sieves, and redistilled immediately before use. Isoprene (Aldrich) was distilled before use and ethylene (Matheson) was used directly from the tank. Regular grade lithium metal (A. D. MacKay Inc.) was used.

General Procedure for Alkenylation Reactions.—The catalyst was prepared by dispersion of 15×10^{-4} g-atom of freshly cut alkali metal under predried *n*-pentane into 0.03 mol of 4-ethylpyridine or 4-isopropylpyridine for 5–10 hr to ensure complete dispersion. The reactions were performed under a slow stream of dry nitrogen in a three-necked flask equipped with reflux condenser, a rubber septum through which additions and withdrawals could be made with a syringe, and a specially designed high-speed stirrer. The active catalyst was a brown-black pseudohomogeneous solution. Isoprene (0.03–0.09 mol) was then added by a syringe to the catalyst solution, and the reaction carried out at room temperature. Samples were withdrawn periodically during the reaction, decomposed with methanol, and analyzed by vpc. At the conclusion of the reaction, the catalyst was decomposed with methanol. It was not possible to disperse lithium in 4-picoline at room temperature; so in this case the 4-picoline was heated to 130° and stirred for 3 hr before all of the lithium was dispersed. The catalyst solution was cooled and isoprepene added when the mixture was at 70°. The reaction was then followed as described above.

Ethylation of 4-Ethylpyridine.—The dispersion of lithium metal was carried out as described for the isoprene reactions. The lithium–4-ethylpyridine catalyst solution was transferred to a 100-ml-capacity Magne-Dash agitated autoclave. The autoclave was sealed, and after flushing with nitrogen it was charged with 40–70 atm of ethylene and heated to the desired temperature (see Table II). Stirring was started and continued for 8–12 hr until the pressure finished dropping. The stirring was then stopped and the autoclave removed from the heating jacket and allowed to cool. After the pressure was released, a few milliliters of methanol was added to the reaction mixture to decompose the organolithium compounds. The crude reaction mixture was then analyzed by vpc.

***n*-Butyllithium-Catalyzed Reactions.**—In a drybox 0.05 mol of 4-picoline was placed in a 30-dram vial, and 0.0025 mol of *n*-butyllithium (Alfa, 90% in hydrocarbon) was slowly added. An exothermic reaction occurred, giving a dark brown solution like that obtained when lithium metal was dispersed in the 4-alkylpyridines. A rubber septum was inserted and the catalyst solution was removed to the laboratory where the reactions were carried out at room temperature. Isoprene (0.015 mol) was then injected through the septum, and samples were removed with a syringe at various intervals, decomposed with methanol, and analyzed by vpc.

Registry No.—4-Isopropylpyridine, 696-30-0; 4-ethylpyridine, 536-75-4; 4-picoline, 108-89-4.

(13) H. Gilman and H. S. Broadbent, *J. Amer. Chem. Soc.*, **82**, 4912 (1960).
(14) C. E. H. Bawn and A. Ledwith, *Quart. Rev.* (London), **16**, 361 (1962).
(15) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).
(16) All compounds were identified by comparison with authentic samples from our laboratories.

Solvent Effects in the Base-Catalyzed Cyclization of 5-Chloro-2-pentanone

RICHARD A. BARTSCH AND DAVID M. COOK[1]

Department of Chemistry, Washington State University, Pullman, Washington 99163

Received November 7, 1969

Cyclization of γ-substituted ketones is an important synthetic route to cyclopropylcarbonyl compounds.[2] The base-catalyzed cyclization of 5-halo-2-pentanones to cyclopropyl methyl ketones is well known.[3,4] The analogous formation of cyclopentanone, though conceivable, is not observed. It has been proposed that the preferred cyclization to a three-membered ring is due to solvation.[5] A high degree of solvation of the enolate anion produced by abstraction of the methyl proton would hinder intramolecular displacement, whereas only slight solvation of the enolate anion formed by removal of the methylene proton would be anticipated and intramolecular substitution would be more facile. If this is correct, the relative amounts of cyclopropyl methyl ketone and cyclopentanone should be strongly influenced by the anion-solvating properties of the reaction medium.

Successful cyclization of 5-halo-2-pentanones has been reported only with potassium or sodium hydroxide in water. Other base–solvent systems gave little or no yield of cyclopropyl methyl ketone.[4,6] Thus, only limited information is available concerning the effect of solvent.

Using gas–liquid partition chromatography (glpc), the cyclization of 5-chloro-2-pentanone in a number of base–solvent systems has been examined. Reaction of 5-chloro-2-pentanone with an excess of base produced the yields of cyclopropyl methyl ketone recorded in Table I. Although an estimated 0.2% yield of cyclopentanone would have been detected, no cyclization to form the five-membered ring was observed.

The results presented in Table I demonstrate that essentially quantitative cyclization of 5-chloro-2-pentanone to cyclopropyl methyl ketone can be induced by a variety of base–solvent systems. In view of the preferred cyclization to a three-membered ring even with wide variation of the anion-solvating capacity of the solvent, the solvation proposal is clearly inapplicable to this system. However, the results do not allow for

(1) National Science Foundation Undergraduate Research Participant.
(2) J. M. Conia, *Angew. Chem. Int. Ed. Engl.*, **7**, 570 (1968).
(3) G. W. Cannon, R. C. Ellis, and J. R. Leal, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y. 1963, p 597.
(4) L. I. Smith and E. R. Rogier, *J. Amer. Chem. Soc.*, **73**, 4049 (1951).
(5) E. Schmitz, *Angew. Chem. Int. Ed. Engl.*, **3**, 333 (1964).
(6) Reference 4 reports reaction of 5-chloro-2-pentanone with $LiNH_2$–Et_2O produces only traces of cyclopropyl methyl ketone. However, a 44% yield of 1-acetyl-2-methylcyclopropane is cited in the sodamide-catalyzed cyclization of 5-chloro-2-hexanone in ether.[7]
(7) G. W. Cannon, A. A. Santilli, and P. Shenian, *J. Amer. Chem. Soc.*, **81**, 1660 (1959).

TABLE I
REACTION OF 5-CHLORO-2-PENTANONE WITH VARIOUS BASE–SOLVENT SYSTEMS

Base–solvent	Yield[a,b] of cyclopropyl methyl ketone, %	Base–solvent	Yield[a,b] of cyclopropyl methyl ketone, %
NaOH[c,d]	85	*t*-BuOK–DMSO[e]	84
NaOH–H_2O[d,e]	98	*t*-BuOK–Et_2O[d,e]	100
NaOH–(50% (DMSO–50% H_2O)[e]	96	PhOK–MeOH[f]	40
MeOK–MeOH[e]	93	K_2CO_3–H_2O[d,e]	7
EtOK–EtOH[e]	100	NaOAc–MeOH[g]	0
t-BuOK–*t*-BuOH[e]	98	Et_3N–C_6H_6[e]	0

[a] Measured by glpc. [b] Estimated uncertainty ±2%. [c] No solvent. Conditions: 120 min at 100°. [d] Heterogeneous. [e] Conditions: 15 min at 30°. [f] Conditions: 15 min at 25°. [g] Conditions: 120 min at reflux.

assessment of the relative importance of stabilizing conjugation of the carbonyl group with the developing three-membered ring,[8] transition state entropy effects, or other factors which might be responsible for preferential cyclization to cyclopropyl methyl ketone.

Experimental Section

The base (3 mmol) in 10 ml of solvent was added to 5-chloro-2-pentanone[3] (2 mmol) and isobutylbenzene (Ethyl Corp., internal standard), and the reaction mixture was magnetically stirred for the desired reaction time. A 1-μl sample was injected directly[9] into a Varian Aerograph flame ionization gas chromatograph using a 20 ft × 1/8 in. column of 20% XF-1150 on Chromosorb P operated at 150°. When the solvent was water or 50% DMSO–50% H_2O, 20 ml of *t*-butyl alcohol was added to make the reaction mixture homogeneous before injection. Peak areas were measured with a Disc integrator.

Registry No.—5-Chloro-2-pentanone, 5891-21-4.

(8) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc., B*, 808 (1967).
(9) A glass insert filled with glass wool prevented column contamination.

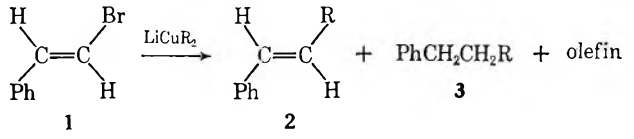
Reduction and Elimination as Side Reactions in the Replacement of Vinylic Bromine Atoms by Means of Lithium–Copper Organometallics

ALLAN T. WORM AND JAMES H. BREWSTER

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received July 28, 1969

The reaction of vinyl halides with lithium dialkylcopper compounds[1-3] appeared promising as a method for the stereochemical correlation of certain chiral olefins. A pilot study with β-bromostyrene (90% *trans*, 10% *cis*) (**1**) has shown that the bromine atom can be replaced by secondary, tertiary, and phenyl groups by this method. Several side reactions, of potential mechanistic interest, were noted. Thus, when the R group was isopropyl, the reduced compound (**3**, R = *i*-C_3H_7) was obtained as 40% of the C_{11} product. With R as *t*-butyl, half of the C_{12} product was **3**, R = *t*-C_4H_9; isobutylene, recovered and identified as the dibromo derivative, was formed during the reaction in this case. Another reduction product, styrene, was always obtained, often as a major by-product. Reaction of the pure stereoisomers of **1** with lithium diphenylcopper gave much biphenyl and styrene. Stilbenes were formed in small amounts, with predominating, but not exclusive, retention of configuration, *trans*-**1** giving 18% *cis*- and 84% *trans*-**2**, and *cis*-**1** giving 70% *cis*- and 30% *trans*-**2**.



Experimental Section[4]

Reaction of Lithium Diisopropylcopper with β-Bromostyrene.—To a suspension of 7.6 g (0.04 mol) of cuprous iodide in 20 ml of ether at −15° was added 0.40 ml (0.076 mol) of commercial 1.9 *M* isopropyllithium in pentane.[5] The solution was cooled to −78°, and 1.5 g (0.008 mol) of β-bromostyrene[6] in 10 ml of ether was added. The mixture was stirred at −78° for 1 hr, warmed to about −15°, and worked up as above to give 0.8 g of a mixture containing (vpc isolation) styrene (trace), 1-phenyl-3-methylbutane (40%), and *trans*-1-phenyl-3-methylbutene (60%). The 1-phenyl-3-methylbutane had nmr ($CDCl_3$) δ 0.95 (d, 6, *J* = 5 cps, CH_3), 1.50 (m, 3, $-CH_2CH-$), 2.60 (m, 2, $ArCH_2$), and 7.17 (m, 5, phenyl); mass spectrum (75 eV) *m/e* (relative intensity) 148 (19) ($C_{11}H_{16}^+$), 92 (100) ($C_7H_8^+$), 91 (64). *trans*-1-Phenyl-3-methylbutene had nmr ($CDCl_3$) δ 1.06 (d, 6, *J* = 6 cps, CH_3), 2.41 (m, 1, >CH), 6.17 (m, 2, vinyl), and 7.2 (m, 5, phenyl); ir (film) 1370, 1385 [*sym* doublet, $-CH(CH_3)_2$], 968 (*trans* $-CH{=}CH-$), and 745, 694 cm^{-1} ($-C_6H_5$); mass spectrum (75 eV) *m/e* (relative intensity) 146 (34) ($C_{11}H_{14}^+$), 131 (100) ($M^+ - 15$), and 91 (49) ($C_7H_7^+$).

Reaction of Lithium Di-*t*-butylcopper with β-Bromostyrene.—To a suspension of 9.5 g (0.05 mol) of cuprous iodide in 20 ml of anhydrous ether at −15° was added 50 ml (0.10 mol) of commercial 2.0 *M* *t*-butyllithium in pentane.[5] The solution was cooled to −78°, 2.0 g (0.011 mol) of β-bromostyrene[6] in 15 ml of ether was added, and the solution was stirred at −78° for 1 hr. It was allowed to warm slowly to 0° with a stream of nitrogen passing through the flask and into a test tube (protected from light) containing bromine in carbon tetrachloride. The bromine solution warmed and decolorized; the solvent was removed; and the residue was distilled to give 1,2-dibromo-2-methylpropane: bp 50° (10 mm); nmr ($CDCl_3$) δ 1.88 (s, 6, CH_3) and 3.88 (s, 2, CH_2Br), comparable with literature values.[7] The main reaction mixture was worked up in the usual way and distilled to give 1.2 g, bp 75–78° (6 mm), of a mixture of 1-phenyl-3,3-dimethylbutane (50%) and *trans*-1-phenyl-3,3-dimethylbutene (50%). The two

(1) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); **90**, 5615 (1968).
(2) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
(3) G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969).

(4) All melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian A-60A instrument and reported in δ units from tetramethylsilane. Mass spectra were obtained on a Hitachi RMU-6A mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord. Unless otherwise stated, vapor phase chromatography (vpc) was carried out on a 25% QF-1 column; analytical compositions have not been corrected for thermal conductivity differences. All reaction vessels were flamed out; anhydrous ether was distilled from an ethereal solution of lithium aluminum hydride.
(5) Obtained from Alfa Inorganics, Inc.
(6) Obtained as a mixture of 90% *trans* and 10% *cis* isomers by action of aqueous sodium carbonate on the dibromide of *trans*-cinnamic acid; see C. Dufraisse, *Ann. Chim.* (Paris), **17**, 133 (1922).
(7) N. S. Bhacca, D. P. Hollis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "Varian NMR Spectra Catalog," Vol. II, National Press, 1963, Spectrum 412.

products were separated by vpc. 1-Phenyl-3,3-dimethylbutane: nmr ($CDCl_3$) δ 0.94 (s, 9, *t*-Bu), 1.50 (m, 2, RCH_2R), 2.55 (m, 2, $ArCH_2R$), and 7.20 (s, 5, phenyl); ir (film) 1370, 1390 (*unsym* doublet, *t*-Bu), and 698, 733 cm^{-1} (C_6H_5); mass spectrum (75 eV) *m/e* (relative intensity) 162 (14) ($C_{12}H_{18}^+$), 57 (100) ($C_4H_9^+$). 1-Phenyl-3,3-dimethylbutene: nmr ($CDCl_3$) δ 0.94 (s, 9, *t*-Bu), 6.24 (s, 2, vinyl), and 7.25 (m, 5, phenyl); ir (film) 1375, 1390 (*unsym* doublet, *t*-Bu), 975 (*trans* –CH=CH–), and 747, 694 cm^{-1} ($-C_6H_5$); mass spectrum (75 eV) *m/e* (relative intensity) 160 (27) ($C_{12}H_{16}^+$), 145 (100) ($M^+ - 15$), 91 (50) ($C_7H_7^+$), and 57 (7) ($C_4H_9^+$).

A repetition, using the products above in place of the β-bromostyrene, gave no change in the composition of the product, indicating that the olefin is not reduced by the organometallic.

Reaction of Lithium Diphenylcopper with *trans*- and *cis*-β-Bromostyrenes.—To a suspension of 5.2 g (0.027 mol) of cuprous iodide in 10 ml of ether at 0° was added 25 ml (0.055 mol) of commercial phenyllithium in 70:30 benzene–ether.[5] The solution was cooled to −78°, and a solution of 1.0 g (0.0055 mol) of vpc-purified *trans*-β-bromostyrene in 10 ml of ether was added. The solution was stirred at −78° for 3 hr and then worked up in the usual way to give 1.0 g of a heavy oil containing large amounts of biphenyl and styrene (80% of the mixture). The stilbene fraction (20%) contained, by vpc analysis and isolation, using a 20% Apiezon L column, 16% *cis*-stilbene, mp 4–7° (lit.[8] mp 5–6°), and 84% *trans*-stilbene, mp 124–125 (lit.[9] mp 124°).

When the above reaction was repeated using vpc-purified *cis*-β-bromostyrene, the stilbene fraction contained 70% *cis*- and 30% *trans*-stilbene.

Registry No.—$LiCuR_2$, R = *i*-C_3H_7, 24012-11-1; $LiCuR_2$, R = *t*-C_4H_9, 23924-63-2; $LiCuR_2$, R = Ph, 23402-69-9; *cis*-**1**, 588-73-8; *trans*-**1**, 588-72-7.

(8) D. S. Brackman and P. H. Plesch, *J. Chem. Soc.*, 2188 (1952).
(9) J. C. Irvine and J. Weir, *ibid.*, **91**, 1384 (1907).

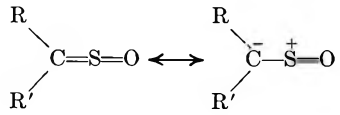
Diphenylcyclopropenethione S-Oxide[1]

J. W. LOWN AND T. W. MALONEY

Department of Chemistry, University of Alberta, Edmonton, Alberta

Received September 8, 1969

The S-oxides of thiocarbonyl compounds have recently attracted considerable attention. Sulfines have been synthesised by Sheppard and Dieckmann,[2] and by Strating and coworkers[3] by dehydrochlorination of sulfinyl chlorides and the oxidation of thio ketones. *syn* and *anti* isomerism in sulfines has been detected by nmr spectroscopy.[2,4] Cycloaddition of enamines occurs across the C=S double bond of sulfines and the related sulfenes by nucleophilic attack at the sulfur,[2,3c] and Ulrich has pointed out that the products obtained are consistent with a bond polarization of the following type.[5]



1

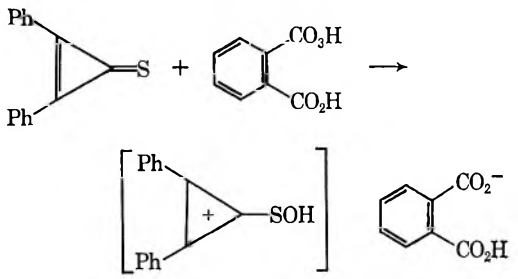
The range of known S-oxides has been extended to include those of thioamides **1** (R′ = NR''_2),[6] thioacid chlorides **1** (R′ = Cl),[7] dithiocarboxylic esters,[3b] and sulfinyl and sulfonyl sulfines.[3a]

Diphenylcyclopropenethione S-oxide was prepared in anticipation of chemical properties quite different from that of S-oxides prepared hitherto.

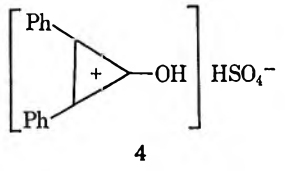
In the initial experiments direct oxidation of diphenylcyclopropenethione (**2**) with lead tetraacetate, following a procedure of Owen,[8] gave diphenylcyclopropenone, elemental sulfur, and lead acetate. Scheme I represents a possible mechanism for this conversion.

The products of the reaction demand attack by the oxidant at the thione carbon rather than at the sulfur. Similar results were obtained with *m*-chloroperbenzoic acid.

A successful route to the S-oxide involved reaction with monoperphthalic acid at low temperature with very rapid work-up of the product. The initial product of the reaction proved to be the salt of the S-oxide with phthalic acid **3** obtained in nearly quantitative yield, analogous to the hydrosulfate of diphenylcyclopropenone (**4**).[9]



3

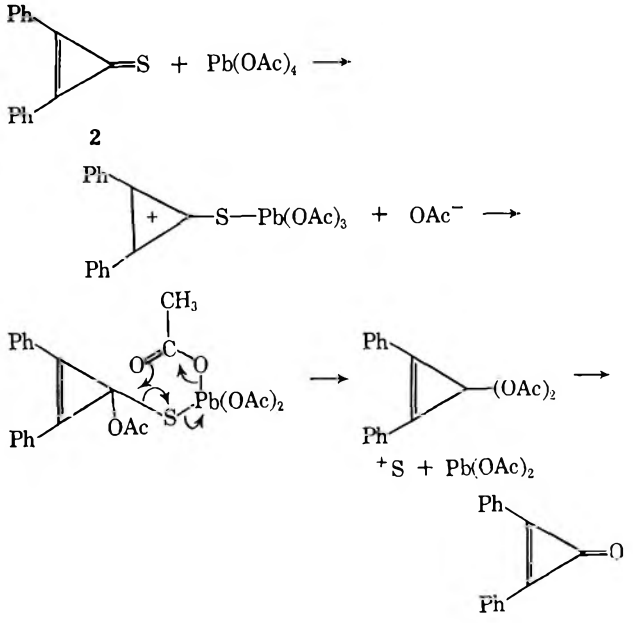


4

Compound **3** was completely insoluble in nonpolar solvents, but the orange solution in acetonitrile allowed determination of the absorption spectrum. This showed maxima at 225, 270, 295, and 310 mμ, consistent with the presence of a diphenylcyclopropene moiety,[9] while the visible absorption maxima at 333 and 438 mμ were tentatively assigned to the S-oxide absorption.[3c] A potassium bromide disk infrared spectrum showed bands at 1685 and 1695 (carboxylate carbonyl), 1842 (cyclopropene C=C stretch[10]), and 3420 cm^{-1} (hydroxyl) consistent with the structure proposed for **3**. The salt **3** was hygroscopic, and, while it was somewhat more stable than the free S-oxide **5**, decomposed slowly at room temperature with the evolution of sulfur dioxide. Owing to the antiaro-

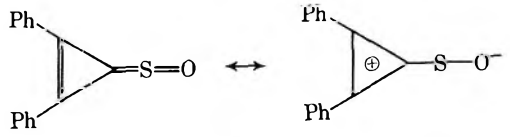
(1) Supported by Grant-A-2305 from the National Research Council of Canada. This support is gratefully acknowledged.
(2) W. A. Sheppard and J. Dieckmann, *J. Amer. Chem. Soc.*, **86**, 1891 (1964).
(3) (a) B. Zwanenberg, L. Thijs, and J. Strating, *Tetrahedron Lett.*, 2871 (1968). (b) B. Zwanenberg, L. Thijs, and J. Strating, *ibid.*, 3453 (1967). (c) J. Strating, L. Thijs, and B. Zwanenberg, *ibid.*, 65 (1966); J. Strating, L. Thijs, and B. Zwanenberg, *Rec. Trav. Chim. Pays-Bas*, **83**, 631 (1964).
(4) S. Ghersetti, L. Lunazzi, G. Maccagnani, and A. Mangini, *Chem. Commun.*, 834 (1962).
(5) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, p 188.
(6) W. Walter and K. D. Bode, *Justus Liebigs Ann. Chem.*, **681**, 64 (1965).
(7) J. F. King and T. Durst, *Tetrahedron Lett.*, 585 (1963).
(8) T. J. Adley, A. K. M. Anisuzzaman, and L. N. Owen, *J. Chem. Soc., C*, 807 (1967).
(9) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1320 (1965).
(10) G. L. Closs, *Advan. Alicycl. Chem.*, **1** (1966).

SCHEME I



matic nature of cyclopropenium anions,[11] the principal resonance contributor existing in the sulfines described above is precluded in **5**.

Instead of this we suggest that diphenylcyclopropenethione S-oxide exists as a type of internal sulfenic acid salt.



5

The free S-oxide **5** could be generated by treatment of the salt with sodium bicarbonate solution and rapid extraction with chloroform. The S-oxide **5** was obtained as a very unstable, orange, crystalline solid, which decomposed violently in bulk when allowed to warm to room temperature, resulting in rapid polymerization accompanied by the evolution of hydrogen sulfide and sulfur dioxide. Fluorenylidene sulfine decomposes slowly at room temperature and rapidly at its melting point, evolving sulfur dioxide,[2] while isopropylidene sulfine polymerizes rapidly at ambient temperatures.[2] Solutions of the S-oxide **5** in methylene chloride or acetonitrile were sufficiently stable to allow determination of the absorption spectrum, which showed absorption maxima at 248 (sh), 270 (sh), 288, and 310 mμ attributed to the cyclopropene moiety[9] and visible bands at 335 and 420 mμ (sh) attributed to the S-oxide grouping.[3c]

Thermal decomposition of **5** in aqueous media gave some hydrogen sulfide and sulfur dioxide, diphenylacetylene (9.4%), and some as yet uncharacterized high molecular weight material. It may be noted that diphenylcyclopropenone affords some diphenylacetylene at much higher temperatures[9] and that photolytic decomposition of a diphenylcyclopropenimine also gives some diphenylacetylene.[12]

Introduction of electron-releasing groups into the aryl rings of **5** should increase the stability of these S-oxides and allow more extensive examination of the chemical properties of these novel compounds. This aspect is currently under investigation.

Experimental Section[13]

Diphenylcyclopropenethione (2).[14]—To a solution of 2.06 g (1.01 mol) of diphenylcyclopropenone[9] in 10 ml of dry cyclohexane was added 2 ml of thionyl chloride and the resultant solution was heated on a steam bath for 15 min. The solvents and unreacted thionyl chloride were removed by distillation and the solid residue was redissolved in 12 ml of dry cyclohexane. To this solution was added dropwise a solution of 1.67 g (0.022 mol) of thioacetic acid in 4 ml of dry cyclohexane. The resulting yellow solid was recrystallized from 80 ml of cyclohexane as deep yellow plates: yield 1.1 g (50%): mp 122° (lit.[12] mp 118.5–119.6°); ir ($CHCl_3$) 1350 cm^{-1} (C=S); nmr ($CDCl_3$) δ 7.36–8.7 (m, aromatic protons).

Anal. Calcd for $C_{15}H_{10}S$: C, 81.09; H, 4.50; S, 14.41; mol wt, 222.0503. Found: C, 81.05; H, 4.51; S, 14.39; mol wt, 222.0502 [mass spectrum (70 eV)].

Oxidation of Diphenylcyclopropenethione in Attempts to Prepare the S-Oxide Derivative 1. A. Using Lead Tetraacetate.—To a solution of 1.11 g (1.005 mol) of **2** in 25 ml of acetic acid was added over 12 min, with stirring, a solution of 4.5 g (1.01 mol) of lead tetraacetate in 190 ml of acetic acid. The solvent was removed by distillation under reduced pressure and the residue was shaken with 20 ml of water. Chloroform (20 ml) was added and the mixture was filtered to remove lead oxide and sulfur. The chloroform layer was dried ($MgSO_4$) and evaporated to yield a red gum. The residual gum was dissolved in the minimum volume of hot cyclohexane, and when the solution was allowed to cool, yellow crystals were deposited, mp 115–119°. Crystallization of the product from cyclohexane gave diphenylcyclopropenone as a white, crystalline solid, mp 120°, identical with an authentic sample.[9]

B. Using *m*-Chloroperbenzoic Acid.—To a solution of 1.11 g (0.005 mol) of **2** in 20 ml of methylene chloride was added over 10 min, with stirring, a solution of 0.90 g (0.0052 mol) of *m*-chloroperbenzoic acid in 15 ml of methylene chloride. The mixture was stirred for 1.5 hr and then washed with a solution of 1.5 g of sodium hydrogen carbonate in 50 ml of water. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave a red gum which was treated with 15 ml of hot cyclohexane. A small quantity of a yellow solid, mp 119°, separated from this solution and was identified as sulfur. The filtrate upon cooling deposited diphenylcyclopropenone (1.55 g, 53%) as a white solid, mp 115–117°, identified by comparison with an authentic sample.[9]

C. Using Monoperphthalic Acid.—A number of trial experiments were necessary using monoperphthalic acid before the optimum conditions were realized. The unsuccessful attempts were largely due to the thermal instability of diphenylcyclopropenethione S-oxide.

(11) R. Breslow, *Chem. Eng. News*, **43**(26), 90 (1965).

(12) N. Obata, A. Hamada, and T. Takizawa, *Tetrahedron Lett.*, 3917 (1969).

(13) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer, and only the principal, sharply defined peaks are reported. Nmr spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on *ca.* 10–15% (w/v) solutions in $CDCl_3$, with tetramethylsilane as a standard. Line positions are reported in parts per million from the reference. Absorption spectra were recorded in spectrograde solvents on a Beckman DB recording spectrophotometer. Mass spectra were determined on an Associated Electrical Industries MS-9 double-focussing, high-resolution spectrometer. The ionization energy, in general was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. Microanalyses were carried out by Dr. C. Daesslé, Organic Microanalysis Ltd., Montreal, Quebec, and by Mrs. D. Mahlow of this department.

(14) Diphenylcyclopropenethione has been reported previously by T. Eicher and G. Frenzel, *Z. Naturforsch.*, **20b**(3), 274 (1965), only in a preliminary communication and no experimental details were given.

A solution of 1.11 g (0.005 mol) of 2 in 50 ml of methylene chloride was cooled to −40°. To this solution was added dropwise over 10 min, with stirring, a solution of 0.985 g (0.0054 mol) of the acid in 20 ml of ether, while the temperature was maintained below −30°. Stirring was continued for 10 min, and after the addition had been completed, the yellow solid which had slowly separated during the addition was collected and identified as diphenylcyclopropenethione S-oxide hydrogen phthalate (**3**): yield 1.99 g (96%); mp 95–98°; ir (KBr disk) 1068 cm^{-1} (m, C=S=O[2]), 1685 (s), 1695 (s, C=O), 1842 (m) (cyclopropene C=C stretch[10]), and 3420 (br, OH); λ_{max} (CH_3CN) 225 mμ (log ε 4.17), 270 (4.21), 295 (sh, 3.86), 310 (sh, 3.77), 333 (3.89), and 478 (3.37).

Anal. Calcd for $C_{23}H_{16}SO_5 \cdot {}^1/_2H_2O$: C, 66.81; H, 4.14. Found: C, 66.71; H, 4.27.

The yellow salt was ground into fine particles and added in one portion to a stirred solution of 50 ml of 4% sodium hydrogen carbonate at a temperature of ≯5°. A reaction ensued with the evolution of carbon dioxide, and **5** was deposited as a bright orange solid, yield 0.8 g (67.1%), mp 40° dec. The product was collected by filtration on a previously cooled apparatus, washed with ice water, and stored and dried in a vacuum desiccator containing pellets of sodium hydroxide.

Further purification was found not to be possible owing to the instability of the product. The microanalytical figures correspond to the inclusion of water in the crystals of this hygroscopic material: ir ($CHCl_3$) 1068 and 1129 cm^{-1} (C=S=O[2]); nmr ($CDCl_3$) δ 7.0–8.3 (m, aromatic protons); λ_{max} (CH_2Cl_2) 248 (sh), 270 (sh), 288, 310, 335, and 430 mμ (sh).

Anal. Calcd for $C_{15}H_{10}SO$: C, 75.60; H, 4.23; S, 13.43. Found: C, 73.16; H, 4.42; S, 12.28. Calcd: C:S, 5.63. Found: C:S, 5.96.

The S-oxide decomposed violently when the bulk material was allowed to reach room temperature and gave a polymer with the evolution of sulfur dioxide and hydrogen sulfide, which were detected by their action on acid dichromate paper and moist lead acetate paper, respectively.

Controlled Decomposition of Diphenylcyclopropenethione S-Oxide (1).—The S-oxide was freshly prepared exactly as described previously and decomposed by steam distillation Hydrogen sulfide and sulfur dioxide were recognized as decomposition products by their characteristic odors and by positive reactions with lead acetate and potassium dichromate papers, respectively. When no more steam-volatile material distilled, the steam distillate (250 ml) was extracted with ether and the ether extract was dried ($MgSO_4$). Evaporation of the solvent afforded an off-white solid, yield 0.083 g (9.4%), mp 60°, unambiguously identified as diphenylacetylene by comparison with an authentic sample (mixture melting point and superimposable infrared spectra). The residue consisted of as yet unidentified high molecular weight material.

Registry No.—**1**, 23516-87-2; **2**, 2570-01-6; **3**, 23516-89-4; **5**, 12408-01-4.

Correlation of the Reactivity of Thiophene Derivatives[1]

DONALD S. NOYCE, CHRISTOPHER A. LIPINSKI, AND GORDON MARC LOUDON[2]

Department of Chemistry, University of California, Berkeley, California 94720

Received August 18, 1969

We have undertaken an investigation of the solvolytic reactivity of a variety of heterocyclic systems. In a recent publication from these laboratories, we have shown[3] that the rates of solvolysis of a variety of substituted furfuryl alcohol derivatives could be smoothly correlated with σ^+ constants. An alternative approach is to examine the possibility that the heterocyclic ring system may be assigned an effective σ^+ constant, for itself. Two additional recent studies have pursued this line of endeavor. Hill and Gross have studied the rates of solvolysis of a wide variety of heterocyclic analogs of benzyl acetate,[4] and Taylor has recently examined the pyrolysis of 1-aryl-2-phenylethyl acetates.[5]

It is the purpose of this note to present data on the rates of solvolysis of 1-(2-thienyl)ethyl *p*-nitrobenzoate and 1-(3-thienyl)ethyl *p*-nitrobenzoate and on the acid-catalyzed isomerization of *cis*-2-styrylthiophene, and to examine the correlation of these rates with other types of reactions. The relationship between benzyl systems and aromatic electrophilic substitution has been explored by several groups, including studies by Dewar,[6] Fierens,[7] and Streitwieser.[8] These authors have pointed out that the reactivities of benzyl systems and their analogs are useful probes for the ability of the aromatic moiety to stabilize a positive charge. Further, very good correlations are observed with σ^+ substituent constants with a wide variety of reactions.

Our new data are summarized in Tables I and II.

TABLE I

RATE OF SOLVOLYSIS OF SUBSTITUTED ETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compound	Temp, °C	k, sec^{-1}
1-(2-Thienyl)ethyl *p*-nitrobenzoate	25.00	$2.27 \pm 0.04 \times 10^{-6}$
	45.00	$2.61 \pm 0.05 \times 10^{-5}$
1-(3-Thienyl)ethyl *p*-nitrobenzoate	75.00	$9.7 \pm 0.25 \times 10^{-6}$
1-(p-Anisyl)ethyl *p*-nitrobenzoate[a]	45.00	2.30×10^{-5}
	75.00	5.02×10^{-4}

[a] From ref 3.

TABLE II

RATE OF ISOMERIZATION OF *cis*-1-ARYL-2-PHENYLETHENES IN AQUEOUS SULFURIC ACID

Compound	H_2SO_4, wt %	H_0	k_{obsd}, sec^{-1}
cis-2-Styrylthiophene	51.6	−3.60	4.0×10^{-3}
cis-4-Methoxystilbene[a]	51.6	−3.60	4.6×10^{-3}

[a] Interpolated from D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 4633 (1968).

The solvolysis rate of 1-(2-thienyl)ethyl *p*-nitrobenzoate is very similar to that of 1-(*p*-anisyl)ethyl *p*-nitrobenzoate.[3] The reduced reactivity of 1-(3-thienyl)-ethyl *p*-nitrobenzoate is reminiscent of the reduced reactivity of the 3 position in detritiation of thiophene studied by Melander and Olsson[9] and the protodesilylation of thiophene derivatives, studied by Eaborn and his coworkers.[10]

(1) Supported in part by grants from the National Science Foundation (GP-1572 and GP-6133X).

(2) National Institutes of Health Predoctoral Fellow, 1966–1968 (GM-32822).

(3) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(4) E. A. Hill and M. L. Gross, Abstracts of papers, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p O-170.

(5) R. Taylor, *J. Chem. Soc., B*, 1397 (1968).

(6) M. J. S. Dewar and R. J. Sampson, *ibid.*, 2946 (1957).

(7) M. Planchen, P. J. C. Fierens, and R. H. Martin, *Helv. Chim. Acta*, **42**, 517 (1959).

(8) *Cf.* A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, p 370.

(9) K. Halvorson and L. Melander, *Ark. Kemi*, **8**, 29 (1956); B. Ortman and S. Olsson, *ibid.*, **15**, 275 (1960).

(10) C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961); F. B. Deans and C. Eaborn, *ibid.*, 2299 (1959).

To examine the relationship of this information to that for a variety of other reactions of thiophene derivatives we have collected the relevant data in Table III. If a single substituent constant will satisfactorily correlate all of the information, then eq 1 should hold, (where ρ is that for the benzene family)

$$\log k_{\text{thiophene}} - \log k_{\text{benzene}} = \rho \cdot \sigma^{+} \qquad (1)$$

for a series of compounds with the substituting group in both the 2 and the 3 position. A plot of the data from Table III is given in Figure 1.

TABLE III

RELATIVE REACTIVITY OF THIOPHENE DERIVATIVES

1. Electrophilic Substitution Reactions

	Reaction	ρ[a]	Log (k_2/k_{Ph})[b]	Log (k_3/k_{Ph})[c]	Ref
A.	Bromination	−12.1	9.70		*d, e*
B.	Chlorination	−10.0	7.11		*d, f*
C.	Protodetritiation	−8.5	7.38	4.27	*g, h*
D.	Protodeboronation	−5.2	5.93	3.85	*i, j*
E.	Iododeboronation	−4.76	3.99	2.84	*k*
		−4.59	3.68		*l*
F.	Protodesilylation	−4.78	3.70	2.06	*l*
G.	Mercuration	−4.00	4.9		See text
H.	Protodemercuration	−2.44	3.23		See text
I.	Nitration	−6.5	1.7–2.9		See text

2. Side-Chain Carbonium Ion Reactions

J.	Solvolysis of 1-arylethyl *p*-nitrobenzoate	−6.0	4.8	3.0	*m*
K.	Isomerization of *cis*-1-aryl-2-phenylethene	−3.3	2.55		*m*
L.	Rearrangement of arylpropenylcarbinol	−2.9	1.7		*n*
M.	Pyrolysis of 1-aryl-2-phenylethyl acetate	−0.66	0.52	0.25	*g*
N.	Ir frequency of acetylarene				See text

[a] ρ for named reaction with substituted benzenes. [b] Rate for 2-thienyl system relative to benzene. [c] Rate for 3-thienyl system relative to benzene. [d] L. W. Stock and F. W. Baker, *J. Amer. Chem. Soc.*, **84**, 1661 (1962). [e] P. Linda and G. Marino, *Chem. Commun.*, 499 (1967). [f] G. Marino, *Tetrahedron*, **21**, 843 (1965). [g] Reference 5. [h] Reference 9. [i] K. V. Nahabedian and H. G. Kuivila, *J. Amer. Chem. Soc.*, **83**, 2167 (1961). [j] R. D. Brown, A. S. Buchanan, and A. A. Humffray, *Aust. J. Chem.*, **18**, 1521 (1965). [k] R. D. Brown, A. S. Buchanan, and A. A. Humffray, *ibid.*, **18**, 1527 (1965). [l] Reference 10. [m] This study. [n] E. A. Braude and E. S. Stern, *J. Chem. Soc.*, 1097 (1947); E. A. Braude and J. S. Fawcett, *ibid.*, 4158 (1952).

Data for many electrophilic aromatic substitution reactions, including bromination (A), chlorination (B), protodetritiation (C), iododeboronation (E), and protodesilylation (F) are satisfactorily correlated with a single substituent constant for the 2-thienyl moiety. Protodeboronation deviates substantially, and Taylor[5] has suggested that this datum may be in error. Additionally, carbonium ion reactions in the side chain correlate satisfactorily, with the exception of the data for the infrared carbonyl stretching frequency reported by Traylor and Ware[11] which predicts a σ^{+} value clearly inconsistent with the rest of the information discussed here.

Data for some other reactions do not correlate at all well, and there appear to be some good reasons for this. Nitration by nitric acid–perchloric acid has been examined recently by Coombes, Moodie, and Schofield.[12] They have concluded that nitration of thiophene is encounter controlled. Thus the reactivity of thiophene, reported as 50 or 150 times benzene in two solvent systems, is not a true measure of relative reactivity.[12] Similar reservations apply to the reported ratio of 850 for nitration in acetic acid–acetic anhydride.[13]

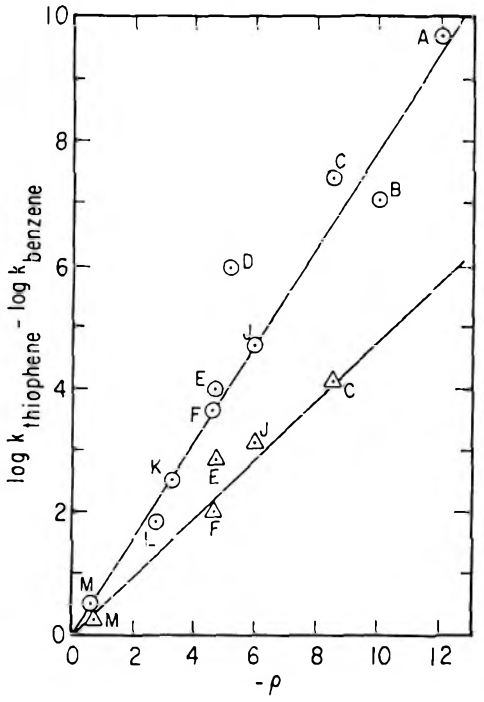


Figure 1.—Correlation of thiophene reactivity with electrophilic reactions in benzene: ⊙, 2-substituted thiophenes; △, 3-substituted thiophenes.

Taylor[5] has presented the arguments for excluding the demercuration by hydrochloric acid[14] from any correlation, because of the well-known coordination propensities of mercury. Similar considerations are likely to apply to the mercuration by mercuric acetate in acetic acid.[15]

In addition to these tabulated reactions, it is apparent that acetylation, for which there is fragmentary information, would correlate well, as thiophene is reported[16] to have nearly the same reactivity as anisole.

With the above reservations in mind, generally satisfactory correlation of a wide variety of reactions involving electron-deficient intermediates may be achieved with a σ^{+} constant for the 2-thienyl group of −0.80, and for the 3-thienyl group of −0.47.

In summary, it might be mentioned that the electronic nature of the thiophene ring shows a dual characteristic. In the original Hammett (σ) sense, the thiophene ring is somewhat electron withdrawing, as evidenced by the fact that thiophene-2-carboxylic acid is a stronger acid than benzoic acid.[17] It thus appears that the difference between σ and σ^{+} for the

(11) T. G. Traylor and J. C. Ware, *J. Amer. Chem. Soc.*, **89**, 2304 (1967).

(12) R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc., B*, 800 (1968); J. G. Hoggett, R. B. Moodie, and K. Schofield, *ibid.*, 1 (1969).

(13) E. Imoto and R. Motoyama, *Kogyu Kagaku Zasshi*, **55**, 305 (1952).

(14) R. D. Brown, A. S. Buchanan, and A. A. Humffray, *Aust. J. Chem.*, **18**, 1513 (1965).

(15) R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi*, **78** 962 (1957).

(16) P. Linda and G. Marino, *Tetrahedron*, **23**, 1739 (1967).

(17) W. Ostwald, *Z. Phys. Chem.*, **3**, 369 (1889).

thiophene ring is substantially larger than for the simple substituents on the benzene ring.

Experimental Section[18]

Preparation of Materials.—2-Acetylthiophene was reduced with sodium borohydride to afford 1-(2-thienyl)ethanol, which was converted into 1-(2-thienyl)ethyl *p*-nitrobenzoate, mp 64.5–65.8° from 20:1 hexane–ethyl acetate, using *p*-nitrobenzoyl chloride and pyridine.

Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.33; H, 4.24; N, 5.06; S, 11.50.

1-(3-Thienyl)ethanol.—The procedure of Gronowitz[19] for the preparation of 3-thienyllithium was followed. To this reagent at −70°, a solution of acetaldehyde in ether was added. The mixture was allowed to warm to room temperature and was worked up in the usual manner. There was obtained 65% 1-(3-thienyl)ethanol, bp 102–105° (15 mm). The ir spectrum and nmr spectrum were consistent. Conversion into the ester was accomplished in the usual manner to give 1-(3-thienyl)ethyl *p*-nitrobenzoate, colorless needles from hexane–ethyl acetate (20:1), mp 54.0–54.5°.

Anal. Found: C, 56.49; H, 3.99.

cis-2-Styrylthiophene.—Condensation of thiophene-2-carboxaldehyde with phenylacetic acid afforded α-phenyl-β-(2-thienyl)-acrylic acid, mp 190–191.5° (lit.[20] mp 188.5–190°). Decarboxylation with copper and quinoline[21] afforded a mixture from which a small amount of the *trans* isomer crystallized. The remaining oil was separated by glpc over 20% SE-30 on 60–80 mesh Chromosorb, at 180°. The early fraction was *cis*-2-styrylthiophene. The spectral characteristics showed the absence of *trans* olefinic absorption in the ir and an uv spectrum distinct from that of authentic *trans*-2-styrylthiophene.

Anal. Calcd for $C_{12}H_{10}S$: C, 77.38; H, 5.41; S, 17.21. Found: C, 77.06; H, 5.42; S, 17.21.

Kinetic Methods.—The procedures for the solvolysis rate measurements have been described.[3] The rate of the acid-catalyzed isomerization was followed by uv spectrometry, using procedures like those described previously.[22]

Registry No.—1-(2-Thienyl)ethyl *p*-nitrobenzoate, 23516-71-4; 1-(3-thienyl)ethyl *p*-nitrobenzoate, 23516-72-5; *cis*-2-styrylthiophene, 23516-73-6.

(18) Melting points and boiling points are uncorrected. Analyses were performed by the Microanalytical Laboratory of The Department of Chemistry, University of California.

(19) S. Gronowitz, *Ark. Kemi*, **8**, 441 (1955).

(20) G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.*, **19**, 1243 (1966).

(21) R. E. Buckles and N. G. Wheeler, *Org. Syn.*, **33**, 88 (1953).

(22) D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 4633 (1968).

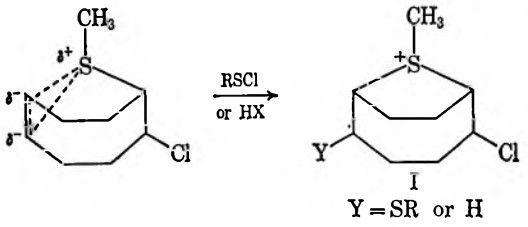
The Reaction of 4-Methylmercaptocyclohexene with Hydrogen Iodide

MARTIN B. DINES AND WOLFGANG MUELLER

Corporate Research Laboratories,
Esso Research and Engineering Company,
Linden, New Jersey 07036

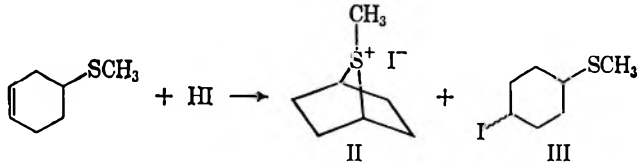
Received October 20, 1969

It has recently been shown that activation of the double bond of the monoadduct of 1,5-cyclooctadiene and methanesulfenyl chloride toward a second molecule of the sulfenyl chloride practically precludes isolation of the monoadduct even when the diolefin is initially present in tenfold excess.[1] To account for this effect, transannular activation of the double bond by the methylmercapto group forming a 9-methyl-9-thiabicyclo[4.2.1]nonanesulfonium ion (I) was invoked and subsequently verified by its isolation.



To test the limits of such transannular interactions, the behavior of 1,4-cyclohexadiene under similar conditions was studied. The difference between the two cases was signaled by the observation that, unlike 1,5-cyclooctadiene, the six-membered-ring analog readily affords a monoadduct with methanesulfenyl chloride. A diadduct can subsequently be prepared which is identical with the product of 1,4-cyclohexadiene and 2 mol of the sulfenyl chloride in one step. Contrary to the finding with the eight-membered-ring diene, it could be demonstrated that the remaining double bond of the monoadduct (sans the chlorine atom) is somewhat *deactivated* toward attack of a second methanesulfenyl chloride in competition with cyclohexene.[2] This deactivation may arise from adverse steric effects of the methylmercapto group which may effectively limit the corridors of approach of an incoming group and thereby hinder addition. These ostensibly contradicting observations may result from subtle differences in geometry between the two monoadducts (evident in their molecular models).[3] Also, in contrast with the results of 1,5-cyclooctadiene, the presently formed diadduct is covalent, and, as expected, indications are that it is a mixture of isomeric dimethylmercaptodichlorocyclohexanes.

Participation of the 4-methylmercapto group was, however, clearly evident in the reaction of 4-methylmercaptocyclohexene with hydrogen iodide. In methylene chloride, a white precipitate which proved to be 7-methyl-7-thiabicyclo[2.2.1]heptanesulfonium iodide (II) was isolated. This substance was identical in all respects with the compound reported by Corey and Block which results from addition of methyl iodide to 7-thiabicyclo[2.2.1]heptane.[4]



An oil containing predominantly *cis*- and *trans*-4-methylmercaptoiodocyclohexane (III) could be isolated from the mother liquors.[5] The structural assignment

(1) W. H. Mueller, *J. Amer. Chem. Soc.*, **91**, 1223 (1969).

(2) The disappearance under competitive conditions of 4-methylmercaptocyclohexene and cyclohexene in the presence of methanesulfenyl chloride was followed by gc. It was found that the latter is consumed 1.17 times as fast as the former.

(3) One alternative rationale for this deactivation involves a fast and reversible attack of electrophiles upon the sulfur atom. The adverse effect can then be both steric and electronic in origin.

(4) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

(5) Although this mixture showed but a single sharp $-SCH_3$ signal in the nmr (in several solvents), gc indicated three products of composition 42:7.5:50.5. The minor isomer is believed to be 3-methylmercaptoiodocyclohexane, the major isomers III.

of III is primarily based on the fact that silver ion induced elimination of hydrogen iodide from the isomeric mixture yields only 4-methylmercaptocyclohexene.

Addition of hydrogen iodide to a solution of 4-methylmercaptocyclohexene in trifluoroacetic acid in an nmr tube followed by spectral examination of the solution clearly indicated *ca.* 15% formation of II, the only other product being III. The formation of compounds II and III is believed to be kinetically controlled since their noninterconvertibility under the conditions employed was demonstrated.

The structure of both products (and the near absence of 3-methylmercaptoiodocyclohexane among them) clearly implies some degree of participation of the sulfur group across the ring in the mechanism of their formation.[6] However, the seemingly inconsistent nature of the results thus far garnered precludes any confident mechanistic interpretation of such interactions.

Experimental Section

General.—Chemicals and solvents used were not specially purified unless specifically stated. Melting and boiling points are uncorrected. Infrared spectra were run on a Beckman IR-20 and nmr spectra were obtained on a Varian A-60. All reactions described were carried out under nitrogen. All gc was done on an Aerograph 1520 instrument with 5% SE-30 on Chromosorb W 5 ft × 0.25 in. columns.

4-Methylmercapto-5-chlorocyclohexene.—To a methylene chloride solution of 1,4-cyclohexadiene (0.10 mol in 50 ml) maintained at −20° a solution of 8.25 g (0.10 mol) of methanesulfenyl chloride in the same solvent was slowly added. After 15 min, the reaction was warmed to room temperature and the solvent was evaporated to yield 15.2 g of clear oil, a single component as assayed by gc. The nmr spectrum ($CDCl_3$) of the oil contained a narrow multiplet at δ 5.60 (2 H), a broad quartet at 4.28 (1 H, $>C<^{H}_{Cl}$), and a multiplet with a strong singlet at 2.2–3.1 (8 H). Further evidence that a double bond was maintained was the presence of weak absorptions at 3050 and 1665 cm^{-1} in the thin-film infrared spectrum. This material was used without further purification.

Diadduct of 1,4-Cyclohexadiene with Methanesulfenyl Chloride.—It was found that the identical product, a faintly yellowish oil, was obtained by either subjecting 1,4-cyclohexadiene under the contitions described above to 2 mol of the sulfenyl halide or by treating 4-methylmercapto-5-chlorocyclohexene with 1 mol of the sulfenyl chloride under those conditions. The identity was ascertained by a comparison of nmr and infrared spectra as well as gc. The oil does not crystallize when standing at room temperature indefinitely and is freely soluble in ether, although insoluble in water.

4-Methylmercaptocyclohexene.—A solution of the monoadduct of methanesulfenyl chloride with 1,4-cyclohexadiene (22.3 g, 0.135 mol) in 25 ml of dry ether was added carefully to a slurry of 3.38 g (0.089 mol) of lithium aluminum hydride (Alfa Inorganics) in 150 ml of dry ether. The reaction was allowed to proceed for 3 days at room temperature; then it was worked up according to the method described in Fieser and Fieser ("Reagents for Organic Synthesis," p 584). From the ether 16.4 g of clear oil was obtained. After a distillation [33° (4 Torr)] 11.0 g of oil, $n^{20}D$ 1.5145, was obtained. The 4-methylmercaptocyclohexene thus afforded had in its nmr spectrum ($CDCl_3$) two narrow multiplets at δ 5.66 (2 H) and 2.10 (10 H). The infrared spectrum (thin film) showed the presence of a double bond ($\nu_{C=C}$ 1655 cm^{-1}).

Anal. Calcd for $C_7H_{12}S$: C, 65.59; H, 9.44; S, 24.97. Found: C, 65.70; H, 9.75; S, 24.99.

Treatment of 4-Methylmercaptocyclohexene with Hydrogen Iodide.—Dry hydrogen iodide (Matheson) was bubbled into a solution of 2.0 g of 4-methylmercaptocyclohexene in 25 ml of methylene chloride. After about 1 hr, the solution became cloudy and a white precipitate fell out. The gas flow was continued for 0.5 hr and the flask was then stoppered and allowed to stand overnight. From this reaction 0.180 g of white solid, II, mp 140–142°, was collected by filtration and ether washing (lit.[4] mp 135.5–136°). The nmr matched that described previously[4] as well.

(6) As implied in footnote 3, the "sulfur group" spoken of may or may not be a sulfonium species reversibly formed by hydrogen iodide addition.

Registry No.—4-Methylmercaptocyclohexene, 23600-52-4; hydrogen iodide, 10034-85-2.

Acknowledgment.—The authors are grateful to Mr. Raymond Kelly for his able assistance.

An Improved Preparation of Tertiary Amine N-Oxides

J. CYMERMAN CRAIG AND K. K. PURUSHOTHAMAN

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122

Received November 10, 1969

Preparation of tertiary amine N-oxides by the use of hydrogen peroxide[1] in water, acetic acid, or acetic anhydride is slow and frequently leads to low yields of products containing varying amounts of hydrogen peroxide[2] and requiring further purification.[3] Organic peracids[4] such as peracetic, perbenzoic, and monoperphthalic acids may be used, but give salts which require further processing. In some cases when the carbon skeleton is highly branched, Cope eliminations have been reported to occur during oxidation of the amine.[5]

We wish to report an improved preparation of amine N-oxides which proceeds rapidly to completion at or below room temperature, requires no basification or extraction procedures, and affords the pure N-oxides in excellent yields, employing entirely nonaqueous solvents.

Using equimolar quantities of pure[6] *m*-chloroperbenzoic acid and the amine, reaction in chloroform at 0–25° gave a solution of the amine N-oxide *m*-chlorobenzoate, from which the pure N-oxide was readily obtained by passage through a column of alumina. The amine N-oxides shown in Table I were obtained in the yields stated. With this procedure it was not necessary to protect the hydroxyl group of morphine as the methoxymethyl ether[7] before carrying out the reaction.

Experimental Section

General Procedure.—A solution of 1.0 mol of *m*-chloroperbenzoic acid in chloroform was added gradually at 0–5° to an ice-

(1) J. Meisenheimer and K. Bratring, *Justus Liebigs Ann. Chem.*, **397**, 286 (1913); D. Jerchel and G. Jung, *Chem. Ber.*, **85**, 1130 (1952); M. Izumi, *Pharm. Bull.* (Tokyo), **2**, 279 (1954).

(2) K. Bodendorf and B. Binder, *Arch. Pharm.* (Weinheim), **287**, 326 (1954); C. C. Sweeley and E. C. Horning, *J. Amer. Chem. Soc.*, **79**, 2620 (1957).

(3) A. C. Cope and P. H. Towle, *ibid.*, **71**, 3426 (1949); E. C. Taylor and N. E. Boyer, *J. Org. Chem.*, **24**, 275 (1959).

(4) M. A. Stahmann and M. Bergmann, *ibid.*, **11**, 586 (1946); D. Swern, *Chem. Rev.*, **45**, 1 (1949).

(5) A. C. Cope, F. M. Acton, and R. A. Pikes, *Org. React.*, **11**, 379 (1960).

(6) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

(7) F. N. H. Chang, J. F. Oneto, P. P. T. Sah, B. M. Tolbert, and H. Rapoport, *ibid.*, **15**, 634 (1950).

TABLE I

Amine N-oxide	Yield, %
Trimethylamine N-oxide	96
Tribenzylamine N-oxide	96
Dimethylaniline N-oxide	94
Nicotine N′-oxide	98
Nicotine N,N′-dioxide	98[a]
Codeine N-oxide	98
Morphine N-oxide	86[b]

[a] Using 2.0 molar equiv of *m*-chloroperbenzoic acid. [b] The solvent in this experiment was tetrahydrofuran. Methylation with diazomethane gave codeine N-oxide, identical by melting point, mixture melting point, and tlc.

cooled, stirred solution of 1.0 mol of the amine in chloroform. Stirring was continued for a total of 3 hr, during which the mixture was allowed to come to room temperature. The solution was passed through a column of alkaline alumina (100–200 mesh, *ca.* 20 times the weight of the combined starting materials), and traces of unreacted amine were removed by washing with chloroform. Elution with methanol–chloroform (1:3) then gave the amine N-oxide in the yield stated in Table I, after crystallization from alcohol–ether or acetone–hexane. All compounds had the melting points reported in the literature, and gave single spots on tlc.

Registry No.—*m*-Chloroperbenzoic acid, 937-14-4; trimethylamine N-oxide, 1184-78-7; tribenzylamine N-oxide, 6852-46-6; dimethylaniline N-oxide, 874-52-2; nicotine N,N′-dioxide, 2055-29-0; codeine N-oxide, 3688-65-1; morphine N-oxide, 639-46-3.

Acknowledgment.—Financial assistance from USPHS Research Grant HE-05881 is gratefully acknowledged.

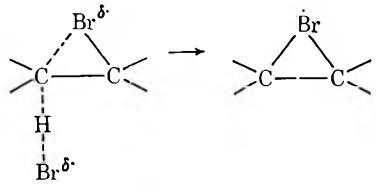
Bridged Polycyclic Compounds. LX. *syn*-Bromine Activation in Free-Radical Bromination of Janusenes[1]

STANLEY J. CRISTOL, MICHAEL A. IMHOFF, AND DAVID C. LEWIS

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received October 6, 1969

Recently, several workers have postulated neighboring-group participation by bromine in the radical bromination of a variety of alkyl bromides.[2-5] They suggest that the bromo substituents assist in the abstraction of a β hydrogen by bridging in the transition state. An *anti* orientation between the β hydrogen and the bromo substituent is presumably required



in the transition state for this mechanism to obtain. We wish now to report an example in which the β hydrogen of an alkyl bromide is activated in a compound where that hydrogen is *cis* to and eclipsed by the bromo substituent.

When janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene, 1)[6] was treated with bromine in carbon tetrachloride, it was observed that replacement of the second hydrogen atom occurred more rapidly than that of the first. From the data in Table I, we calculate[7] that k_2/k_1 in eq 1 is 1.4 at 72°. As

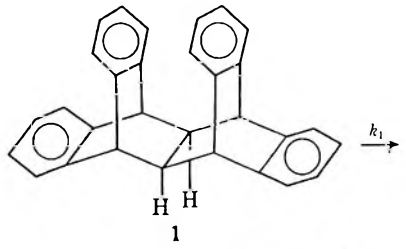
TABLE I

PRODUCT DISTRIBUTIONS FROM PHOTOBROMINATION OF JANUSENE (1) IN CARBON TETRACHLORIDE AT 72°

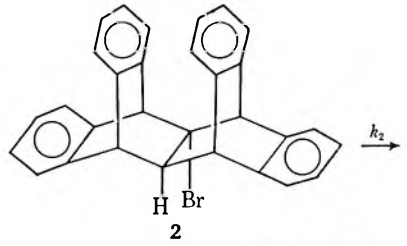
% 1	% 2	% 3
76	19	5
66	25	9
51	28	20
50	30	20
36	31	33
32	26	42
31	28	41[a]
8	14	78

[a] These data were from a reaction that was run until only 40% of the initial bromine added had been consumed.

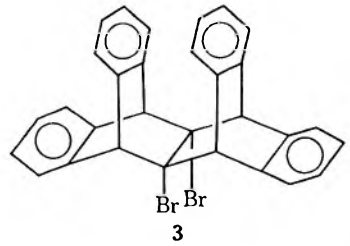
there are two reactive hydrogen atoms in 1 and only one in 2, this means that, compared with hydrogen, bromine activates the β hydrogen by a factor of 2.8 Similar data at 12° gave a factor of 5.2.



1



2



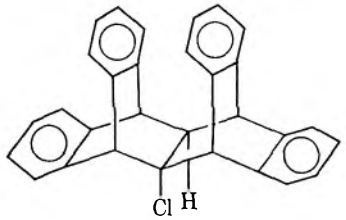
3

(1)

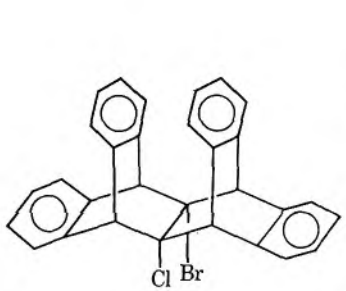
Unlike bromine, chlorine decreased reactivity. A competitive photobromination experiment between 5a-chlorojanusene (4) and janusene (1) at 72° revealed

(1) Previous paper: S. J. Cristol, R. J. Bopp, and A. E. Johnson, *J. Org. Chem.*, **34**, 3574 (1969).
(2) W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).
(3) P. S. Skell, D. L. Tuleen, and P. D. Readio, *ibid.*, **85**, 2849 (1963).
(4) P. S. Skell and P. D. Readio, *ibid.*, **86**, 3334 (1963).
(5) J. Traynham and W. Hines, *ibid.*, **90**, 5208 (1968).
(6) S. J. Cristol and D. C. Lewis, *ibid.*, **89**, 1476 (1967).
(7) S. Glasstone, "Textbook of Physical Chemistry," 2nd ed, Van Nostrand-Reinhold Co., New York, N. Y., 1946, p 1075.

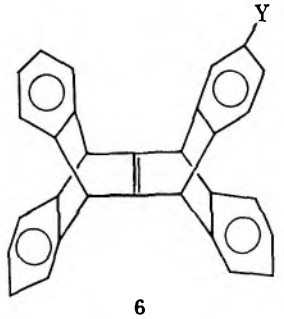
that chlorine had a deactivating effect upon the β hydrogen compared with hydrogen ($k_4/0.5\ k_1 = 0.5$). From a competitive bromination experiment between 5a-bromojanusene (2) and 5a-chlorojanusene (**4**) k_2/k_4



4



5

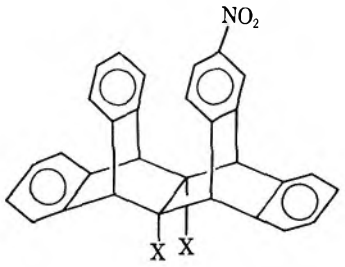


6

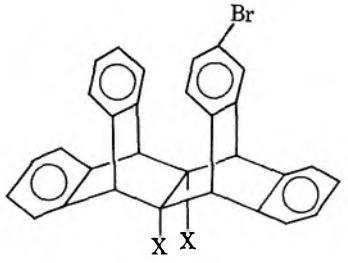
was 6.0 (calcd 5.6). These results are consistent with those in acyclic systems.[8] All of the products from these radical bromination experiments were prepared independently by additions to dehydrojanusene (**6H**).

It has been suggested[9,10] that the apparent enhanced reactivity of hydrogen atoms β to bromine atoms described earlier and ascribed to bridged bromine radicals is an artifact which disappears under appropriate experimental conditions. For example, Tanner and his coworkers[10] showed that the 2 position of 1-bromobutane was not significantly different in reactivity from other 1-substituted butanes toward bromine atoms. However, attack at this position led *via* elimination of a bromine atom, to 1-butene which then added bromine to give 1,2-dibromobutane. On the other hand, radicals formed at carbon atoms other than C-2 suffered capture by hydrogen bromide formed during the course of the reaction. Put another way, a β-bromo radical led principally to dibromide product, while other radicals returned in large part to starting material. The conclusion[9,10] that at least a part, and perhaps all, of what has been ascribed to anchimeric assistance has this alternative explanation now seems inescapable, and presumably many or all such cases may have similar explanations.

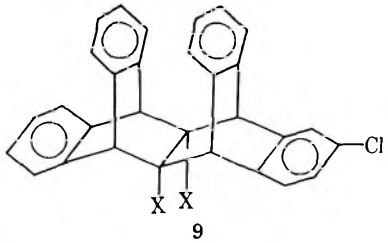
For this reason, we needed to show that an elimination–addition mechanism involving olefin **6H** as an intermediate did not obtain. To this end, bromination of two face-ring-labeled janusenes, **7a** and **8a**, and one lateral ring-labeled compound, **9a**, was carried out. In each case, the corresponding dibromide, **7b**, **8b**, and **9b** was obtained without scrambling of the ring label. If the ring-labeled intermediate **6Y** had been produced, a mixture of face- and ring-labeled dibromojanusenes should have resulted. It has also been reported that 2-bromo-2,3-dimethylbutane is brominated in the dark.[11] This was ascribed to an ionic mechanism. **1** and **2** are inert to bromine in the dark in the absence of Lewis acids.



7a, X = H
b, X = Br



8



9

Clearly the removal of a hydrogen atom from 5a-bromojanusene (2) cannot involve a transition state similar to that proposed[2–5] for the presumed anchimeric assistance, as an *anti* configuration from 2 would have prohibitively high strain. It would seem possible to explain the enhanced reactivity (note that the factor of 6 is not a large one) by the assumption of a *syn* hyperconjugative electron delocalization in the *syn*-bromo radical and in the transition state leading to it.

Experimental Section

All nmr spectra were taken on a Varian A-60A instrument as saturated solutions in chloroform-d_1, using tetramethylsilane as an internal standard. All chemical shifts are reported in τ units (τ = 10.00 for tetramethylsilane). Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr. All elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were uncorrected.

Preparation of 5a-Bromojanusene (2).—Hydrogen bromide was bubbled through a solution of 405 mg (1.07 mmol) of dehydrojanusene (6),[12] mp 361°, in 100 ml of CH_2Cl_2 for 30 min. After 1.5 hr, the solvent was evaporated and the residue was dissolved in 100 ml of ether, treated with charcoal, and dried ($MgSO_4$). Evaporation of the solvent from the filtered mixture under reduced pressure gave 418 mg (85%) of 5a-bromojanusene (2): mp 262–263° dec, after recrystallization from benzene; pmr ($CDCl_3$) τ 6.79 (t, 1, J = 2 Hz), 5.74 (d, 2, J = 2 Hz), 5.23 (s, 2), and 2.80–3.40 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{21}Br$: C, 78.09; H, 4.56. Found: C, 78.06; H, 4.68.

(8) H. Singh and J. M. Tedder, *J. Chem. Soc.*, 4737 (1964).
(9) W. O. Haag and E. I. Heiba, *Tetrahedron Lett.*, 3683 (1965).
(10) D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *J. Amer. Chem. Soc.*, **91**, 7398 (1969).
(11) G. A. Russell and H. C. Brown, *ibid.*, **77**, 4025 (1955).
(12) The preparation of dehydrojanusene *via* treatment of **3** with zinc will be reported later, as will its characterization.

Preparation of 5a,11a-Dibromojanusene (3).—To a solution of 850 mg (2.23 mmol) of dehydrojanusene (6) in 100 ml of CH_2Cl_2 was added 360 mg (2.23 mmol) of bromine. Work-up as described above gave 1.05 g (89%) of 5a,11a-dibromojanusene (3).[13] Crystallization was from acetone–95% EtOH: mp 268–270° dec; pmr ($CDCl_3$) τ 5.13 (s, 4) and 2.87–3.30 (m, 16, aromatics); ν_{max} 1450, 1165, 850, 753, and 685 cm^{-1} (KBr).

Preparation of 5a,11a,Dibromojanusene (3). Photobromination.—A solution of 10.3 g (27.1 mmol) of janusene (1) in 130 ml of CCl_4 was irradiated and heated to reflux with a 150-W tungsten bulb. To this solution was added, over a 30-hr period, 9.2 g (57.5 mmol) of bromine and 290 mg of benzoyl peroxide in 30 ml of CCl_4. The reaction was halted after 68 hr. During the course of the reaction dibromide **3** precipitated out of solution and, after the reaction was stopped, it was allowed to stand for 2 days so that more dibromide **3** could crystallize. The dibromide was filtered and the filtrate was diluted with 100 ml of CH_2Cl_2, washed four times with 300-ml portions of water, and then dried ($MgSO_4$). The mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was crystallized from CH_2Cl_2–benzene to give about 2 g of dibromide **3**. This was combined with the dibromide obtained from the initial filtration to give 13.7 g (94%) of 5a,11a-dibromojanusene. Recrystallization was from acetone–95% EtOH: mp 268–270° dec: pmr ($CDCl_3$) τ 5.13 (s, 4) and 2.87–3.30 (m, 16, aromatics); ν_{max} 1450, 1165, 850, 753, and 685 cm^{-1} (KBr).

Anal. Calcd for $C_{30}H_{20}Br_2$: C, 66.67; H, 3.70. Found: C, 66.55; H, 3.77.

Preparation of 5a-Chlorojanusene (4).—Hydrogen chloride was bubbled through a solution of 300 mg (0.79 mmol) of dehydrojanusene (6) in 60 ml of CH_2Cl_2 for 30 min at room temperature. The reaction mixture was allowed to stand for 3 hr and then worked up as described for **2**. Crystallization from acetone–95% EtOH gave 232 mg (70%) of 5a-chlorojanusene (4): mp 260–262° (lit.[6] mp 260–262°); pmr ($CDCl_3$) τ 7.04 (t, 1, J = 2 Hz), 5.77 (d, 2, J = 2 Hz), 5.43 (s, 2), and 2.80–3.40 (m, 16, aromatics).

Preparation of 5a-Bromo-11a-chlorojanusene (5).—A solution of bromine chloride in CH_2Cl_2 was added dropwise to a solution of 150 mg (0.40 mmol) of dehydrojanusene (6) in 25 ml of CH_2Cl_2 until the brownish red color persisted. The solution was boiled to drive off the excess bromine chloride and then diluted with 50 ml of CH_2Cl_2. This solution was washed twice with 100-ml portions of 10% Na_2CO_3 solution and twice with 100-ml portions of water and dried ($MgSO_4$). Filtration and evaporation under reduced pressure gave a residue, weighing 172 mg (85%), of 5a-bromo-11a-chlorojanusene (5). Crystallization was from acetone–95% EtOH: mp 319–322° dec; pmr ($CDCl_3$) τ 5.35 (s, 2), 5.15 (s, 2), and 2.83–3.30 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{20}BrCl$: C, 72.65; H, 4.04. Found: C, 72.41; H, 4.08.

Photobromination of Janusene (1).—In a 50-ml, one-neck, round-bottom flask, a solution of 200 mg (0.52 mmol) of janusene (1) in 25 ml of CCl_4 was irradiated and heated to reflux with a 60-W tungsten bulb. To this solution was added 10 ml of 0.06 M Br_2–CCl_4 solution. After 10 hr the reaction mixture was colorless. It was washed with 100 ml of water, twice with 60-ml portions of 10% Na_2CO_3 solution, twice with 60-ml portions of water, and once with 100 ml of saturated NaCl solution. The CCl_4 solution was dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure, giving 230 mg of a yellow oil. The oil was identified by its pmr spectrum as 36% unreacted janusene (1), 31% 5a-bromojanusene (2), and 33% 5a,11a-dibromojanusene (3).

Photobromination of a Mixture of Janusene (1) and 5a-Chlorojanusene (4).—A mixture of 168 mg (0.44 mmol) of janusene (1), 184 mg (0.44 mmol) of 5a-chlorojanusene (4), and 15 mg (0.09 mmol) of *p*-dinitrobenzene was dissolved in 50 ml of CCl_4. This solution was irradiated and heated to reflux with a 60-W tungsten bulb. To this solution was added 6 ml of 0.15 M Br_2–CCl_4 solution, and the reaction was stopped after 1.5 days. The reaction mixture was worked up as described above and the product was identified by pmr as 14% janusene (1), 43% 5a-chlorojanusene (4), 14% 5a-bromojanusene (2), 21% 5a,11a-dibromojanusene (3), and 8% 5a-bromo-11a-chlorojanusene (5). The yield, based upon internal standard (*p*-dinitrobenzene), was 94%, which indicated that no preferential decomposition of any of the products had occurred.

Photobromination of a Mixture of 5a-Bromojanusene (2) and 5a-Chlorojanusene (4).—A mixture of 117 mg (0.25 mmol) of 5a-bromojanusene (2), 188 mg (0.45 mmol) of 5a-chlorojanusene (4), and 18 mg of *p*-dinitrobenzene, dissolved in 50 ml of CCl_4, was treated with 7 ml of 0.04 M Br_2–CCl_4. The reaction procedure was essentially the same as the previous experiment. The product mixture was identified by its pmr spectrum as 15% 5a-bromojanusene (2), 54% 5a-chlorojanusene (4), 22% 5a,11a-dibromojanusene (3), and 9% 5a-bromo-11a-chlorojanusene (5). The yield, based upon internal standard, was 98%.

Photobromination of Fβ-Nitrojanusene (7a).—In a procedure idential with those previously described, 2.16 g (5.06 mmol) of Fβ-nitrojanusene (7a) in 120 ml of CCl_4 was treated with 1.62 g (10.1 mmol) of bromine. The isolated oil was identified from its pmr spectrum as 5a,11a-dibromo-14-nitrojanusene (7b). Crystallization from acetone–95% EtOH gave 1.7 g (58%) of white crystals: mp 261–263° dec; pmr ($CDCl_3$) τ 5.07 (s, 2), 5.00 (s, 2) 3.29 (m, 5, aromatics), 2.77 (m, 8, aromatics), and 2.38 (s, 2, aromatics). The pmr spectrum indicated that the nitro substituent in the product is in the Fβ position.[6]

Anal. Calcd for $C_{30}H_{19}NO_2Br_2$: C, 61.54; H, 3.25. Found: C, 61.56; H, 3.41.

Photobromination of Fβ-Bromojanusene (8a).—In a manner identical with that previously described, 934 mg (2.02 mmol) of Fβ-bromojanusene (8a) in 50 ml of CCl_4 was treated with 650 mg (4.04 mmol) of bromine. The yield of 5a,11a,14-tribromojanusene (8b), which was identified by its pmr spectrum, was 800 mg (58%). The aromatic absorptions in the pmr spectrum showed that the bromine substituent was in the F ring.[6] Crystallization was from acetone–95% EtOH: mp 248–249° dec; pmr ($CDCl_3$) τ 5.24 (s, 1), 5.16 (s, 3), 3.26 (m, 7, aromatics), and 2.90 (m, 8, aromatics).

Anal. Calcd for $C_{30}H_{19}Br_3$: C, 58.16; H, 3.07. Found: C, 58.41; H, 3.02.

Photobromination of Lβ-Chlorojanusene (9a).—In a manner identical with that previously described, 925 mg (2.22 mmol) of Lβ-chlorojanusene (9a) in 50 ml of CCl_4 was treated with 710 mg (4.44 mmol) of bromine. The isolated oil, 730 mg, was identified by pmr as 85% 5a,11a-dibromo-2-chlorojanusene (9b). The aromatic absorptions in this spectrum indicated that the chlorine substituent was in the L ring, since the F-substituted compound would have given a spectrum similar to that of tribromide **8b**. Crystallization was from acetone–95% EtOH: mp 265–267° dec; pmr ($CDCl_3$) τ 5.25 (s, 1), 5.18 (s, 3), 3.37 (m, 8, aromatics), and 2.90 (m, 7, aromatics).

Anal. Calcd for $C_{30}H_{19}Br_2Cl$: C, 62.66; H, 3.31. Found: C, 63.09; H, 3.38.

Registry No.—**1**, 23646-37-9; **2**, 23646-38-0; **3**, 23646-39-1; **4**, 23646-40-4; **5**, 23646-41-5; **7a**, 17344-73-9; **7b**, 23646-43-7; **8a**, 23646-46-0; **8b**, 23646-44-8; **9a**, 17604-06-7; **9b**, 23646-45-9.

Acknowledgments.—The authors are indebted to the National Science Foundation, to the Institute of General Medical Sciences (Public Health Service Grant GM-12139), and to the University of Colorado for support of this work.

(13) The structure of dibromide **3** has been determined from X-ray analysis by W. M. Macintyre and A. Tench.

$[(C_6H_5)_3P]_3RhCl$

Tris(triphenylphosphine)rhodium(I) chloride

At Alfa, we also stock technical know-how.

Ask us for any of over 2500 inorganic and organometallic research chemicals, ultrapure chemicals, and pure metals, and you'll get off-the-shelf, immediate delivery.

Ask us for technical assistance, and you'll get that too. That's what distinguishes Alfa from the order takers.

While investigating the properties of phosphine complexes of transition metals, Wilkinson and co-workers found that this red, crystalline, air-stable solid derivative of rhodium has several extremely useful applications. Soluble in non-polar solvents such as benzene and methylene chloride, it reacts rapidly and reversibly with molecular hydrogen, acting as an effective *low temperature, low pressure hydrogenation catalyst* (1). The catalyst is specific for olefins and acetylenes – other groups such as C=O or NO_2 are unaffected. Hydrogenation is stereospecific for *cis*-addition, generally without isomerization of the olefin (1,2).

Other important applications of the Wilkinson catalyst include aldehyde and acyl *decarbonylation* (3,4):

$$(Ph_3P)_3RhCl + RCOCl \rightarrow (Ph_3P)_2Rh(CO)Cl + RH$$

(a reaction which becomes catalytic above 180°C) and, under some conditions, as an oxidation catalyst, converting cyclohexene to cyclohexene-1-one and cyclohexene-1-ol (5).

Research samples are offered by Alfa as follows:

63111 $[(C_6H_5)_3P]_3RhCl$ 1 g. – $9.50
5 g. – 7.00/g.
25 g. – 5.60/g.

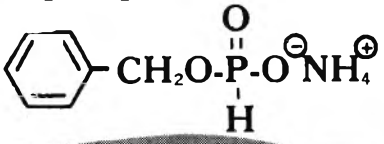
Write for your free Alfa '70 Catalog. Alfa Inorganics, Inc., 80 Congress Street, Beverly, Mass. 01915. Tel: (617) 922-0768.

References:

1. J.A. Osborn, F.H. Jardine, J.F. Young, and G. Wilkinson. *J. Chem. Soc.*, (A), *1966*, 1711.
2. (a) A.J. Birch and K.A.M. Walker, *J. Chem. Soc.* (C), *1966*, 1894.
   (b) C. Djerassi and J. Gutzwiller, *J.A.C.S.* *88*, 4537, (1966).
3. M.C. Baird, J.T. Mague, J.A. Osborn, and G. Wilkinson, *J. Chem. Soc.*, A, 1347, (1967).
4. J. Tsugi and K. Ohno, *J.A.C.S.*, *88*, 3452, (1966), and references therein.
5. V.P. Kurkov, J.Z. Pasky, and J.B. Lavigne, *J.A.C.S.*, *90*, 4743, (1968) and references therein.

Ventron
ALFA INORGANICS, INC.

Benzyl phosphite ammonium salt



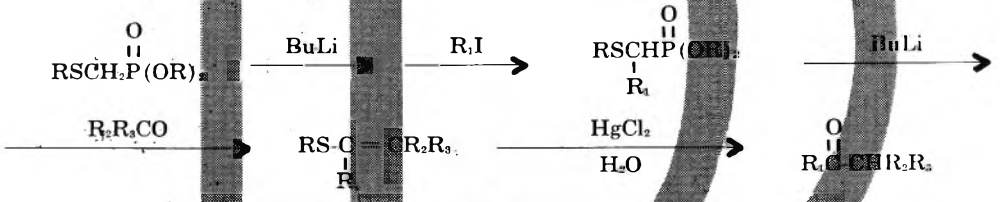
The anhydride of monobenzyl phosphite and diphenyl phosphate, $C_6H_5CH_2OPH(O)OP(O)(OC_6H_5)_2$, is a useful reagent in the preparation of deoxyribonucleoside-3'-phosphates.[1,2] It must, however, be prepared *in situ* immediately before use and is conveniently prepared from a salt of monobenzyl phosphite and diphenyl chlorophosphate (Aldrich Cat. No. D20,655-5).[1,3]

[1]H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, New York, N.Y., 1969, pp. 22-23.
[2]D. M. Brown, in "Advances in Organic Chemistry, Methods and Results," Vol. III, R. A. Raphael, E. C. Taylor, and H. Wynberg, eds.), Interscience Publishers New York, N.Y., 1963, p. 101.
[3]N. S. Corby, G. W. Kenner, and A. R. Todd, *J. Chem. Soc.* 3663 (1952).

#15,622-1 Benzyl phosphite ammonium salt 10g.—$9.00 50g.—$37.50

Diethyl ethylthiomethylphosphonate
$CH_3CH_2SCH_2P(O)(OCH_2CH_3)_2$

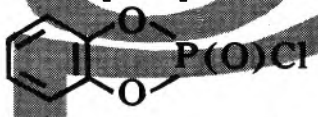
E. J. Corey[1] described the preparation of unsymmetrical ketones as follows:



[1]E. J. Corey and J. I. Shulman, *J. Org. Chem.*, 35, 777 1970).

#15,653-1 Diethyl ethylthiomethylphosphonate 5g.—$6.50 25g.—$19.80

o-Phenylene phosphorochloridate

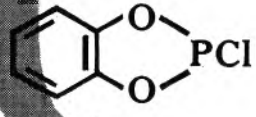


This reagent reacts with primary aliphatic alcohols to produce the corresponding o-hydroxyphenyl phosphate ester,[1] which is readily dephenylated by bromine water[1] or by hydrogenolysis with Adams' catalyst[2] to produce the phosphate monoester of the alcohol. The reagent appears to be one of the most convenient and powerful phosphorylating agents available.[1]

[1]T. A. Khawaja and C. B. Reese, *J. Amer. Chem. Soc.*, 88, 3446 (1966) and references therein.
[2]J. Calderon and C. Moreno, *An. Real Soc. Espan., Fis. Quim., Ser. B*, 56, 603 (1960); *Chem. Abstr.*, 55, 883] (1961).

#15,614-0 o-Phenylene phosphorochloridate 5g.—$6.00 25g.—$23.85

o-Phenylene phosphorochloridite



This powerful phosphorylation agent is utilized in peptide synthesis.[1] Alcohols react with o-phenylene phosphorochloridite to produce alkyl-o-phenylene phosphites which react with iodine to yield the corresponding alkyl iodides.[2] This method is especially useful for alcohols prone to elimination.

[1]M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, New York, N.Y., 1966, pp. 90-91 and references therein.
[2]E. J. Corey and J. E. Anderson, J. Org. Chem., 32, 4160 (1967).

#15,576-4 o-Phenylene phosphorochloridite 10g.—$5.50 50g.—$14.00

For our latest Catalog, write to—

Aldrich Chemical Company, Inc.

CRAFTSMEN IN CHEMISTRY

940 WEST SAINT PAUL AVENUE MILWAUKEE, WISCONSIN 53233