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Synthesis and Chemistry of Some Tricyclo[4.2.1.0^{2,5}]nonane Derivatives[1]

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Syntheses of *exo*- and *endo*-tricyclo[4.2.1.0^{2,5}]nonanes (**1** and **2**) and several of their derivatives are described. The key intermediates were *exo*- and *endo*-tricyclo[4.2.1.0^{2,5}]non-7-enes (**23** and **24**) which were prepared by cyclization of diiodides **25** and **26** with phenyllithium. Reactions involving carbonium ions generated at C-7 invariably produced derivatives of alcohol **35** as the major product.

Our continuing interests in the synthesis and chemistry of tricyclic ring systems prompted a survey of reactions designed to lead to the *exo*- and *endo*-tricyclo[4.2.1.0^{2,5}]nonane systems **1** and **2**. Although numerous reports dealing with derivatives of these systems have appeared in the recent literature,[2] the parent hydrocarbons **1** and **2** have not yet been described. Furthermore, the syntheses of related systems are either not readily adaptable to large-scale work or to systematic derivitization.

1

2

The systems in question are of importance in that they bridge the gap between the relatively well-known tetrahydrodicyclopentadiene[3] (**3**) and the more recently investigated tricyclo[3.2.1.0^{2,4}]octyl systems[4] **4**.

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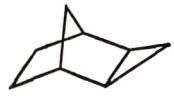

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Thus, a study of the chemistry of suitable derivatives of **1** and **2** is clearly of importance before complete analysis of the behavior of these substituted norbornyl systems can be made.[5] This paper enumerates some synthetic studies in this area as well as the results of some carbonium ion reactions in this series.

Results and Discussion

Synthetic Studies.—Initial studies involved reactions of derivatives of tricyclo[3.2.1.0^{2,4}]octylcarbinyl systems (**5**) which by ring expansion would be expected to lead to tricyclo[4.2.1.0^{2,5}]nonyl systems (*e.g.*, **6**). This method was appealing owing to the availability of the precursors *via* the reaction of ethyl diazoacetate with norbornene.[6]

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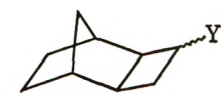

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Amine **9** was readily obtained by reduction of amide **8** with lithium aluminum hydride. Deamination of **9**

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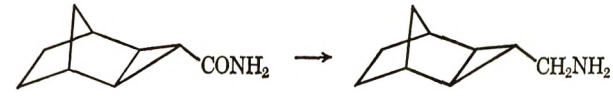


8 **9**

(1) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 38S.

(2) For some other recent syntheses of these ring systems, see (a) L. G. Cannell, *Tetrahedron Lett.*, 5967 (1966); (b) L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **88**, 623 (1966); (c) C. D. Smith, *ibid.*, **88**, 4273 (1966); (d) G. N. Schrauzer and P. Glockner, *Chem. Ber.*, **97**, 2451 (1964); (e) R. L. Cargill and M. R. Willcott, III, *J. Org. Chem.*, **31**, 3938 (1966); (f) D. Scharf and F. Korte, *Tetrahedron Lett.*, 821 (1963).

(3) (a) S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jurale, *J. Amer. Chem. Soc.*, **84**, 3918 (1962); (b) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Jap.*, **38**, 1318 (1965); (c) P. D. Bartlett, Abstracts, 12th National Organic Chemistry Symposium, June 1951, p 1.

(4) (a) R. R. Sauers, J. A. Beisler, and H. Feilich, *J. Org. Chem.*, **32**, 569 (1967); (b) K. B. Wiberg and G. Wenzinger, *ibid.*, **30**, 2278 (1965); (c) A. K. Colter and R. C. Musso, *ibid.*, **30**, 2462 (1965); (d) K. B. Wiberg and W. J. Bartley, *J. Amer. Chem. Soc.*, **82**, 6375 (1960); (e) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

(5) For other data on these and related systems, see G. D. Sargent, *Quart. Rev.* (London), **20**, 319 (1966).

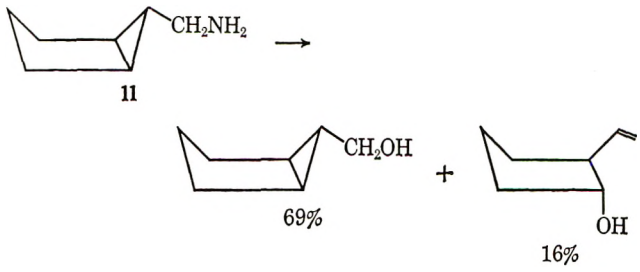
(6) R. R. Sauers and P. E. Sonnet, *Tetrahedron*, **20**, 1029 (1964). In the present work variable amounts (12–18%) of an isomer of the *exo-anti* adduct **7** were obtained. That this material was the *exo-syn* adduct was shown by ethoxide-catalyzed epimerization.

with nitrous acid led to a complex mixture of products. The major constituent (44%) was shown to be identical with the carbinol (**10**) obtained by reduction of **7**. The

10

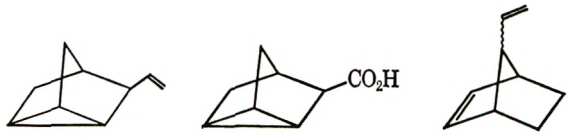
other two important products were present in nearly equal amounts and were characterized as vinyl alcohols as shown by the presence of appropriate infrared and nmr absorptions.[7]

These results are not surprising in view of the recent findings of Bond and Scerbo with the closely related bicyclic system **11**.[8] These workers found no cyclobutyl product in a similar reaction sequence.



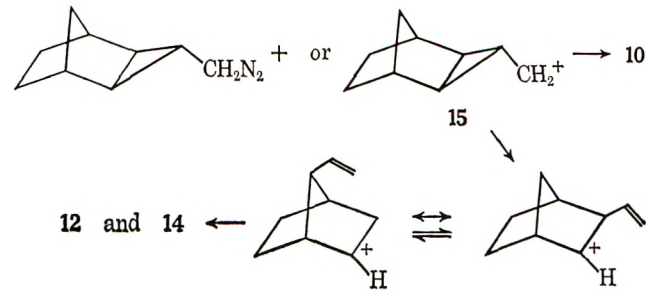
11 69% 16%

In a subsequent experiment, amine **9** was subjected to deamination under poorly solvating conditions.[9] The hydrocarbon fraction (34%) from this reaction was isolated and shown to consist of two isomers in a 7:1 ratio. The major product proved to be 3-vinylnortricyclene (**12**) as shown by degradation to the known acid **13**. The minor constituent was most likely *anti*- or *syn*-7-vinylnorbornene (**14**) as evidenced by the appearance of typical vinyl absorptions superimposed on norbornene absorptions in the infrared and nmr spectra.

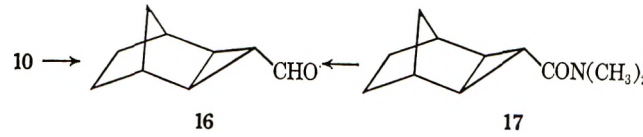


12 **13** **14**

These rearrangements seem best rationalized by competitive ring opening of the cation **15** or the corresponding diazonium ion with the formation of a substituted norbornyl ion. Subsequent loss of a proton or reaction with solvent would lead to the observed products[10] **12** and **14**.

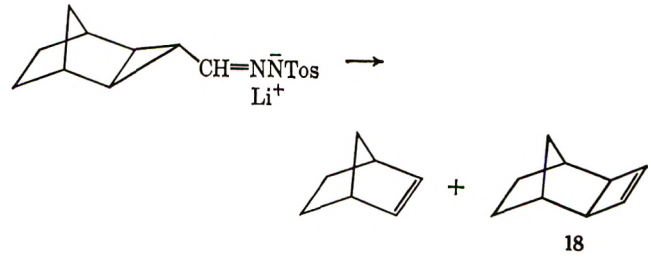


Attention was next turned to the possibility of utilizing carbenic routes. A relatively high degree of success has been attained in the preparation of cyclobutenes from cyclopropylcarbinyl derivatives in this way.[11] In the case at hand, it was necessary to prepare the aldehyde **16** for conversion into the tosylhydrazone. Mild oxidation of alcohol **10** with manganese dioxide[12] or partial reduction[13] of the amide **17** with a mixed hydride both served to produce the aldehyde **16** in modest yields.



16 **17**

Pyrolysis of the lithium salt of the tosylhydrazone of **16** led[14] to a mixture of two hydrocarbons in a 1:3:4 ratio.



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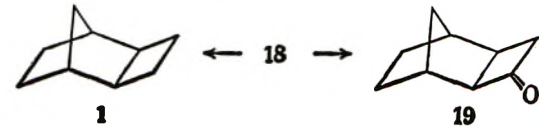
The minor product proved to be norbornene. The major product was a C_9H_{12} hydrocarbon which showed a strong absorption at 14.30 μ in the infrared spectrum and two protons as a sharp singlet at 5.85 ppm in the nmr spectrum.[15] Chemical evidence in support of structure **18** was provided by quantitative catalytic reduction to *exo*-tricyclo[4.2.1.$0^{2,5}$]nonane (**1**) which was identical with the sample prepared independently below. In addition, hydroboration of **18** followed by chromic acid oxidation gave a ketone **19** with a carbonyl



1 **19**

absorption band at 5.62 μ in agreement with the cyclobutanone structure.

(7) The complete structure proofs of these products have not been completed. Evidence for the presence of *syn*-7-vinyl-*exo*-norbornanol is presented in the Ph.D. Thesis of P. E. Sonnet, Rutgers, The State University, 1963. That the other product is not a 3-vinylnorboranol has been shown by P. E. Pfeffer (Ph.D. Thesis, Rutgers, The State University, 1966).

(8) F. T. Bond and L. Scerbo, *Tetrahedron Lett.*, 4255 (1965). For a detailed discussion of the intermediates in these reactions, see K. B. Wiberg and A. J. Ashe, III, *J. Amer. Chem. Soc.*, **90**, 63 (1968), and P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966).

(9) J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Shechter, *ibid.*, **87**, 661 (1965).

(10) The hydrocarbon fraction from the solvolysis of norbornyl brosylate has been shown to consist of 98% nortricyclene and 2% norbornene. *Cf.* S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, **87**, 376 (1965).

(11) L. Friedman and H. Shechter, *ibid.*, **82**, 1002 (1960); W. Kirmse and K. H. Pook, *Chem. Ber.*, **98**, 4022 (1965).

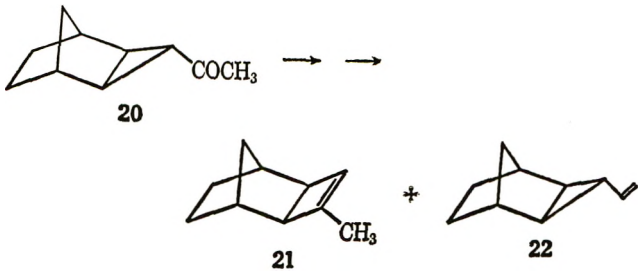
(12) L. Crombie and J. Crossley, *J. Chem. Soc.*, 4983 (1963).

(13) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **81**, 502 (1959).

(14) G. M. Kaufman, J. A. Smith, G. G. Van der Stouw, and H. Shechter, *ibid.*, **87**, 935 (1965).

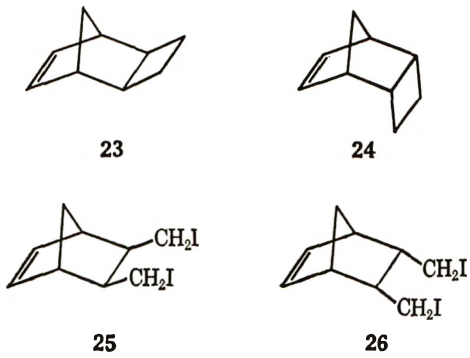
(15) Cyclobutene displays a singlet at 5.95 ppm; see S. Borčić and J. D. Roberts, *ibid.*, **87**, 1057 (1965). A compound assigned this structure by M. Hara, Y. Odiara, and S. Tsutsumi [*Tetrahedron*, **22**, 95 (1966)] showed peaks of unspecified multiplicity at 5.87, 2.87, and 2.22 ppm. Our material is apparently *not* the same substance.

This synthetic method was also extended to the methyl homolog (**21**) *via* a sequence starting with the methyl ketone **20**. A small amount (12%) of a second



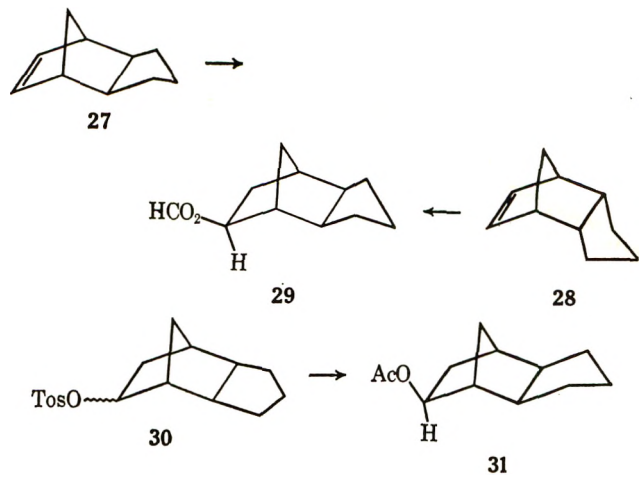
product was also obtained. Infrared and nmr absorptions characteristic of vinyl groups appeared in the spectra of this product. These findings and analogy[14] support **22** as a reasonable structure for this product.

The second phase of the synthetic studies dealt with possible methods for construction of the two tricyclo[4.2.1.0^{2,5}]non-7-enes **23** and **24**. These olefins were considered key intermediates for the completion of the mechanistic studies already mentioned.

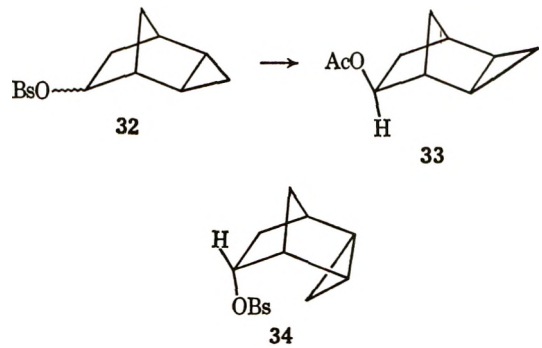


The availability of the two isomeric diiodides **25** and **26**[16] prompted a study of possible ring-closure reactions. Smooth cyclization was effected with phenyllithium in a synthesis patterned after that developed for bicyclo[4.2.0]octane.[17] The nature of the cyclized products was revealed by the presence of absorptions in both the infrared and nmr spectra attributable to norbornene-type double bonds.[18] Quantitative catalytic hydrogenation led to the saturated hydrocarbons **1** and **2** with the absorption of 1 mol of hydrogen in both cases. The identity of the reduction product of **23** with that of **18** firmly establishes the structure and stereochemistry of these compounds.

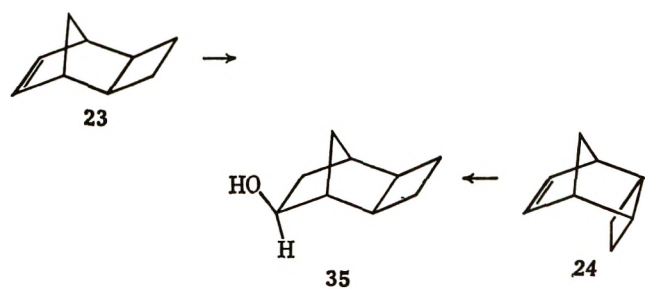
Addition and Solvolysis Reactions.—In this section product studies of reactions involving carbonium-ion intermediates at C-7 will be discussed. By way of comparison, the homologous series **3** and **4** do not present a completely consistent picture. For example, addition of formic acid to either olefin **27** or **28** produced the formate **29**.[3a] Likewise, acetolysis of any of the four tosylates with gross structure **30** produced the *exo-exo* system **31** as the major product.



An interesting observation was that only three of the four isomeric tricyclo[3.2.1.0^{2,4}]octyl brosylates (**32**) reacted analogously to **27** yielding **33**. The *endo-endo* system **34** apparently underwent a more complex rearrangement.[4b]



With this background it was not surprising that addition of formic acid to either **23** or **24** yielded essentially the same mixtures of formates in the ratio 98:2. After conversion into alcohols, the major product was isolated and shown to be identical with the hydroboration–oxidation product (**35**) of the *exo* olefin **23**. The reaction sequence clearly produces the product (**35**) with *exo*



stereochemistry by analogy with norbornene and **27**.[19] The minor alcohol formed in the addition was assumed to be the *endo* derivative **36** based on retention time comparisons with a sample prepared by hydroboration–oxidation of **24**.[20]

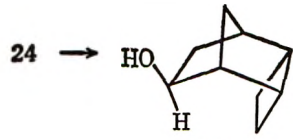
(16) K. Alder and W. Roth, *Chem. Ber.*, **87**, 161 (1954).

(17) K. Alder and H. A. Dortman, *ibid.*, **87**, 1492 (1954).

(18) The chemical shifts of the olefinic protons are sensitive to the stereochemistry of the attached rings. The downfield shift in the absorption of the olefinic protons in **24** relative to **23** of *ca.* 0.5 ppm has also been noted in various norbornadiene dimers by D. R. Arnold, D. J. Trecker, and E. B. Whipple [*J. Amer. Chem. Soc.*, **87**, 2596 (1965)] and attributed to van der Waals interactions.

(19) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961); S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

(20) The chemical shifts of the carbinol protons in **35** and **36** provide a clear example of steric deshielding.[18] Whereas the carbinol proton of **35** and *exo*-norbornanol have similar chemical shifts (3.55 and 3.52 ppm, respectively), the analogous proton in **36** appears at 4.37 ppm. For other examples, see S. Winstein, P. Carter, F. A. L. Anet, and A. J. F. Bourn, *ibid.*, **87**, 5247 (1965).



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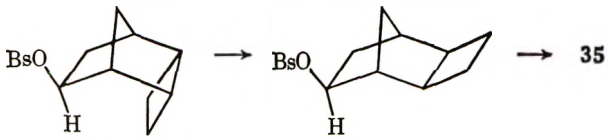
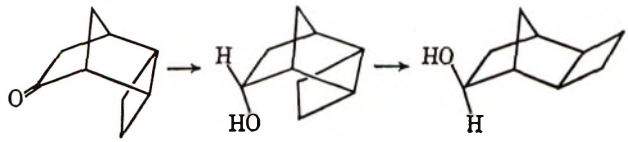
The availability of alcohols **35** and **36** prompted studies of the behavior of their bromobenzenesulfonate esters in buffered acetic acid. Analogous[3b,4b] to the behavior of the higher and lower homologs, **37** underwent a rapid rearrangement at 25° to form the *exo* isomer **38**. At elevated temperatures, acetolysis ensued



37 38

and the product isolated proved to be the *exo-exo* alcohol **35**.

Finally, the *endo-endo* brosylate **41** was synthesized *via* the ketone **39** and the alcohol **40**. Acetolysis of **41**, in contrast to the lower homolog produced the *exo-exo* system **35** in 95.5% yield.



39 40 35

Thus, the outcome of the product-forming steps in all but one[4b] of these solvolysis reactions of fused norbornyl derivatives follows a general pattern; namely, predominant *exo* substitution and *exo*-ring junctures.[21] The latter result is most likely a reflection of the greater stability of *exo*-fused bridges.[22] Interpretation of the high degree of stereoselectivity toward *exo* substitution is complex since the exact structure of the intermediate ions is not known with certainty.[23]

Experimental Section

Microanalyses were performed by G. Manser, Herliberg Switzerland; G. Robertson, Florham Park, N. J.; and Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded from carbon tetrachloride solutions or as noted on a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained in carbon tetrachloride solutions with tetramethylsilane as an internal standard on a Varian Model A-60 spectrophotometer. Gas chromatograms were determined on an Aerograph Model A-90 P instrument in the preparative and analytical runs. All columns were 0.25 in. (o.d.) and Chromosorb G was the solid phase. The abbreviations used refer to the following columns: C, Carbowax 20M, 9–15 ft; A, Apiezon L, 9 ft. Capillary gas chromatograms were determined on a Barber–Colman flame ionization system (Model 5000). The column (0.01 in.) was U (Ucon, 50 ft).

Ethyl *exo*-Tricyclo[3.2.1.$0^{2,4}$]octane-3-*syn*- and -*anti*-carboxylates (7).—The addition of ethyl diazoacetate was carried out as previously described.[6] Gas chromatographic analysis on a 9-ft Apiezon L (190°) column revealed the presence of 12–18% of a second product. The two isomers were separated by gas chromatography and examined separately. The most significant difference in the nmr spectra was the position of the bridgehead protons. The *anti* isomer showed these protons as a singlet at 2.37, whereas in the *syn* epimer they appeared at 2.45 ppm. These two peaks could be seen in the initial mixture of the two. The infrared spectrum of the *anti* isomer showed maxima at 5.77 (s), 6.83, 7.10, 7.63 (s), 7.95 (s), 8.56 (s), 8.80, 9.13, 9.50, and 9.75 μ. The *syn* isomer showed maxima at 5.77 (s), 6.83, 7.12, 7.46, 7.57, 7.72, 8.42 (s), 8.72 (s), 8.85, 8.98, and 9.17 μ.

Epimerization Experiment.—The separated esters were placed in nmr tubes containing ethanol and a small piece of sodium. The spectrum of the substance assigned the *anti* structure remained unchanged over a 40-day period. The other isomer gradually became converted into the *anti* system during this period. Gas chromatographic analysis at the end of the period indicated complete absence of the *syn* isomer and the presence of only the *anti* isomer **7** in both tubes.

***exo*-Tricyclo[3.2.1.$0^{2,4}$]octane-3-carbinol (10).**—The tricyclic esters (65.5 g, 0.37 mol) were dissolved in 60 ml of ether and the solution was added to a stirred suspension of 15 g (0.39 mol) of lithium aluminum hydride in 600 ml of ether. The resulting mixture was heated at reflux for 4 hr at which time water was added to hydrolyze the salts and to destroy excess hydride. The precipitate was removed and washed with methylene chloride. The combined organic phases were distilled under vacuum, whereupon a residue, bp 85–90° (0.9 mm), was obtained. The yield was 43.8 g (86%).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.20. Found: C, 78.23; H, 10.14.

The nmr spectrum displayed two doublets (J = 7 cps) in the region expected for H–C–O protons at 3.20 and 3.68 ppm. The area ratios were 10:1, respectively. The minor component (presumably) is the *syn*-carbinol. The bridgehead protons appeared at 2.25 ppm.

The 3,5-dinitrobenzoate of **10** was prepared in pyridine and had mp 92–94° after crystallization from methanol.

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.82; H, 4.91; N, 8.44.

***exo*-Tricyclo[3.2.1.$0^{2,4}$]octane-3-*anti*-carboxamide (8).**—To a solution of 25 g (0.164 mol) of the acid of **7**[6] in 100 ml of ether was added 98.5 g (0.828 mol) of thionyl chloride over 25 min. The resulting mixture was heated at reflux for 15 hr after which the excess thionyl chloride was removed by distillation under aspirator vacuum. Addition of 150 ml of anhydrous ether to the residue was followed by passage of ammonia gas through the solution for 2 hr. The white precipitate was removed by filtration and extracted with benzene in a Soxhlet apparatus for 24 hr. The extracts and the original ether filtrate were combined and cooled, whereupon 22.2 g (90%) of colorless crystals formed, mp 172–175°. Crystallization from benzene raised the melting point to 173.5–175°.

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.40; H, 8.50; N, 8.98.

***exo*-Tricyclo[3.2.1.$0^{2,4}$]octane-3-*anti*-carbinylamine (9).**—A solution of 6.0 g (0.040 mol) of amide **8** in 300 ml of benzene was treated with 3.04 g (0.080 mol) of lithium aluminum hydride over a period of 0.5 hr. The resulting slurry was heated at reflux for 20 hr. Hydrolysis was effected by cautious addition of 7.7 ml of water. The salts formed were collected and washed twice with ether. The combined extracts were evaporated to yield 5.42 g (92%) of an oil which was characterized by the preparation of the phenylurea derivative, mp 158–159.5°.

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.94; H, 8.01; N, 10.88.

Nitrous Acid Deamination of 9.—A solution of 1.5 g (0.01 mol) of amine **9** in 62 ml of glacial acetic acid was cooled and treated with 8.01 g (0.010 mol) of sodium nitrite. The resulting solution was stirred at room temperature for 24 hr after which it was poured into a cold aqueous solution which contained an excess of sodium carbonate. The crude acetates were removed by ether extraction. The dried ($MgSO_4$) extracts were added dropwise to a stirred suspension of 0.50 g (0.013 mol) of lithium aluminum hydride in 50 ml of ether. After stirring for 2 hr the reaction mixture was treated with water. The precipitate was collected and washed with ether. The combined extracts were washed with dilute hydrochloric acid, sodium carbonate solution, and water. Removal of the ether yielded 1.04 g (69%) of product. Analysis of the mixture by gas chromatography (C, 175°) indicated the presence of three major components in the

(21) The recent results of R. Baker and J. Hudec, *Chem. Commun.*, 929 (1967) with the benzotricyclo[4.2.1.$0^{2,5}$] nonyl system also are consistent with this generalization.

(22) P. von R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960).

(23) For references and a recent discussion of this problem, see P. von R. Schleyer, *ibid.*, **89**, 701 (1967).

ratio 1:1:1.6. The last peak proved to be identical in retention time with **10**. The nmr spectrum of a collected sample was superimposable on the spectrum of **10**.

The first two components were collected and submitted for elemental analysis.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.20. Found for peak 1: C, 78.11; H, 10.24. Found for peak 2: C, 78.40; H, 10.21.

The nmr spectrum of peak 1 showed complex vinyl absorption extending from 6.2 to 5.0 ppm and strong vinyl absorptions in the infrared spectrum at 9.9, 10.0, 10.3, and 11.0 μ. The second peak likewise showed nmr absorptions from 5.7 to 5.0 ppm (3 H) and strong infrared maxima at 9.9, 10.1, and 11.0 μ.

Isoamyl Nitrite Deamination of 9.[9]—A solution of 2 g (0.013 mol) of amine **9** in 50 ml of chloroform was treated successively with 1.3 g (0.01 mol) of isoamyl nitrite and 0.66 g (0.01 mol) of acetic acid. The resulting solution was heated at reflux for 12 hr. Sodium carbonate solution was added to neutralize the acid. Evaporation of the chloroform yielded 0.54 g of an oil, bp 135–145°. Gas chromatographic analysis (D, 95°) revealed two major peaks in the ratio 1:7. The nmr spectrum of the minor product displayed a complex vinyl group pattern extending from 4.8 to 6.15 ppm. Superimposed were absorptions due to norbornene olefinic protons at 5.90 ppm. The total relative area of the low field protons was 5. Bridgehead proton absorption (2 H) appeared at 2.85 ppm and other complex absorptions (5 H) extended from 2.20 to 0.8 ppm. The infrared spectrum displayed strong absorptions at 7.5 and 11.0 μ characteristic of vinyl groups.

The major product **12** likewise displayed a complex vinyl group pattern (3 H) centered at 5.38 ppm in the nmr spectrum. The infrared spectrum displayed vinyl group absorptions at 7.2, 10.2, and 11.05 μ.

Anal. Calcd for C_9H_{12}: C, 89.93; H, 10.07. Found: C, 89.95; H, 9.97.

The high boiling (75–85° at 0.25 mm) fraction of the product was converted into alcohols with lithium aluminum hydride and shown to consist of the rearranged alcohols and **10** in the ratios 1:1:10, respectively. The yield of the alcohols was 0.77 g (38%).

Ozonolysis of 12.—Ozone was passed through a solution of 0.10 g of the mixed olefinic products of the preceding experiment in 10 ml of methanol at 0°. After warming to room temperature a solution of 1.6 g of sodium hydroxide in 25 ml of water was added followed by 4.0 ml of 30% hydrogen peroxide solution. The resulting solution was heated at reflux for 12 hr and then evaporated in a stream of air. Acidification followed by ether extraction yielded 0.075 g of crude acid. Crystallization from pentane gave 0.015 g of **13**, mp 48–50° (lit.[24] mp 48–50°). Infrared and nmr spectra were identical with those of an authentic sample upon comparison.

***exo*-Tricyclo[3.2.1.0^{2,4}]octane-3-*anti*-carboxaldehyde (16). Hydride Reduction of Amide 17.**—The dimethylamide **17** was prepared using the same procedure as was used for the unsubstituted amide. From 11.5 g of the acid of **7**[6] there was obtained 11.07 g (83%) of amide **17**, mp 84.5–86°.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.63; H, 9.64; N, 7.78.

The methyl protons appeared as a broad singlet (6 H) at 2.95 ppm in the nmr spectrum. Amide carbonyl absorption appeared at 6.12 μ in the infrared spectrum.

The reduction was carried out according to the procedure of Brown and Tsukamoto[13] using a solution of mixed hydride prepared from 1.5 g (0.039 mol) of lithium aluminum hydride and 3.5 g (0.040 mol) of ethyl acetate in 87 ml of ether. The resulting solution was added to a stirred solution of 11.0 g (0.062 mol) of amide **17** in 43 ml of ether at 0°. The resulting mixture was heated at reflux for 1.5 hr and hydrolyzed with sulfuric acid. The salts were removed by filtration and the filtrate was evaporated to give 3.69 g (43%) of a liquid, bp 60–80° (1 mm). Gas chromatography (C, 145°) revealed two major products in the ratio 1:5.6. The major product proved to be aldehyde **16** as determined by nmr absorptions at 9.1 (1 H, doublet J = 5 cps), 2.45 (2 H), 1.28 (1 H, quintuplet, 2.5 cps splitting), and complex absorptions between 1.45–0.5 ppm. The infrared spectrum showed carbonyl absorption at 5.85 μ.

The 2,4-dinitrophenylhydrazone had mp 208.5–209.5° after crystallization from ethanol–ethyl acetate.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.69; H, 5.15; N, 17.36.

Manganese Dioxide Oxidation of 10.[12]—A solution of 5 g (0.036 mol) of **10** in 350 ml of methylene chloride was stirred with 75 g of manganese dioxide[25] for 2 hr at reflux. The mixture was filtered and the solids were washed with more methylene chloride. The combined extracts were washed with sodium carbonate solution prior to evaporation. There was obtained 3.35 g (68%) of aldehyde **16**, bp 70° (1 mm), on distillation of the residue.

***exo*-Tricyclo[4.2.1.0^{2,5}]non-3-ene (18).**—The tosylhydrazone of **16** was prepared by the procedure of Kirmse and Pook[11] and had mp 118–120°.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.12; H, 6.57; N, 9.20. Found: C, 62.73; H, 6.59; N, 9.44.

To a solution of 5.50 g (0.018 mol) of the tosylhydrazone in 100 ml of dry tetrahydrofuran was added 11.35 ml of 1.6 M butyllithium in n-hexane (0018 mol). After stirring for 30 min the solvents were removed on a rotary evaporator at aspirator pressure. The last traces of solvents were removed with a vacuum pump at 0.25 mm and 40°. The salt was then pyrolyzed at 95–110° (0.25 mm) over 45 min. The volatile products (0.65 g) were collected in a Dry Ice trap as an orange oil which showed absorptions at 4.90 and 4.50 μ in the infrared spectrum. On standing, the color disappeared. Gas chromatography of this material (A, 145°) revealed two components in the ratio 1:3.4. The minor component proved to be norbornene by comparison of its infrared spectrum with that of an authentic sample. The major product **18** showed a singlet (2 H) at 5.85, a singlet (2 H) at 2.45, a broad singlet (2 H) at 1.90, and a complex multiplet (6 H) centered at 1.2 ppm. The infrared spectrum showed absorptions at 3.22, 3.30, 3.42 (s), 3.49, 6.44 (w), 6.80, 7.74, 11.95, and 14.30 (vs) μ.

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 90.13; H, 10.06.

Catalytic Reduction of 18.—A solution of 0.10 g of **18** in 3 ml of ether was reduced with hydrogen in the presence of platinum oxide. Within 20 min hydrogen uptake (96%) had ceased. Gas chromatography (A, 160°) revealed one component. Infrared and nmr spectra were identical with those of the sample of **1** prepared below.

***exo*-Tricyclo[4.2.1.0^{2,5}]nonan-3-ol.**—Addition of 5.5 ml of 0.5 M diborane solution to a solution of 1.97 g of the mixture of **18** and norbornene in 40 ml of tetrahyrofuran was followed by stirring at 25° for 2 hr. The boranes were oxidized by addition of 1.82 ml of 3 N sodium hydroxide solution followed by 1.82 ml of 30% hydrogen peroxide. The reaction mixture was poured into 200 ml of water and extracted with ether. The combined extracts were washed with sodium bisulfite solution prior to evaporation. A viscous oil (1.43 g) was obtained which displayed two main peaks on gas chromatography (C, 150°) in the ratio 1:3.4. The minor peak had the same retention time as *exo*-norbornanol. The major product displayed a complex nmr peak at 3.75 ppm assigned to the proton adjacent to the hydroxyl group. The infrared spectrum showed absorptions at 3.00 (s), 3.45 (s), 6.85, 7.02, 8.65, and 9.50 μ.

Anal. Calcd for $C_9H_{14}O$: C, 78.20; H, 10.15. Found: C, 78.51; H, 10.32.

***exo*-Tricyclo[4.2.1.0^{2,5}]nonan-3-one (19).**—The above mixture of alcohols was oxidized using a two-phase system[26] of ether and sodium dichlormate solution. The oxidation of 0.4 g of alcohols was incomplete after 12 hr as shown by gas chromatography. Preparative gas chromatography (C, 165°) yielded 0.11 g of ketone **19** as an oil. The infrared spectrum showed a strong carbonyl absorption at 5.62 μ. Other absorptions appeared at 6.75, 6,80, 7.20, 7.55, 7.70, 9.22 (s), and 11.70 (s) μ.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.68; H, 9.07.

3-*anti*-Acetyl-*exo*-tricyclo[3.2.1.0^{2,4}]octane (20).—To a stirred solution of 16.5 g (0.11 mol) of the acid of **7**[6] in 100 ml of ether was added 175 ml of 1.67 M methyllithium (0.29 mol) in ether. The addition required 2 hr and was followed by stirring 4.5 hr at reflux temperature. Hydrolysis was effected by addition of 200 ml of water. The organic layer was washed with saturated ammonium chloride solution and water. The aqueous layer was neutralized with ammonium chloride and extracted with ether.

(24) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Amer. Chem. Soc.*, **72**, 3116 (1950).

(25) J. Attenburrow, A. F. Cameron, J. H. Chapman, R. M. Evans, B. A. Heins, A. B. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(26) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

The combined extracts were dried ($MgSO_4$) and evaporated to give 13.8 g (85%) of a crude solid. Two components in the ratio of 1:9 were present as shown by gas chromatography (C, 170°). The major constituent was isolated and had mp 38–40°.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.00; H, 9.41.

Infrared absorptions ($CHCl_3$) appeared at 3.30, 5.90 (s), 7.20, 7.60, 8.40, 8.60, 10.90, and 11.80 μ. The nmr spectrum showed a sharp singlet (3 H) at 2.10, bridgehead protons (2 H) at 2.25, and other complex peaks (9 H) in the high field region from 1.8 to 1.0 ppm.

The tosylhydrazone of **20** was prepared in boiling 60% aqueous methanol and had mp 158.0–159.0° after crystallization from methanol.

Anal. Calcd for $C_{17}H_{22}N_2SO_2$: C, 64.12; H, 6.96; N, 8.80. Found: C, 64.18; H, 6.92; N, 8.74.

***exo*-3-Methyltricyclo[4.2.1.0^{2,5}]non-3-ene (21).**—The lithium salt of the above tosylhydrazone was prepared and pyrolyzed by the above procedure. From 4.06 g there was obtained 2.4 g of a light yellow oil. Gas chromatography (C, 95°) indicated two components in the area ratio 13:87. The nmr spectrum of the major component was consistent with structure **21** in showing a broad singlet (1 H) at 5.60, broad singlets at 2.30 (2 H), and 1.90 (2 H) and complex high field absorptions (9 H) superimposed on a sharp singlet between 0.8 and 1.8 ppm. The infrared spectrum displayed absorptions at 3.35, 3.41, 6.17, 6.96 (s), 7.30, 7.60, 7.75 and 12.50 (s) μ.

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.54; H, 10.43.

The minor component presumably had structure **22** as evidenced by the appearance of vinyl absorptions at 4.9 (3 H) in the nmr spectrum and strong infrared absorptions at 10.15, 11.3, and 12.05 μ.

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.45; H, 10.65.

***endo*-Tricyclo[4.2.1.0^{2,5}]non-7-ene (24).**—The diiodide **26** was prepared as described by Alder and Roth[16] and was obtained as a yellow oil in agreement with the literature. The crude product (59.0 g, 0.16 mol) in 100 ml of ether was added rapidly to an ice-cold solution of phenyllithium which had been prepared from 7.0 g (1 g-atom) of lithium and 33.0 g (0.21 mol) of bromobenzene in 100 ml of ether. After stirring at 25° for 2 hr the reaction mixture was filtered through a Büchner funnel (no paper) onto crushed Dry Ice. After the mixture warmed to room temperature, 500 ml of water was added. The ether layer was washed with water, dried, and distilled through a short Vigreux column. The residual oil was distilled in a Holzman column to yield 13.99 g of a colorless oil, bp 81–84° (67–68 mm). Gas chromatographic analysis (A, 135°) revealed 18% of an impurity. A pure sample was collected and had mp 54.5–55.5°.

Anal. Calcd for C_9H_{12}: C, 89.93; H, 10.07. Found: C, 89.66; H, 10.28.

The infrared spectrum of **24** displayed absorptions at 3.22, 6.02 (s), 6.13 (w), 6.36 (w), 10.93, 11.17, 11.43, and 14.42 (s) μ. The nmr spectrum consisted of a poorly resolved triplet (2 H) at 6.34, a broad multiplet (4 H) at 2.68, and complex absorption (6 H) between 2.28 and 0.69 ppm.

***exo*-Tricyclo[4.2.1.0.^{2,5}]non-7-ene (23).**—The *exo*-diiodide was prepared according to the literature[16] and was obtained as a crystalline solid, mp 48.5–50° (lit.[16] oil). Cyclization was effected as in the previous experiment on 31.8 g (0.085 mol) of **25**. The distilled product (8.04 g) was collected between 41 and 43° (14–15 mm) and was 90% homogeneous. A pure sample of **23** was collected by gas chromatography (A, 135°).

Anal. Calcd for C_9H_{12}: C, 89.93; H, 10.07. Found: C, 89.68; H, 9.93.

The infrared spectrum of **23** showed absorptions at 3.17, 6.41 (w), 6.23 (w), 6.06 (s), 11.04, 11.20, and 14.57 (s) μ. The nmr spectrum consisted of a poorly resolved triplet at 5.89 (2 H), a multiplet at 2.57 (2 H), and complex absorption (8 H) between 2.38 and 0.83 ppm.

***exo*-Tricyclo[4.2.1.0^{2,5}]nonane (1).**—Catalytic reduction of 0.512 g of **23** in 5 ml of anhydrous ether was rapid in the presence of platinum oxide. The product was isolated as an oil by gas chromatography (A, 135°).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.27; H, 11.50.

Double-bond absorptions were absent in the nmr spectrum. Two broad areas of absorption were seen of equal integrated centered area at 2.03 and 1.2 ppm. Distinctive infrared absorptions appeared at 10.42, 10.68, and 11.01 μ.

***endo*-Tricyclo[4.2.1.0^{2,5}]nonane (2).**—The *endo* olefin **24** was similarly hydrogenated. Purification by gas chromatography gave a solid, mp 62–63° (sealed capillary).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.10; H, 11.63.

The nmr spectrum displayed extremely complex absorptions between 3.00 and 0.94 ppm. The infrared spectrum showed strong bands at 11.51, 10.44, and 9.92 μ.

Addition of Formic Acid to 23 and 24.—In separate experiments, mixtures of 0.20 g of **23** and 1.0 ml of 97% formic acid and 0.135 g of **24** and 1.0 ml of formic acid were shaken vigorously for 4 days. Both reactions were homogeneous at this time. The solutions were quenched with 10 ml of water and the products were extracted into ether. After washing with sodium bicarbonate solution and water, the extracts were evaporated. The crude formates were reduced with lithium aluminum hydride in ether. From the *exo* olefin, there was obtained 80 mg (50%) of crude alcohols. From the *endo* olefin there was obtained 140 mg (61%) of crude alcohols. Gas chromatography (C, 170°) revealed two products in 97:3 and 99:1 ratios from the two experiments. The major product was collected in both cases and shown to be identical with *exo*-7-hydroxy-*exo*-tricyclo[4.2.1.0^{2,5}]nonane (**35**) by comparative infrared and nmr spectra. The minor peak had a retention time identical with that of **36** (U, 115°).

***exo*-7-Hydroxy-*exo*-tricyclo[4.2.1.0^{2,5}]nonane (35).**—Hydroboration–oxidation of **23** was carried out as described by Brown and coworkers[19] using the sodium borohydride–boron trifluoride etherate system in tetrahydrofuran. From 2.40 g of olefin there was obtained 1.65 g (60%) of a viscous oil, bp 77–84° (0.2 mm). Purity was assessed at greater than 95% by gas chromatography (C, 170°).

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 78.17; H, 10.00.

The nmr spectrum consisted of a multiplet (1 H) centered at 3.55, a singlet (OH) at 2.73, and complex peaks (12 H) between 2.40 and 0.95 ppm. The infrared spectrum showed absorptions at 11.26, 11.00, 10.82, and 10.37 μ.

The *p*-bromobenzenesulfonate **38** was prepared in pyridine and had mp 62.5–63.5° on crystallization from petroleum ether (30–60°).

Anal. Calcd for $C_{15}H_{17}BrO_3S$: C, 50.43; H, 4.80; Br, 22.37. Found: C, 50.70; H, 4.90; Br, 22.13.

***exo*-7-Hydroxy-*endo*-tricyclo[4.2.1.0^{2,5}]nonane (36).**—The *endo* olefin (**24**) was similarly converted into the alcohol in 72% yield. The product was purified by gas chromatography (C, 170°) and had mp 56–60° (sealed capillary).

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 78.37; H, 10.26.

The nmr spectrum showed a doublet at 4.37 (1 H), a singlet at 2.28 (OH) and complex absorption (12 H) extending from 3.00 to 0.83 ppm. The infrared spectrum had peaks at 11.14, 10.85, 10.08, and 9.86 μ.

The *p*-bromobenzenesulfonate derivative **37** had mp 83.7–84.7° after crystallization from petroleum ether (30–60°).

Anal. Calcd for $C_{15}H_{17}BrO_3S$: C, 50.43; H, 4.80; Br, 22.37. Found: C, 50.47; H, 4.90; Br, 22.38.

Acetolyses Products.—The brosylate **37** was shown to rearrange rapidly to the *exo-exo* isomer **38** at room temperature in glacial acetic acid–sodium acetate solution. The reaction could be followed by nmr spectroscopy. From 53 mg of **37** in 0.50 ml of acetic acid there was recovered 44 mg of crude **38** after 18 hr at 25°. After crystallization the melting point was 59.0–60.5°. A preparative acetolysis on 2.73 g of **37** in 25 ml glacial acetic acid which contained 0.7 g of sodium acetate was carried out for 20 hr at 90°. Quenching with water and ether extraction gave 1.57 g of crude acetates. Reduction with lithium aluminum hydride in ether gave essentially pure *exo*-7-hydroxy-*exo*-tricyclo-[4.2.1.0^{2,5}]nonane (0.63 g, 60%) as shown by gas chromatography and comparative nmr spectroscopy.

***endo*-Tricyclo[4.2.1.0^{2,5}]nonan-7-one (39).**—The alcohol **36** was oxidized in a two-phase ether–water system[28] From 1.106 g (8.0 mmol) of **36**, there was obtained 289 mg of crude product which contained 17% of unreacted alcohol by gas chromatography (C, 170°). A preparatively purified sample of the ketone had mp 91.2–93.2° (sealed capillary).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.68; H, 8.99.

The infrared spectrum revealed a strong carbonyl absorption at 5.71 μ.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol–ethyl acetate mixtures, mp 159.0–160.0°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.09; N, 17.71. Found: C, 57.08; H, 5.33; N, 17.52.

The same ketone was obtained *via* manganese dioxide oxidation in methylene chloride and by Sarett oxidation.[27] The yields in the latter case (43%) were superior to those in the other procedures.

endo-7-Hydroxy-*endo*-tricyclo[4.2.1.$0^{2,5}$]nonane (40).—The ketone **39** was reduced with lithium aluminum hydride in ether. From 3.29 g (24 mmol) of **39** there was obtained 2.48 g of alcohol. Gas chromatography (C, 170°) revealed the presence of *ca.* 6% of alcohol **36**. A pure sample of **40** was collected for analysis.

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 77.95; H, 10.29.

The infrared spectrum displayed distinctive absorptions at 10.53, 11.12, and 11.39 μ. The nmr spectrum showed a broad multiplet (1 H) at 4.45 attributed to the H–C–O proton and complex absorptions extending from 3.20 to 0.83 ppm.

The bromobenzene sulfonate **41** was recrystallized from petroleum ether (30–60°) and had mp 82.8–83.8°.

Anal. Calcd for $C_{15}H_{17}BrO_3S$: C, 50.43; H, 4.80; Br, 22.37. Found: C, 50.44; H, 4.56; Br, 22.56.

Acetolysis of brosylate **41** by the above procedure led to a 58% yield of alcohols which contained 95.5% **35**, 3% **26**, and 1.5% **40**, as shown by gas chromatography (U, 115°). The major component was isolated by preparative gas chromatography (C, 170°) and shown by nmr spectroscopy to be identical with **35**. The small amount of **40** found may have resulted from reduction of unreacted **41** (sulfide odor).

(27) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953); see also S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

Registry No.—**1**, 16526-27-5; **2**, 16526-28-6; *exo-syn* **7**, 16545-17-8; *exo-anti* **7**, 16529-68-3; **8**, 16529-69-4; **9**, 16529-70-7; **10**, 16529-71-8; **10** 3,5-dinitrobenzoate, 10414-10-5; **12**, 16545-19-0; **16**, 16529-72-9; **16** 2,4-dinitrophenylhydrazone, 16529-73-0; **16** tosylhydrazone, 16529-74-1; **17**, 16529-75-2; **18**, 16529-76-3; **19**, 16529-77-4; *exo*-tricyclo[4.2.1.$0^{2,5}$]nonan-3-ol, 16545-20-3; **20**, 16529-78-5; **20** tosylhydrazone, 16529-79-6; **21**, 16529-80-9; **22**, 16529-81-0; **23**, 16529-82-1; **24**, 16529-83-2; **35**, 16529-84-3; **36**, 16529-91-2; **37**, 16529-85-4; **38**, 16529-86-5; **39**, 16529-87-6; **39** 2,4-dinitrophenylhydrazone, 16529-90-1; **40**, 16529-88-7; **41**, 16529-89-8.

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Synthesis of (−)-(3*S*)- and (+)-(3*R*)-4-Methyl-3D$_1$-pentan-1-ols and (−)-(3*S*)- and (+)-(3*R*)-3D$_1$-Isocaproic Acids[1a,b]

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The (+)-(3*R*)- and (−)-(3*S*)-hydroxytetrahydropyranyl ethers (IVb) were prepared by asymmetric reduction of the keto ether (V) using (+)- and (−)-diisopinocampheylborane,[3] respectively. The absolute configurations at C-3 of the two hydroxy ethers were determined by the method of Horeau and the results were rationalized on the basis of Brown's model for the (+)- and (−)-diisopinocampheylboranes. The enantiomeric hydroxy ethers were converted into the mesylates and hydrogenolyzed with lithium aluminum deuteride. It is assumed that introduction of deuterium proceeded with inversion at the asymmetric center. However, in addition to hydrogenolysis, other significant side reactions were noted. Removal of the tetrahydropyranyl moiety from the resulting (−)-(3*S*)-3D$_1$ and (+)-(3*R*)-3D$_1$ ethers (VIb) gave the alcohols (VIa) which were oxidized to the corresponding (−)-(3*S*)-3D$_1$ and (+)-(3*R*)-3D$_1$ acids (VII).

For studies of the biosynthesis of polyisoprenoids the enantiomeric (3*R*)- and (3*S*)-3D$_1$-4-methylpentan-1-ols and (3*R*)- and (3*S*)-3D$_1$-4-methylpentanoic acids were required. The synthesis of the four specimens and their configurational assignments are described.

Two synthetic approaches were projected both of which were based on the use of optically active dialkylboranes.[2] In one instance it was planned to hydroborate asymmetrically the olefin $(CH_3)_2C{=}CHCH_2R$ (II or III) (Figure 1) and displace stereospecifically the derived hydroxyl with deuterium. The alternative route, which proved successful, consisted of the asymmetric reduction of the carbonyl in $(CH_3)_2CHCOCH_2CH_2R$ (V) and subsequent displacement of the hydroxyl with deuterium.

Diisopinocampheylborane has been used as a highly selective reagent for the preparation of optically active alcohols from olefins and ketones.[2,3] Recently Streitwieser, *et al.*,[4] employed optically active diisopinocampheylborane to synthesize optically active 1-butanol-1-D from *cis*-1-butene-1-D. Preparation of optically active benzyl alcohol-1-D by reduction of benzaldehyde with diisopinocampheyldeuterioborane has also been reported.[5] The reduction of carbonyl groups with fermenting yeast is not practical for α-branched ketones.[6]

The starting material for the syntheses, methyl 4-methyl-3-pentenoate (IIb), was prepared from I,

(1) (a) This work was supported by Grant B6-1877R from the National Science Foundation and CA-K3-16614 from the U. S. Public Health Service. (b) For the configurational notations, see R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964); R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Intern. Ed. Engl.*, **5**, 385 (1966). (c) Postdoctoral Fellow, 1966–present.

(2) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 205.

(3) (a) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1964); (b) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 486 (1961); (c) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *ibid.*, **86**, 1076 (1964); (d) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961).

(4) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(5) S. Wolfe and A. Rauk, *Can. J. Chem.*, **44**, 259 (1966).

(6) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966), and earlier papers.

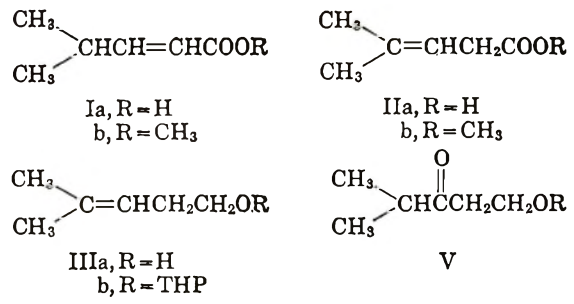

Figure 1.

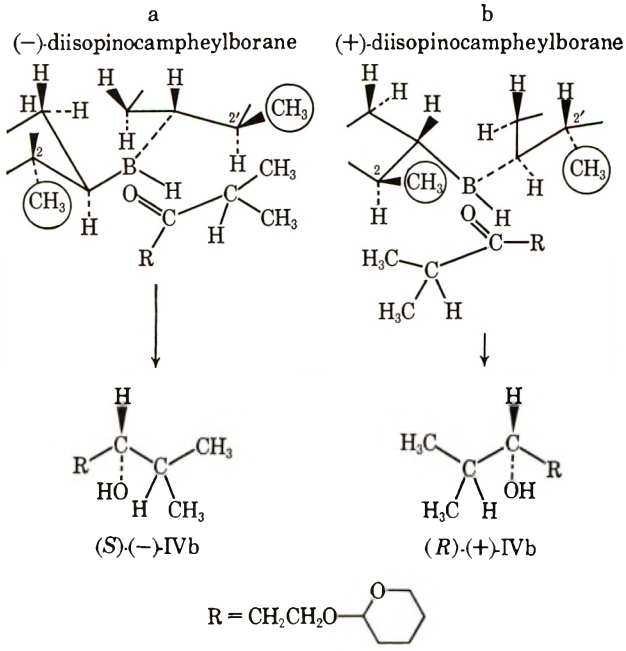

Figure 2.

essentially as previously described.[7,8] Attempted selective hydroboration of the double bond in the ester (IIb) with diisopinocampheylborane in diglyme or tetrahydrofuran failed. Under the conditions employed, the hydroboration was incomplete and the ester group was reduced first.

In an attempt to circumvent this difficulty, the ester was reduced with lithium aluminum hydride to IIIa and the resulting alcohol was converted into the ether (IIIb). Unfortunately the reaction of the ether (IIIb) with (+)-diisopinocampheylborane still did not proceed to completion and in the best case only about 50% hydroboration was achieved. These results were not totally unexpected in view of the reported resistance of trialkylated double bonds to the attack of diisopinocampheylborane.[9] However, a matter of much greater concern was the fact that the derived alcohol (IVb) was devoid of optical activity. The lack of asymmetric selectivity was disappointing and it could be the result of certain side reactions. It is known that diisopinocampheylborane exists in equilibrium with small amounts of the monoalkylborane. The considerably less stereoselective monoalkylborane could have reacted preferentially with the olefin. Alternatively, the displacement of α-pinene from diisopinocampheylborane by the olefin could have occurred.

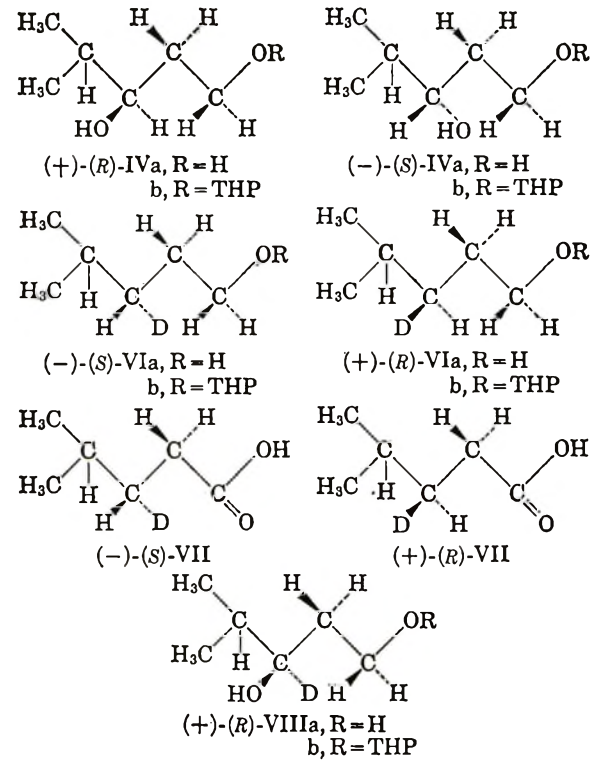

Figure 3.

In view of these results the approach was abandoned and the asymmetric reduction of the ketone (V) was explored. For the preparation of the ketone the olefinic ether (IIIb) was hydroborated and oxidized in the conventional manner to yield the racemic hydroxy ether (IVb) along with a small amount of the isomeric tertiary alcohol. Oxidation of the (±)-IVb with the aqueous chromium trioxide–pyridine reagent described by Cornforth, *et al.*,[10] yielded the keto ether (V). Attempts to oxidize (±)-IVb with chromium trioxide in acetic acid, Jones reagent, Brown's[11] method (at 0°), and Sarrett's procedure failed.

A tetrahydrofuran suspension of (+)-diisopinocampheylborane was prepared from (−)-α-pinene (α^{23}D −39.15°) as described by Brown, *et al.*[3] Reduction of ketone V with the (+) reagent gave the dextrorotatory hydroxy ether (IVb), $[\alpha]^{25}$D + 2.4° (Figure 2). A product of similar optical purity was obtained when the reaction was carried out in diglyme. With (−)-diisopinocampheylborane prepared from (+)-α-pinene (α^{25}D +39.65°), the reduction of V yielded the levorotatory alcohol (IVb), $[\alpha]^{25}$D −2.33°. Exposure of the (+)- and (−)-hydroxy ethers (IVb) to methanolic hydrochloric acid gave the $[\alpha]^{23}$D +7.84° and $[\alpha]^{25}$D −8.02° diols (IVa), respectively (Figure 3). The infrared, nuclear magnetic resonance, and mass spectra were in full agreement with the assigned structures. The (−)-diol (IVa), $[\alpha]^{27}$D −6.9 ± 0.2°, has been previously prepared by a different route by Büchi, *et al.*[12] Evi-

(7) K. Babor and I. Jezo, *Chem. Zvesti*, **8**, 18 (1954); *Chem. Abstr.*, **49**, 7495*g* (1955).

(8) For pertinent references, see J. B. Rogan, *J. Org. Chem.*, **27**, 3910 (1962).

(9) (a) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 2055 (1963); (b) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964); (c) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 1071 (1964).

(10) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *Tetrahedron*, **18**, 1357 (1962).

(11) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(12) G. Büchi, L. Crombie, P. J. Godin, J. S. Katlenbronn, K. S. Siddalingaiah, and D. A. Whiting, *J. Chem. Soc.*, 2843 (1961).

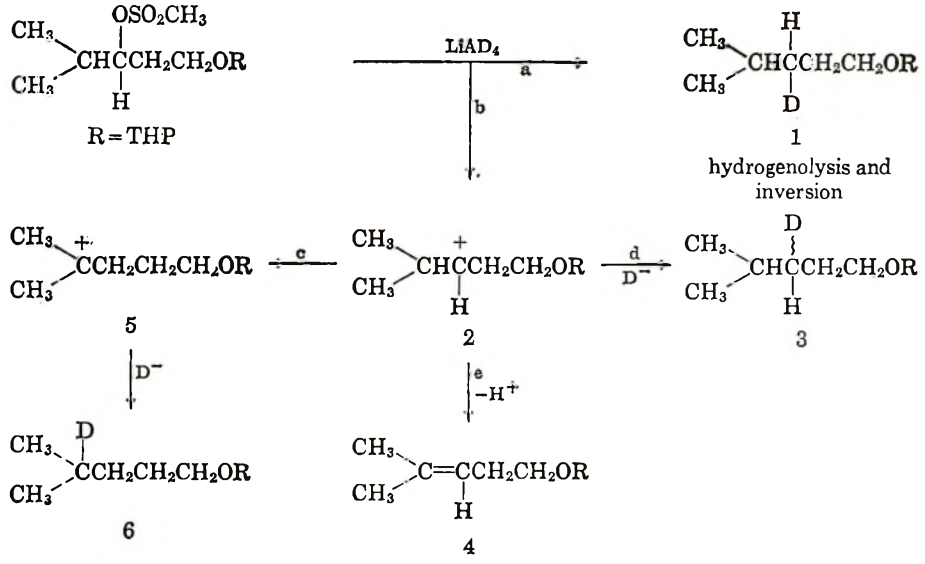

Figure 4.

dently the present sample is of a higher optical purity.

We now turned our attention to the question of the absolute configurations at C-3 of the enantiomeric alcohols IV. The configurations were determined for the (+) and (−) ethers (IVb) by the method of Horeau, *et al.*[13] Esterification of (−)-hydroxy ether (IVb) with racemic α-phenylbutyric anhydride led to the recovery of (−)-α-phenylbutyric acid. Consequently, the (−)-hydroxy ether (IVb) has the (3*S*) configuration.[13] From the analogous experiment with (+)-hydroxy ether (IVb), (+)-α-phenylbutyric acid was recovered indicating the (3*R*) configuration. Obviously the diols (IVa) will have the same configurations as the respective parent ethers (IVb). As indicated above the (−)-(3*S*) ether (IVb) gave the (−)-(3*S*)-diol (IVa) and the (+)-(3*R*) ether (IVb) gave the (+)-(3*R*)-diol (IVa). Our assignment of the (3*S*) configuration to the (−)-diol (IVa) agrees with that of Büchi, *et al.*, who have correlated the glycol with L-glyceraldehyde.[12] Therefore the (+)-diol must have the (3*R*) configuration.

A model of (−)-diisopinocampheylborane obtained from (+)-α-pinene (Figure 2) has been proposed by Brown and coworkers[9b,c] and has been successfully used to predict the configurations of alcohols resulting from hydroboration of acyclic *cis* olefins. Accordingly, all acyclic *cis* olefins on hydroboration with the (−) reagent should give the (*R*) alcohol. Similarly, alcohols resulting from hydroboration with (+)-diisopinocampheylborane prepared from (−)-α-pinene will have the (*S*) configuration. The same model was applied also to the reduction of carbonyl compounds. In actuality the dimeric tetraisopinocampheyldiborane is the reactive species and the group of McKenna has advanced a model based on this dimer.[14] The latter proposal is more encompassing since it is applicable to acyclic *cis* and *trans* olefins.

The reduction of ketone V to the enantiomeric alcohols (IVb) can be correctly interpreted on the basis of both the Brown and McKenna hypotheses. An interpretation of the reduction based on Brown's model is presented. The most stable conformations of the (−)- and (+)-diisopinocampheylboranes can be represented as is shown in Figure 2. The carbonyl may approach the B—H bond from the top or the bottom side of the reagent. However, inspection of models (Prentice-Hall F. M. U. models) reveals that the carbonyl can reach within reacting distance of the B—H bond only when the isopropyl group is directed away from the 2 (Figure 2, pathway a) or 2′ methyl (pathway b). The configurations predicted for the hydroxy ethers (IV) on this basis agree fully with those derived by Horeau's[13] and Büchi's[12] methods. In any event we have obtained from (−)-diisopinocampheylborane derived from (+)-α-pinene the (−)-(3*S*)-hydroxy ether (IVb) and from (+)-diisopinocampheylborane derived from (−)-α-pinene the (+)-(3*R*)-hydroxy ether (IVb) as anticipated.

With the two enantiomeric hydroxy ethers (IVb) in hand, it was possible to plan the stereoselective introduction of deuterium at C-3. The method adopted was to convert the alcohols into the corresponding tosylates or mesylates and then to hydrogenolyze these esters with lithium aluminum deuteride. It has been established that the hydrogenolysis proceeds with inversion and is accompanied by partial racemization.[15,16]

When the mesylate or tosylate of (+)-(3*R*)-hydroxy ether (IVb) was treated with lithium aluminum deuteride in ether the sulfonate group was cleaved, but the reduction was accompanied by formation of *ca.* 30% of the olefinic ether (IIIb) and of a small amount of hydroxy ether (IVb). To facilitate separation of the products it was advantageous to hydroborate the crude mixture, whereby the olefin was converted into the higher boiling alcohol. Deuterio ether VIb (Figure 3) was isolated by fractional distillation and glpc, $[\alpha]^{25}D$ −0.80°. When subjected to the same procedures, the (−)-hydroxy ether (IVb) gave (+)-deuterio ether VIb $[\alpha]^{24}D$ +0.82°. The deuterium content of the two

(13) A. Horeau and B. Kagan, *Tetrahedron*, **20**, 2431 (1964), and references therein.

(14) D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 667 (1967).

(15) G. K. Helkamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

(16) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

ethers was determined by combustion analysis and mass spectroscopy and was *ca.* 100%.

The nmr spectra of the enantiomeric ethers (VIb) were revealing and interesting. In each case, in addition to the doublet for the isopropyl methyls, a less intense singlet was centered between the peaks of the doublet. The relative intensities of the doublet and the singlet were of the order of 9:1. This led us to suspect that a certain amount (11%) of the deuterium was located at the methine carbon of the isopropyl moiety. That this was the case was proved by an alternative synthetic route.

The (3*R*)-deuteriohydroxy ether (VIII), $[\alpha]^{24}D$ +4.0° (Figure 3), was prepared by reduction of keto ether V with (+)-diisopinocampheyldeuterioborane. The deuterated reagent was prepared in the conventional way from (−)-α-pinene and deuteriodiborane. The derived D-mesylate was reduced with lithium aluminum hydride to furnish (+)-(3*R*)-3D_1 ether (VIb), $[\alpha]^{24}D$ +0.55°. Hydrolysis of the 3D_1 ether (VIb) provided the (3*R*)-3D_1 alcohol (VIa) which showed a somewhat lower deuterium content (84.5%). In this instance the nmr spectrum of the D ether (VIb) exhibited only a sharp doublet for the isopropyl methyls. The (3*R*) configuration of VIII follows from the positive rotations of derived 3D_1 ether (VIb) and 3D_1 alcohol (VIa).

The formation of the observed products can be rationalized by assuming that the $LiAlD_4$ (or $LiAlH_4$) reaction with mesyl esters proceeds by two competing routes. Apparently the hydrogenolysis (pathway a, Figure 4) is accompanied by some C—O bond breakage and formation of the cation 2 (pathway b). Addition of a deuteride to 2 will give the racemic ether 3 (pathway d). Alternatively elimination of a proton will result in the olefin 4 (pathway e). Rearrangement of the secondary cation 2 to the more stable tertiary cation 5 (pathway c) and subsequent addition of a deuteride will yield 6. That pathway b is a major competing route is evident from the amounts of the olefin 4 (30%), the product 6 (*ca.* 10%), and the racemic ether 3 formed. The magnitude of racemization was not determined but was estimated by others[16] to be of the order of 20%. Obviously the methyl "singlet" was absent in the nmr of the product of reduction of the mesylate of VIII with $LiAlH_4$ because in this instance a hydride ion rather than a deuteride ion was added to the methine carbon.

The lithium aluminum deuteride reduction is known to proceed with inversion.[15] Therefore, the (−)-deuterio ether (VIb) and (−)-4-methyl-3-deuteriopentanol (VIa) derived from the (+)-(3*R*)-hydroxy ether (IVb) must have the (3*S*)-3D_1 configuration. Alternatively, the (+)-deuterio ether (VIb) and (+)-4-methyl-3-deuteriopentanol (VIa) derived from (−)-(3*S*)-hydroxy ether (IVb) have the (3*R*)-3D_1 configuration.

Certain observations, not of immediate consequence to this study, deserve mention. Of interest were the nmr and mass spectra of the tetrahydropyranyl ethers. The magnetic nonequivalence of protons of the X group in systems of type X_2 AB where A and B are different groups or atoms have been studied in some detail.[17-19] Protons of a methylene group or isopropyl group removed by one or more bonds from a center of asymmetry may be magnetically nonequivalent and display AB-type quartets. In the present case no such splitting was observed and only doublets for the isopropyl methyls were recorded.

Without exception the mass spectra of the tetrahydropyranyl ethers were devoid of peaks for molecular ions and showed low intensity peaks corresponding to $(M - 1)^+$ ions. This led to some initial confusion because the D ethers VIb (M = 187) obtained by $LiAlH_4$ reduction of mesyl esters had only the $(M - 1)^+$ peak (*m/e* 186) which could correspond to the nondeuterated molecular ion. The point was cleared up when it was observed that methoxytetrahydropyranyl ether (M = 116) and the nondeuterated tetrahydropyranyl ether VIc (M = 186) both gave only the $(M - 1)^+$ peaks. This observation is analogous to results obtained by Friedel and Sharkey[20] for the mass spectra of acetals.

There remained the problem of oxidizing the alcohols (VIa) to the required 3D_1-isocaproic acids. The acids were prepared by treating the hydroxy products with Jones reagent, whereby the (−)-(3*S*) alcohol (VIa) gave (−)-(3*S*)-3D_1-isocaproic acid ($[\alpha]^{23}D$ −0.453°) and the (+)-(3*R*) alcohol (VIa) gave (+)-(3*R*)-3D_1-isocaproic acid ($[\alpha]^{23}D$ +0.486°).

Experimental Section

Tetrahydrofuran, diglyme, and boron trifluoride etherate were purified according to procedures previously described.[3a] The sodium borohydride (minimum 98% pure) was used as supplied by Fisher Scientific Co. The lithium aluminum deuteride and sodium borodeuteride (purchased from Metal Hydride Inc.) were of high isotopic purity (at least 95% D content). The samples of α-pinene used in this investigation showed specific rotations of $\alpha^{23}D$ −39.15° and +39.65° (neat, *l* = 1).

Preparative and analytical gas–liquid partition chromatography were carried out on an F & M Model 720 dual-column, programmed instrument and helium was used as carrier gas. Two columns were employed: column A, 5% XE 60 on Chromosorb (8 ft × 0.25 in. o.d.); column B, 5% SE-30 on Chromosorb (8 ft × 0.25 in. o.d.). In all cases the identity of samples was confirmed by mixed injection with authentic samples. Solutions were dried with anhydrous sodium sulfate prior to distillation. The melting points were determined on a hot plate and are corrected. The ir spectra were recorded on a Perkin-Elmer spectrophotometer, Model 237. The mass spectra were run on a Varian Associates M-66 instrument. The nmr spectra were recorded at 60 Mc on a Varian A-60 instrument either neat or in the indicated solvents using tetramethylsilane as an internal standard. The peak positions (in cycles per second), number of protons, nature of signal (s, singlet; d, doublet; bs, broad singlet; q, quartet; m, multiplet), splitting constant (*J*, Hz), and their assignments are indicated in that order. Analyses were by I. Beetz, Kronach, Germany. Deuterium analyses by combustion method were carried out by J. Nemeth, Urbana, Ill. The Hilger MK-III polarimeter was used.

4-Methylpent-2-enoic Acid (Ia).—A mixture of isobutyraldehyde (62 g, 1 mol) and malonic acid (156 g, 1.5 mol) in pyridine (150 ml) was heated on a steam bath. Vigorous evolution of carbon dioxide was noticed in the early stages and, after 3.5 hr, the evolution of gas had nearly stopped. The mixture was cooled and poured over excess hydrochloric acid and ice. The oily layer was separated and the aqueous phase was extracted twice with ether. The oil and the extracts were combined, washed with dilute hydrochloric acid and a saturated sodium chloride solution, and dried. The solvent was removed and the remaining liquid was distilled through a 6-in. packed column under reduced pressure to yield 4-methylpent-2-enoic acid: bp 83–85° (1.85 mm); 86% yield; ν_{max}^{film} 1700, 1650 cm^{-1}.

(17) E. I. Snyder, *J. Amer. Chem. Soc.*, **85**, 2624 (1963).
(18) G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964).
(19) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965.
(20) R. Friedel and A. G. Sharkey, *Anal. Chem.*, **28**, 940 (1956).

4-Methylpent-3-enoic Acid (IIa).—The isomerization of Ia was carried out essentially according to the published procedure[11] except that a lower concentration of alkali was used.

The acid (250 g) was mixed with potassium hydroxide (1.5 kg) and water (2 l.) and refluxed for 20 hr, in an atmosphere of nitrogen. The mixture was cooled in ice and acidified with concentrated hydrochloric acid. The obtained oil was separated and the aqueous layer extracted with ether. The oil and the extracts were combined and the solution was washed with brine and dried. The solvent was removed and the residue was distilled through a 1-ft.-long Vigreux column under reduced pressure. The fraction with bp 77–85° (2.4–2.7 mm) contained IIa (yield, 89.5%): ν_{max}^{film} *ca.* 1725 (broad C=O) and 1665 (double bond) cm^{-1}.

Methyl 4-Methylpent-3-enoate (IIb).—The published procedure was followed.[11] Esterification of the crude isomerized acid (IIa) gave, after distillation through a short column, 4-methylpent-3-enoate (98 g): bp 153–154° (1 atm); ν_{max}^{film} 1745 cm^{-1} (broad, ester); nmr (neat), 96.0 and 101.5 [6, d, *ca.* 1, $(CH_3)_2$–C=C], 177.0 (2, d, 7, =CH–CH_2–$COOCH_3$), 213.5 (3, $COOCH_3$), and 316 [1, quartet of a triplet, J = 7 and 1.5, $(CH_3)_2$–C=CH]. Judging from the spectrum the sample contained *ca.* 1–2% of the isomeric methyl 4-methylpent-2-enoate. No other impurity was detected by glpc.

The recovered acids were again deconjugated to yield upon esterification more of IIb.

4-Methylpent-3-en-1-ol (IIIa).—To a stirred and cooled suspension of $LiAlH_4$ (8.0 g) in ether (500 ml) methyl 4-methylpent-3-enoate (IIb, 26.05 g) was added during 20 min and the mixture was refluxed for 1 hr. The reaction was terminated by the addition of moist ether which was followed by a saturated solution of ammonium chloride. The ether phase was separated and the aqueous layer was extracted with ether. The ether extracts were combined, then washed with a saturated ammonium chloride solution and dried. The solvent was removed through a 100-cm Vigreux column and the residual liquid (21.2 g) proved to be IIIa. Upon distillation an analytical sample was obtained: bp 105–106° (110 mm); ν_{max}^{film} 3350 (strong, –OH), 1660 (weak, C=C) cm^{-1}; nmr (CCl_4), 97.0 (s) and 101 (d) [6, ≃1.0, $(CH_3)_2$–C=C–], 130 (2, sym q, $J_{ax} \simeq J_{bx} \simeq 6.5$, =CH–$CH_2$–$CH_2OH$), 204.25 (3, unsym q, 7–8, –CH_2–OH + CH_2–OH), 304 [1, q of t, 7 and 1.5, $(CH_3)_2$–C=CH–]. The sample was contaminated with *ca.* 1% of 4-methylpent-2-en-1-ol.

4-Methylpent-3-en-1-ol Tetrahydropyranyl Ether (IIIb).—A mixture of the crude alcohol (IIIa, 21.2 g), benzene (300 ml), dihydropyran (19.5 g), and several crystals of *p*-toluenesulfonic acid was left at ambient temperature. Periodically samples were removed for ir analysis and after 3 hr the hydroxyl band disappeared. The reaction mixture was washed with a dilute sodium carbonate solution and water and dried. Removal of the solvent in a rotary evaporator furnished a liquid (38.5 g) with a characteristic sweet odor. Upon distillation through a short Vigreux column (it was advantageous to add Triton X-100 as an antifoaming agent) IIIb was isolated, bp 96.5–98.5° (9–10 mm), in an 89.3% yield. In contrast to the ir spectrum of IIIa, the spectrum of IIIb showed in addition to the expected ether bands, a complex pattern of peaks. The nmr spectrum (CCl_4) showed peaks at 100 [6, d, 1.0, $(CH_3)_2$–C=CH–], 131.5 (2, sym q, 7, =CH–CH_2–), ∼206 (4, m, –O–CH_2–C), 269 (1, s, –O–CH–O), 304.5 [1, complex t, ∼7.5, $(CH_3)_2$–C=CH–]. Glpc on columns A and B (140–150°) showed that the ether IIIb is contaminated with *ca.* 2% of an impurity with a higher retention time.

Hydroboration of IIIb with (+)-Diisopinocampheylborane.—The apparatus consisted of a 100-ml flask carrying a side arm and a socket for a thermometer. The flask was equipped with a dry nitrogen inlet, a thermometer, and a magnetic stirring bar. The system was flamed and cooled in a flow of nitrogen and the side arm was closed with a rubber stopple. A positive pressure of nitrogen was maintained thereafter.

A. Experiment in Diglyme.—A mixture of sodium borohydride (0.7125 g, 18.5 mmol), (−)-α-pinene (7.48 g, 55 mol), and dry diglyme (45 ml) was cooled to 0° in an ice bath.[21] To the stirred slurry, purified boron trifluoride etherate (3.15 ml, 25 mmol) was added from a hypodermic syringe during 15 min and the stirring was continued at 0–3° for 5 hr. To the stirred white suspension of the reagent the olefinic ether (IIIb, 4.60 g, 25 mmol) was added during 5 min at 0–3°. The stirring was continued at 0–3° for 3 hr and then at 8–9° for 18 hr. The solution at this point was clear. Careful addition of water from a syringe liberated 10 mmol of hydrogen indicating the consumption of 15 mmol of hydride.

The organoborane was oxidized by adding first 3 *N* sodium hydroxide (20 ml) and then 30% hydrogen peroxide (11 ml) and stirring the mixture for 2 hr at *ca.* 40°. The product was recovered with ether; the extract was washed with ice-cold water and dried. The solvent was removed *in vacuo* and the residual liquid was fractionated through a short, packed column. Fraction 1, bp 45–48° (14–15 mm), consisted of α-pinene and diglyme as indicated by glpc analysis on column B. Fraction 2, bp 86–96° (1.6 mm), was a mixture of unreacted IIIb and isopinocampheol (glpc). Fraction 3, bp 77–84° (0.1 mm), was mainly the hydroxy ether (IVb) contaminated with some isopinocampheol. Fraction 3 was purified by preparative glpc on column B at 180° to furnish (after redistillation) a colorless viscous oil: bp 100° (0.35 mm) (bath temp); ν_{max}^{film} 3450 cm^{-1} (–OH). The ir, nmr, tlc, and glpc data of this material were identical with those of (+)- or (−)-IVb described below. A 10% chloroform solution of the product in a 1-dm tube did not show detectable optical rotation.

B. Experiment in Tetrahydrofuran.—The previous experiment was repeated on a 10-mmol scale using sodium borohydride (0.313 g, 8.14 mmol), tetrahydrofuran (25 ml), (−)-α-pinene (3.1 g, 11 mmol), boron trifluoride etherate (1.26 ml, 10 mmol), and the olefinic ether (1.84 g, 10 mmol). The reagent was stirred at 0–3° for 4 hr. Subsequently, the olefinic ether was added slowly and stirred at 8–9° for 24 hr. The reaction mixture was not clear and hydrolysis gave *ca.* 5 mmol of hydrogen suggesting the consumption of *ca.* 50% of the hydride.

The product was oxidized in the usual manner (H_2O_2 + NaOH) and the resulting alcohol was recovered with ether. Analytical glpc showed the presence of α-pinene, isopinocampheol, unreacted olefinic ether, and hydroxy ether (IVb). The hydroxy ether was purified by preparative glpc and distilled to furnish pure IVb (750 mg) whose physical characteristics were identical with those of the compound prepared by procedure A. A 10% chloroform solution in a 1-dm tube was optically inactive.

(±)-4-Methyl-1,3-dihydroxypentan-1-tetrahydropyranyl Ether (IVb).—A 2-l., three-necked flask was equipped with a magnetic stirring bar, a dropping funnel, a thermometer, and an inlet through which a positive pressure of dry nitrogen could be maintained. The system was flamed in a flow of dry nitrogen and cooled to room temperature. The flask was charged with sodium borohydride (14.3 g, 360 mmol) and dry tetrahydrofuran (1 l.); then the mixture was stirred and cooled in an ice–salt bath. Subsequently, boron trifluoride etherate (480 mmol, 68.2 g) was slowly added from the dropping funnel (0–5°). After about 30 min the olefinic ether (IIIb, 176.6 g, 960 mmol) was added dropwise and the mixture was stirred for 4 hr (0–3°). The excess hydride was decomposed with water.

Oxidation was carried out with 3 *N* sodium hydroxide (220 ml) and 30% hydrogen peroxide (110 ml) first by stirring the reaction mixture for 1 hr at the temperature of an ice bath and then for 2 hr at 40°. The tetrahydrofuran phase was separated and the aqueous portion was extracted with small amounts of ether. The combined tetrahydrofuran and ether solution was washed with brine and dried and the solvent was removed *in vacuo*. The residual liquid was distilled through a 6-in. Vigreux column.

The bulk of IVb distilled at 77–80° (0.25 mm). An additional amount of the product, bp 77–80° (0.25 mm), was obtained upon redistillation of the forerun (15 g). A total of 153 g (79% yield) of (±)-IVb was obtained. Analysis (glpc) on columns A and B revealed that the material is slightly contaminated (*ca.* 4%) with an alcohol (ir) having a lower retention time. Judging from the stability of the hydroxyl group toward chromic acid the impurity seemed to be the isomeric 4-hydroxy ether (glpc, see below).

The crude (±)-IVb showed ν_{max}^{film} 3475 cm^{-1} (–OH); nmr (CCl_4), 53.5 [6, d, 7, $(CH_3)_2$CH–], 219 (5, m, –CH_2–O and –CH–OH), 176 (1, broad s, –OH, exchanged with D_2O), 277 (1, s, –O–CH–O); mass spectrum, *m/e* 85 (100%), 57 (52%), 55 (52%), 101 (46%), 56 (30%), 73 (27%).

4-Methyl-3-keto-1-pentanoltetrahydropyranyl Ether (V).—A solution of chromic oxide (50 g) in water (30 ml) was added to pyridine (500 ml) in an ice bath under stirring.[10] To this reagent, the hydroxy ether (IVb, 33.7 g) in pyridine (100 ml) was added slowly with stirring. Glpc of aliquots removed periodically showed that the oxidation was completed after 48 hr. The reac-

(21) A small excess of sodium borohydride was employed to ensure complete consumption of boron trifluoride etherate. To minimize dissociation of the dialkylborane a 10% excess of α-pinene was used.

tion mixture was diluted with a large volume of ethyl acetate, the precipitate was filtered off and washed with small amounts of ethyl acetate. The filtrate was stirred with solid sodium bicarbonate (150 g) and filtered over Celite. The treatment was repeated once more. The slightly colored filtrate was concentrated on a rotary evaporator and the combined material from three oxidations was fractionated through a 1-ft packed column. After an initial forerun [bp 68° (2 mm)] product V distilled at 70–71° (0.3 mm) (82% yield): ν_{max}^{film} 1716 cm^{-1} (strong, C=O); nmr (CCl_4), 64.5 [6, d, 7.0, $(CH_3)_2CH$–], 93.5 (6, broad, ring methylene protons), 153.5 (3, m, –CH–CO–CH_2–), 222.5 (4, m, –CH_2–O), 270.5 (1, s, –O–CH–O–); mass spectrum, *m/e* 85 (100%), 101 (66%), 71 (51%), 117 (14%), 111 (9%), 142 (4%), 182 (4%), 157 (2%). The purity of the material was established by tlc [silica gel; benzene–ethyl acetate (1:1)] and by glpc on columns A and B at 160–180°.

(+)-4-Methyl-1-(3*R*)-dihydroxypentan-1-tetrahydropyranyl Ether (IVb).—(−)-α-Pinene (136.8 g, 1008 mmol) was added to a cooled (0–3°) and stirred solution of diborane in tetrahydrofuran[3a] (558.4 ml, 0.752 *M* in borane). A white precipitate appeared soon after the addition and the reagent was stirred overnight in an ice bath at 6–7°. The keto ether (V, 70.0 g, 350 mmol) was added at 0–3° during 30 min and the mixture was stirred overnight in an ice bath (6–7°). The solution was clear and the excess hydride was decomposed with water. Then 3 *N* sodium hydroxide (280 ml) was added and this was followed by a slow addition of 30% hydrogenperoxide (113 ml) (*cooling*). The mixture was stirred at *ca.* 40° for 1.5 hr. The tetrahydrofuran layer was separated and the aqueous layer was extracted with ether. The tetrahydrofuran solution was combined with the ether extracts, washed with brine, and dried and the solvent was removed *in vacuo*. The residual liquid was distilled through a 1-ft packed column. The excess α-pinene and isopinocampheol were removed below 70° (0.6 mm) and the product (+)-IVb, bp 85–86° (0.55 mm) (yield, 57.5 g), was collected. More of IVb (6.5 g) was isolated by redistillation of the forerun thus increasing the yield to 64.0 g (91.4%). The ir spectrum of the sample was identical with that of (±)-IVb. The optically active specimen had a specific rotation of $[\alpha]^{23}D$ +2.43° (*c* 30%, chloroform); nmr (CCl_4), 56.5 [6, d, 6.5, $(CH_3)_2$–CH], 175 (1, s, –OH, exchanged with D_2O), 277.5 (1, s, –O–CH–O), 228.5 (5, m, O–CH_2–C + –CH–OH). The sample contained traces of isopinocampheol (glpc) and was purified by preparative glpc on column B and then distilled to furnish material with a specific rotation of $[\alpha]^{25}D$ +2.40° (*c* 30%, chloroform). The homogeneity of the sample was confirmed by tlc (silica gel).

(+)-4-Methyl-1-(3*R*)-dihydroxypentane (IVa).—To a solution of (+)-IVb (1.5 g) in methanol (10 ml) concentrated hydrochloric acid (2 drops) was added and the mixture was warmed (40–50°) for 30 min. The reaction was terminated by the addition of solid sodium hydrogen carbonate (1 g) and then diluted with ether (50 ml). The inorganic solid was separated by filtration and the solvent was removed through a Vigreux column. The diol (IVa) was isolated by fractional distillation of the residue. A sample, purified twice by glpc first on column A and then on column B and distilled, gave (+)-IVa as a viscous oil: ν_{max}^{film} 3350 cm^{-1} (broad, –OH); $[\alpha]^{23}D$ +7.84° (*c* 30.7%, chloroform). The solid 1,3-bis-3,5-dinitrobenzoyl ester was prepared and showed mp 117–120° (ethanol–methylene chloride).

Anal. Calcd for $C_{20}H_{18}N_4O_{12}$: N, 11.07%. Found: N, 10.9%.

(−)-4-Methyl-1-(3*S*)-dihydroxypentane-1-tetrahydropyranyl Ether (IVb).—The experiment was carried out exactly as described for the (+)-hydroxy ether (IVb). The keto ether (V, 50 g) was reduced with (−)-diisopinocampheylborane [from (+)-α-pinene] to give (−)-hydroxy ether IVb (84% yield): bp 73–76° (0.15 mm); $[\alpha]^{25}D$ −2.33° (*c* 30%, chloroform). The ir spectrum and the chromatographic behavior of this material were identical with those of the previously described enantiomeric product.

(−)-4-Methylpentane-1-(3*S*)-diol (IVa).—Cleavage of (−)-hydroxy ether (IVb) with methanolic hydrochloric acid was carried out as described above for (+)-4-methylpentane-1-(3*R*)-diol (IVa). A sample twice purified by glpc on column B at 140° and distilled showed $[\alpha]^{25}D$ −8.02°. The purity and identity of the product was confirmed by glpc and tlc.

Configurational Assignment to the (+)- and (−)-Hydroxy Ethers (IVb) by Horeau's Method.[20]—α-Phenylbutyric anhydride was prepared by the general procedure for anhydrides.[22] The anhydride was freed of excess acid and acid chloride by washing with a dilute sodium bicarbonate solution and water and dried. The product was distilled under high vacuum to furnish a slightly colored material which was shown to be homogeneous by tlc; ir showed ν_{max}^{film} 1815 (strong) and 1748 (m) cm^{-1}.

The (+)- and (−)-hydroxy ethers IVb were treated in an identical manner. The ether IVb (202 mg) was dissolved in 7 ml of a 0.4 *M* solution of α-phenylbutyric anhydride in dry pyridine and stored for 24 hr in a well-stoppered flask at ambient temperature. To decompose the excess anhydride, water (1 ml) was added and the mixture was kept for 1 hr at room temperature. Benzene (1 ml) was added and the excess acid was titrated with 1 *N* sodium hydroxide (phenolphthalein). In each case 4.62 mmol of free acid was found. The neutral material was recovered with several 10-ml portions of chloroform. The combined chloroform extracts was washed with dilute hydrochloric acid and water and dried. Removal of the solvent under reduced pressure provided the ester (340 mg). The ir spectrum of each ester was devoid of hydroxylic absorption and showed a strong band for a carbonyl indicating complete esterification.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with several 10-ml portions of chloroform. The chloroform extracts were combined, washed with water, and dried and the solvent was removed *in vacuo* to furnish the acids.

The acid (763.0 mg) recovered from the esterification of (+)-hydroxy ether (IVb) had a specific rotation of $[\alpha]^{25}D$ +0.982° (*c* 32.6%, benzene), optical yield 4.68%. This indicates the (3*R*) configuration for the (+)-hydroxy ether (IVb).

The acid (763.5 mg) recovered from the esterification of (−)-hydroxy ether (IVb) had a specific rotation of $[\alpha]^{25}D$ −1.04° (*c* 25.0%, benzene), optical yield 4.96%. This indicates the (3*S*) configuration for the (−)-hydroxy ether (IVb).

Preparation of Mesyl and Tosyl Esters of (+)- and (−)-Hydroxy Ethers (IVb). A. Mesylate.—To a cooled solution of the hydroxy ether (IVb, 31.0 g, 155 mmol) in pyridine (100 ml), methanesulfonyl chloride (22.0 g, 186 mmol) was added and the mixture was left for 2.5 hr at room temperature. After dilution with ice and water the mixture was extracted several times with ether. The ether extracts were combined, washed successively with cold dilute hydrochloric acid, a sodium bicarbonate solution, and water, and dried. The solvent was removed *in vacuo* (bath temperature was below 40°) to furnish the mesylate as an oil (41.0 g) which had no hydroxyl absorption in the ir spectrum.

B. Tosylate.—The tosylates were prepared in an identical manner except that *p*-toluenesulfonyl chloride was used instead of the methanesulfonyl chloride. The product was devoid of hydroxyl absorption in the ir spectrum.

(−)-(3*S*)-3D$_1$-4-Methyl-1-hydroxypentane-1-tetrahydropyranyl Ether. A. Reduction with Lithium Aluminum Deuteride of the Tosyl Ester of (+)-IVb.—A solution of the crude tosylate (5.8 g) in dry ether (30 ml) was added slowly to a cooled and stirred suspension of lithium aluminum deuteride (1 g) in dry ether (50 ml). After completion of the addition, stirring was continued for 30 min at room temperature and then the mixture was refluxed for 5 hr. The reaction was terminated with water and the solids were removed by filtration. The filtrate was washed with a sodium carbonate solution and water, dried, and concentrated to a residue (2.92 g); the ir spectrum, ν_{max}^{film}, contained a trace hydroxyl band.

Glpc analysis on column A at 150° revealed the presence of three components of retention times 7.9, 10.0, and 12.0 min in a ratio of 75:32:2. The 7.9- and 10.0-min components were (−)-(3*S*)-3D$_1$-4-methyl-1-hydroxypentane tetrahydropyranyl ether (IVb) and the olefinic ether (IIIb). The unidentified component (retention time 12 min) was presumably an olefin isomeric with IIIb.

The crude product was distilled under reduced pressure and the fraction distilling below 100° (2 mm) was collected. This fraction was twice purified by preparative glpc to furnish, after distillation, 1.6 g of (−)-VIb: ν_{max}^{film} 2160 (w, –D); $[\alpha]^{24}D$ −0.80° (*c* 30%, chloroform); nmr (CCl_4), 53.75 [d, 6.5 $(CH_3)_2CH$–], 53 [s, $(CH_3)_2$–CD–]; the total number of protons in the methyl signals was six. The mass spectrum had peaks at *m/e* 85 (100%), 86 (68%), 57 (41%), 56 (40%), 84 (28%), 186 (15%), 101 (13%), 87 (11%), 115 (8%), 185 (1%). The amount of D$_1$ product estimated from the mass spectrum was 99–100%.

(22) C. F. H. Allen, C. J. Kilblev, D. M. McLachlin, and C. V. Wilson, *Org. Syn.*, **26**, 1 (1946).

Reduction of the tosylate of (±)-IVb with lithium aluminum hydride gave a mixture of VIc (79.7%) and the olefin IIIb (20.3%). The mixture was purified as above to yield pure (±)-D_0 VIc. The mass spectrum of the product was devoid of a peak for M^+ but showed a peak at *m/e* 185 $(M - 1)^+$ and 85 (100%).

B. Reduction of the Mesyl Ester.—To a cooled and stirred suspension of lithium aluminum deuteride (5.5 g) in dry ether (200 ml) a solution of the crude mesyl ester (35.5 g) of (+)-IVb in dry ether (50 ml) was slowly added and the mixture was stirred for 16 hr at room temperature. Subsequently the mixture was refluxed for 1 hr; then after cooling the reaction was terminated with water. Solid sodium carbonate (10 g) was added, the stirring was continued for 1 hr, and finally the solids were separated by filtration over celite. The filtrate was freed of solvent by evaporation through a Vigreux column and the remaining liquid (23.1 g) was devoid of hydroxyl bands in the ir spectrum. Glpc (column B; 150°) indicated the presence of VIb (72.5%) and IIIb (27.5%).

To the crude product (23 g) in tetrahydrofuran (50 ml) at 0–3° a diborane solution in the same solvent (27 ml, 0.75 *M* in borane) was added. After 3 hr the mixture was oxidized in the usual manner [3 *N* sodium hydroxide (25 ml), 30% hydrogen peroxide (10 ml); stirring at *ca.* 40°, 1.5 hr] to yield upon the conventional work-up an oily residue. The residue was distilled and the fraction with bp 44–47° (0.25 mm) consisted of nearly homogeneous (−)-VIb (13.4 g), $\alpha^{24}D$ −0.80° (c 30%, chloroform). Glpc (column B; 150°) revealed the presence of a trace amount of IIIb. The mass spectrum (D content *ca.* 100%) was identical with that of the sample prepared by reduction of the tosylate. Combustion analysis indicated *ca.* 95% incorporation of deuterium; the nmr spectrum (CCl_4) showed peaks at 54 [d, 6, $(CH_3)_2CH-$], 58.5 [s, $(CH_3)_2CD-$], 205 (4, m, $O-CH_2-C-$), 268 (1, s, $O-CH-O$). The total number of protons in the methyl signals was six.

(−)-(3S)-3D1-4-Methylpentan-1-ol (VIa).—A mixture of (−)-VIb (12.0 g), methanol (25 ml), and concentrated hydrochloric acid (5 drops) was warmed at 45–50° for 3 hr. The acid was neutralized with solid sodium hydrogen carbonate (2.0 g), then ether was added (100 ml), and the solids were separated by filtration.

Most of the solvent was removed by distillation through a 30-cm packed column and the residual liquid was fractionated through a 15-cm packed column at atmospheric pressure. The fraction boiling below 135° (750 mm) contained ether, methanol, tetrahydropyranyl ether of methanol, and a small amount of the deuterio alcohol VIa. The next fraction [bp 149–51° (750 mm), 5.6 g] was nearly 99% pure (glpc) deuterio alcohol VIa. A sample purified by preparative glpc and distilled furnished VIa: $[\alpha]^{25}D$ −0.168° (*c* 31.6%, chloroform), $\alpha^{25}D$ −0.17° (neat, *l* = 1); nmr (CCl_4), 54 [*ca.* 6, d, 6, $(CH_3)_2CH-$], 53 [d, *ca.* 1, $(CH_3)_2CD-$], 85.5 (4, t, 6.0 and 8.5, other protons), 209 (2, t, 6.5, $-CH_2-OH$), 252 (1, s, −OH, exchanged with D_2O); mass spectrum, *m/e* 57 (100%), 28 (92%), 43 (84%), 70 (65%), 85 (18%), 84 (2%), 83 (2%). The mass spectrum indicated that the product contains *ca.* 100% monodeuterated species. The behavior of the sample on glpc and tlc was identical with that of authentic 4-methyl-1-pentanol (Aldrich Chemical Co.) whose mass spectrum showed peaks at *m/e* 56 (100%), 69 (90%), 43 (81%), 28 (75%), 84 (27%), 83 (7%).

(+)-(3R)-3D1-4-Methylpentan-1-ol Tetrahydropyranyl Ether (VIb). A.—The (−)-(3*S*)-hydroxy ether (IVb) was converted into the mesylate (41.0 g) and treated with $LiAlD_4$ (6.0 g) exactly as previously described. The resulting products contained VIb (72.5%) and IIIb (27.5%). The crude mixture was hydroborated and oxidized in the conventional manner to yield, after fractional distillation 12.8 g of (+)-VIb: bp 67–68° (1.5 mm); $[\alpha]^{24}D$ +0.82° (c 30%, chloroform). The sample was more than 99% pure when analyzed by glpc and the main contaminant was the olefinic ether (IIIa). Its tlc and nmr and mass spectra were identical with those of the (−) enantiomer.

B.—(+)-(3*R*)-3D1-3-Hydroxy ether (VIII, 3.2 g) was converted into the mesylate (4.25 g) by the general procedure described previously and the mesylate was reduced with lithium aluminum hydride (0.75 g) in ether (80 ml). The product was worked up as in the previous cases and was shown by glpc to be a mixture of the ether VIb (79%) and the olefinic ether IIIb (21%). The crude material was purified by preparative glpc on column A and distilled to furnish pure (+)-(3*R*)-3D1 ether (VIb, 1.3 g): ν_{max}^{film} 2125 (w, −D); $[\alpha]^{24}D$ +0.55° (*c* 20%, chloroform); nmr (CCl_4), 54.25 [6, d, 6.5, $(CH_3)_2CH-$], 204 (4, m, 7 and 3.5, $-O-CH_2-C-$), 269 (1, s, $-O-CH-O-$); mass spectrum, *m/e* 57 (100%), 43 (76%), 70 (46%), 28 (43%), 85 (15%). The sample was more than 99% pure when analyzed at *150° on columns* A and B and the main impurity was the olefinic ether (IIIb).

(+)-(3R)-3D1-4-Methylpentan-1-ol (VIa). A.—The (+)-deuterio ether VIb (11.8 g) was cleaved as described above for the (−)-deuterio ether VIb. The product was fractionated through a 15-cm packed column to furnish (+)-(3*R*)-3D1-4-methylpentan-1-ol (VIa, 5.5 g): bp 150–51° (753 mm); ir spectrum identical with that of VIa; $\alpha^{25}D$ +0.19° (neat, *l* = 1); nmr (CCl_4), 54 [*ca.* 6, d, 6, $(CH_3)_2-CH-$], 53.5 [d, *ca.* 1, $(CH_3)_2-CD-$], 86 (4, t, 6.5 and 7.5, other protons), 209 (2, t, 6.5, $-CH_2-OH$), 251 (1, s, −OH exchanged with D_2O); mass spectrum, *m/e* 57 (100%), 43 (76%), 70 (46%), 28 (43%), 85 (15%). Analysis of the mass spectrum indicated the presence of *ca.* 100% monodeuterated species. A sample subjected to preparative glpc on column B at 100° and distilled showed the same optical rotation.

B.—The (+)-(3*R*)-3D1 ether obtained *via* VIII was hydrolyzed and purified as described in procedure A to yield (+)-(3*R*)-3D1 alcohol VIa. Microanalysis indicated 80.5% deuterium incorporation and the mass spectrum indicated 84.5% of monodeuterated species.

(+)-(3R)-3D1-4-Methyl-1,3-dihydroxypentan-1-tetrahydropyranyl Ether (VIII).—A solution of deuteriodiborane in tetrahydrofuran was prepared from sodium borodeuteride and boron trifluoride etherate.[3a]

To a cooled and stirred solution of deuterioborane in tetrahydrofuran (67.6 ml, 0.22 *M* in deuteriodiborane) at 0–3° (−)-α-pinene (9.3 g, 72 mmol) was added through a hypodermic syringe and then the mixture was stirred at 0–5° overnight. The keto ether (V, 5.0 g, 25 mmol) was added to the stirred reagent at 0–3° during 10 min and the mixture was stirred for 24 hr at 0–5°. The excess deuteride in the clear solution was decomposed by the addition of water. The organoborane was oxidized with alkaline hydrogen peroxide as described above. The product was isolated in the usual manner and the solvent was removed *in vacuo*. The residual liquid was fractionally distilled through a 15-cm packed column to furnish 5.22 g of (+)-VIb, bp 72–73° (0.15 mm), which was contaminated with a small amount of isopinocampheol. A sample twice purified by preparative glpc on column B at 180° and distilled *in vacuo* furnished pure VIII: $[\alpha]^{24}D$ +4.0° (c 30%, chloroform); ν_{max}^{film} 3450 (s, −OH), 2100 (w, −D) cm^{-1}; nmr (CCl_4), 54 [6, d, 6, $(CH_3)_2CH-$], 179 (1, s, −OH), 221 (4, m, $-O-CH_2-C-$), 272.5 (1, s, $-O-CH-O$); mass spectrum, *m/e* 85 (100%), 101 (74%), 84 (56%), 83 (47%), 86 (42%), 102 (33%), 160 (11%), 100 (8%), 118 (5%). The homogeneity of the material was established by glpc and tlc.

(+)-(3R)-3D1-4-Methylpentan-1-oic Acid (VII).—To a solution of (+)-4-methyl-(3*R*)-3D1-pentan-1-ol (VIa, 500 mg) in acetone (10 ml) at 0°, Jones reagent was added until the color persisted. The mixture was stirred at 0° for 10 min, diluted with water, (100 ml) and extracted several times with small amounts of ether. The ether extracts were combined and washed once with water and the acidic material was extracted with 5% sodium hydroxide solution (30 ml). The aqueous alkaline solution was acidified with concentrated hydrochloric acid and the acidic material was isolated with ether. The solvent was removed and the residual oil was distilled through a short-path column to furnish (+)-(3*R*)-3D1-4-methylpentanoic acid (VII, 450 mg), $[\alpha]^{23}D$ +0.486° (*c* 28%, chloroform). The acid proved to be homogeneous by tlc (silica). The purity of the material was further established by glpc analysis of the methyl ester (diazomethane). Glpc analysis of the ester on columns A and B at 120° showed it to be more than 99% pure and its retention time was identical with that of authentic methyl 4-methylpentanoate.

(−)-(3S)-3D1-4-Methylpentan-1-oic Acid (VII).—The (−) acid (VII) was prepared from the (−) alcohol (VIa) as described above. The (−) acid (VII) had a specific rotation of $[\alpha]^{23}D$ −0.453° (c 30%, chloroform). The acid was homogeneous when tested on tlc (benzene (67%), methanol (21%) and glacial acetic acid (12%)). The methyl ester (diazomethane) was homogeneous when analyzed on column B.

Registry No.—Ia, 10321-71-8; IIa, 504-85-8; IIb, 2258-65-3; IIIa, 763-89-3; IIIb, 16451-46-0; (±)-IVb, 16451-47-1; (+)-(3*R*)-IVa, 16451-48-2; 1,3-bis-3,5-dinitrobenzoyl derivative of (+)-(3*R*)-IVa, 16451-49-3;

(−)-(3S)-IVa, 16451-50-6; (+)-(3R)-IVb, 16451-51-7; (−)-(3S)-IVb, 16451-52-8; V, 16451-53-9; (+)-(3R)-VIa, 16451-54-0; (−)-(3S)-VIa, 16451-55-1; (+)-(3R)-VIb, 16451-56-2; (−)-(3S)-VIb, 16451-57-3; (+)-(3R)-VII, 16503-30-3; (−)-(3S)-VII, 16462-50-3; (+)-(3R)-VIIIb, 16503-31-4.

The Stereochemistry of Methylene Transfer from Sulfonium Ylides to Unsaturated Bicyclic Ketones[1]

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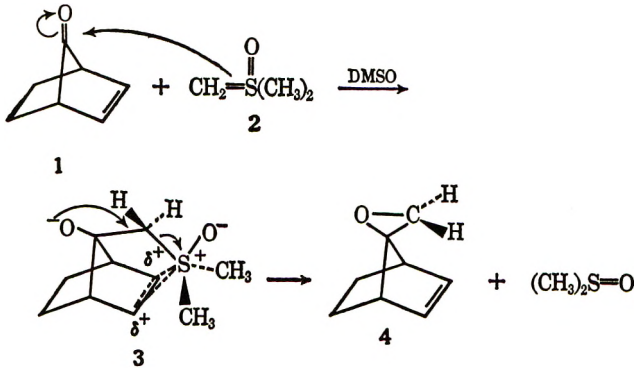
In contrast to other nucleophilic reagents, dimethyloxosulfonium methylide attacks dehydronorcamphor predominantly from the *endo* direction to yield a 71:29 ratio of spiro[norborn-2-en-*exo*- and -*endo*-5,2′-oxacyclopropanes]. Dimethylsulfonium methylide, however, produces the same two oxides in a 6:94 ratio. Both the oxosulfonium and the sulfonium ylide attack norcamphor preponderantly from the *exo* side to yield spiro[norbornan-*exo*- and -*endo*-2,2′-oxacyclopropanes] in a 10:88 or 5:95 ratio, respectively. Competitive rate studies have been used to demonstrate that dehydronorcamphor exhibits an enhanced *endo* and decreased *exo* reactivity toward the oxosulfonium ylide. Participation by the π electrons of the double bond has been suggested as the cause of this unusual kinetic and stereochemical effect.

During the course of some synthetic investigations undertaken in connection with another problem, it was observed that the reaction of norbornen-7-one (**1**) with dimethyloxosulfonium methylide (**2**) occurs in a stereospecific manner to yield spiro[norbornen-*anti*-7,2′-oxacyclopropane] (**4**)[2] and suggested that π-electron participation *via* the intermediate **3**[3-5] might be responsible for the preferential *syn* addition, *viz.*



However, since the *syn* side of a 7-substituted norbornene is apparently less sterically hindered than the *anti*—the irreversible reaction of norbornen-7-one (**1**) with a mixed-metal hydride or an organometallic produces an *anti* alcohol predominantly,[2] while equilibration of the mixed 7-carbomethoxynorbornenes with methanolic sodium methoxide yields more *syn* than *anti* ester[6]—a steric factor could not be ruled out as the cause of the observed stereospecificity. To test these ideas and to learn more of the path by which sulfur ylides react with ketones to yield epoxides, we have extended our investigations to include the ketones norcamphor (**13**), dehydronorcamphor (**5**), and norbornan-7-one (**18**) and the ylide dimethylsulfonium methylide (**12**).[7]

Results

The reaction of dehydronorcamphor (**5**) at 25° with a 10% excess of dimethyloxosulfonium methylide (**2**)[7] in dimethyl sulfoxide (DMSO) yields a mixture containing 65% spiro[norbornen-*exo*-5,2′-oxacyclopropane] (**7**), 27% spiro[norbornen-*endo*-5,2′-oxacyclopropane] (**9**), and 8% the unreacted ketone, **5**. The composition of the product mixture was determined by gas–liquid partition chromatography (glpc) on a basic Quadrol/SAIB column[8] at 115°, conditions which permit analysis of the reactive unsaturated *anti* oxide, **4**,[2] without rearrangement. The major products, **7** and **9**, respectively, were identified from their analyses and infrared and nmr spectra (see Experimental Section) and by their reduction with lithium aluminum hydride to the known[9] unsaturated alcohols 5-methylnorbornen-*exo*- and -*endo*-5-ols (**10** and **11**), respectively (Chart I).

At a lower temperature **5** reacts with an ~20% excess of dimethylsulfonium methylide (**12**) in DMSO to yield a mixture containing 6% the unsaturated *exo* oxide **7** and 94% the unsaturated *endo* oxide **9**.

$$5 + \underset{12}{CH_2{=}S(CH_3)_2} \longrightarrow 7\ (6\%) + 9\ (94\%)$$

In contrast to dehydronorcamphor (**5**), norcamphor (**13**) reacts with **2** to produce a mixture containing about 10% spiro[norbornan-*exo*-2,2′-oxacyclopropane] (**15**), at least 88% spiro[norbornan-*endo*-2,2′-oxacyclopropane] (**17**), and less than 2% unreacted norcamphor (**13**). Since the two saturated oxides, **15** and **17**, which constitute at least 98% (by glpc) of the distilled reaction product could not be separated by glpc, they were collected together, and their relative proportion

(1) Portions of this work have been presented before the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p 8K.

(2) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

(3) We represent this intermediate as charge delocalized purely as a matter of convenience and analogy,[4] but do not intend to imply that our experimental results permit us to distinguish it from a tricyclic charge-localized structure(s).

(4) Analogous structures have been suggested to accommodate the observed stability of positively charged carbon,[5a-c] and sulfur[5d] exocyclic, *syn* and β to the 5 or 7 position of 2-norbornene.

(5) (a) E. L. Allred and T. J. Maricich, *Tetrahedron Lett.*, 949 (1963); (b) R. M. Hawthorne, Jr., Ph.D. Dissertation, Rutgers, 1963, part II; (c) R. S. Bly, R. K. Bly, A. O. Bedenbaugh, and O. R. Vail, *J. Amer. Chem. Soc.*, **89**, 880 (1967); (d) P. Wilder, Jr., and L. A. Feliu-Otero, *J. Org. Chem.* **31**, 4264 (1966).

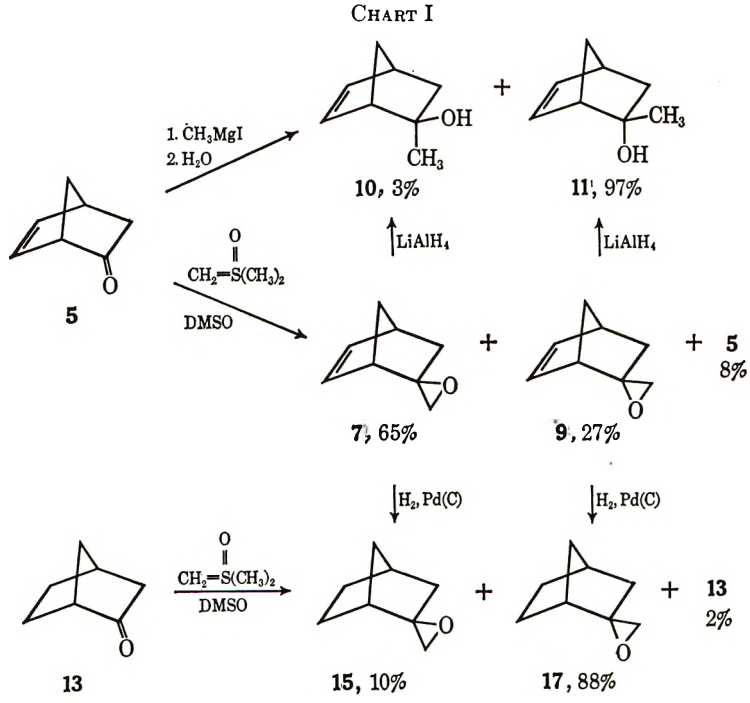
(6) R. R. Sauers and R. M. Hawthorne, Jr., *ibid.*, **29**, 1685 (1964).

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(8) The preparation and properties of this liquid phase have been described earlier; *cf.* J. A. Broderick, "Aerograph Research Notes," Wilkins Instrument and Research, Walnut Creek, Calif., Fall Issue, 1960.

(9) (a) N. J. Toivonen and P. J. Mälkönen, *Suomen Kemistilehti*, *B*, **32**, 277 (1959); (b) *ibid.*, **33**, 53 (1960).

CHART I

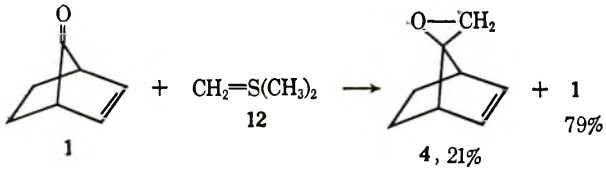


was determined by nmr spectroscopy. The oxirane-type hydrogens of authentic **15**, prepared by catalytic hydrogenation of **7**, appear as a two-hydrogen singlet at δ 2.61, while the corresponding hydrogens of the saturated *endo* oxide **17**, prepared in a similar manner from **9**, appear as an AB-type quartet[10] (H_A, δ 2.72; H_B, δ 2.54; J_{AB} = 5.8 cps) centered at 2.63. The collected reaction mixture from **13** is revealed by integration of its nmr spectrum to consist of nine parts **17** and one part **15** (Chart I).

Norcamphor (**13**) reacts with dimethylsulfonium methylide (**12**) to give a mixture of 2% **15**, 41% **17**, and 57% unreacted ketone **13**.

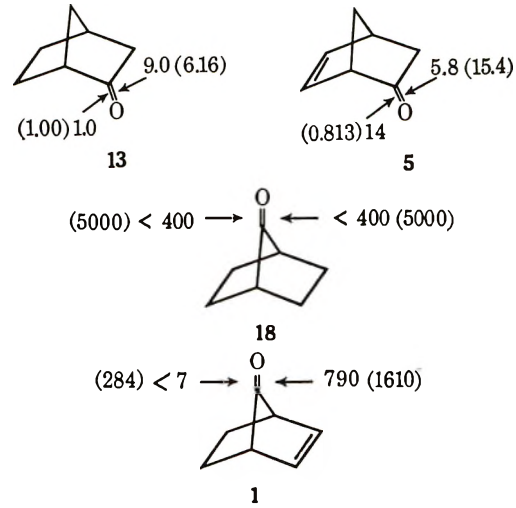
$$13 + 12 \longrightarrow 15 + 17 + 13$$

Norbornen-7-one (**1**), in analogy to its reaction with dimethyloxosulfonium methylide (**2**), yields the unsaturated *anti* oxide, **4**, exclusively, when treated with dimethylsulfonium methylide (**12**), *viz.*



In order to determine the relative reactivity of the ketones **1**, **5**, and **13** toward dimethyloxosulfonium methylide (**2**), known mixtures of **1** and **5** and of **5** and **13** were allowed to react for 1 hr at 26.0° with less than stoichiometric amounts of **2** in DMSO solution.[11] The reaction mixtures were then analyzed by glpc under conditions at which both the unreacted starting ketone and the products were not only stable but completely resolved. The relative rate of reaction of dimethyloxosulfonium methylide at each position of three ketones[11] was calculated from these data[14] and is indicated diagrammatically and compared with that of sodium borohydride[15] in Chart II.

CHART II
RELATIVE REACTIVITY TOWARD DIMETHYLOXOSULFONIUM METHYLIDE OR (SODIUM BOROHYDRIDE)[a]



[a] Calculated from the data of ref 15.

Discussion

Dimethyloxosulfonium methylide (**2**) reacts in an unusual manner with dehydronorcamphor (**5**). Toward the saturated ketone, norcamphor (**13**), dimethyloxosulfonium methylide behaves as do other nucleophiles (Table I) and yields predominantly the product

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 89 ff.

(11) Although norbornan-7-one (**18**) was also included in our competitive rate studies, a quantitative comparison of its reactivity toward epoxide formation is not too meaningful because of the large amounts of sulfur-containing by-products which are also formed and because of some uncertainty about the origin of the epoxide, spiro[norbornan-7,2'-oxacyclopropane], which is produced.[12] However, in the sense that less unsaturated ketone (**1**) than saturated ketone (**18**) remains unreacted when an equimolar mixture of the two is allowed to react with insufficient dimethyloxosulfonium methylide in DMSO, norbornen-7-one (**1**) is apparently somewhat more reactive than norbornan-7-one (**18**).[13]

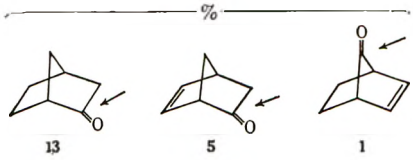
(12) We plan to discuss this reaction in a future publication.

(13) See Chart II.

(14) T. S. Lee in "Technique of Organic Chemistry," Vol. VIII, S. L. Friess and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1953, p 100 ff.

(15) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

TABLE I
PROPORTION OF PRODUCT RESULTING FROM *exo* OR *syn* ATTACK ON SOME BICYCLIC KETONES



Reactant/solvent	% 13	% 5	% 1
$NaBH_4/i$-PrOH[a]	86	95	85
$LiAlH_4/Et_2O$	94[b]	91[b]	86[c]
$LiAlH(t\text{-}OBu)_3/THF$[d]	>92	77	...
CH_3MgI/Et_2O	100[e]	97[f]	100[g]
C_2H_5MgBr/Et_2O[h]	...	100	...
$(CH_3)_2CHMgBr/Et_2O$[h]	...	100	...
C_6H_5MgBr/Et_2O	~100[i]	...	~67[i]
$CH_2{=}CHMgBr$[k]	...	...	~75
$n\text{-}C_4H_9Li/C_7H_{16}$[c]	...	...	61
$(CH_3)_2S{=}CH_2$[f]	95	94	100
$(CH_3)_2S(=O){=}CH_2$	90[f]	29[f]	100[g]

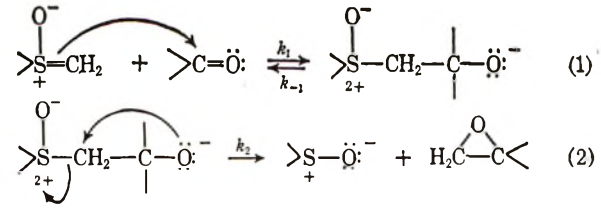
[a] See ref 15. [b] S. Beckmann and R. Mezger, *Chem. Ber.*, **89**, 2738 (1956). [c] R. K. Bly, unpublished work. [d] C. H. DePuy and P. R. Story, *J. Amer. Chem. Soc.*, **82**, 627 (1960). [e] N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae*, AII No. 64 (1955). [f] This work. [g] See ref 2. [h] S. J. Cristol and P. K. Freeman, Abstracts of the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958, p 6N; P. K. Freeman, *Dissertation Abstr.*, **20**, 2012 (1958). [i] This and other aryl Grignard reagents apparently react exclusively from the *exo* side; *cf.* D. C. Kleinfelter and P. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961); and H. C. Brown, F. S. Chloupek, and M.-H. Rei, *J. Amer. Chem. Soc.*, **86**, 1246 (1964). [j] Private communication from P. G. Gassman, Department of Chemistry, The Ohio State University. [k] J. A. Berson and M. Jones, Jr., *ibid.*, **86**, 5019 (1964).

of *exo* attack, *viz.*, the saturated *endo* oxide **17**. Mixed-metal hydrides and Grignard reagents also react in this manner with the *unsaturated* ketone, dehydronorcamphor (**5**), *i.e.*, approach exclusively or predominantly from the *exo* side to produce an *endo* alcohol (Table I). Dimethyloxosulfonium methylide (**2**), however, reacts with this ketone preferentially from the *endo* side to yield the unsaturated *exo* oxide **7**, predominantly. Furthermore, while with sodium borohydride in isopropyl alcohol the actual rate of *exo* addition *increases* and that of *endo* addition *decreases* slightly in passing from norcamphor (**13**) to dehydronorcamphor (**5**) (Chart II),[15] with dimethyloxosulfonium methylide (**2**) the opposite is true: *endo* attack becomes 14 times more facile while *exo* addition occurs only 0.64 times as fast (Chart II).

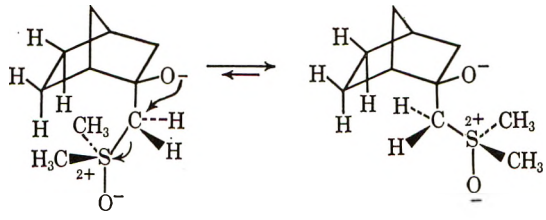
A similar kinetic effect may also be apparent in the attack of the oxosulfonium ylide **2** on norbornen-7-one (**1**). This ylide appears to be somewhat more reactive toward the unsaturated ketone **1** than toward the saturated norbornan-7-one (**18**).[11] In this respect it contrasts sharply with sodium borohydride which reacts ten times more rapidly with **18** (Chart II).[15]

Although the exact course of the reaction of oxosulfonium ylides with ketones has not yet been established,[7] it is now thought to consist of eq 1, a reversible nucleophilic addition by the "methylene" carbon of the ylide at the electron-deficient carbonyl carbon of the ketone to form a betaine intermediate, followed by eq 2, an irreversible intramolecular nucleophilic displacement of the sulfoxide by the oxide of the betaine.[16]

(16) The current status of mechanistic thought on sulfonium ylide reactions is summarized in A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, Chapter 9.

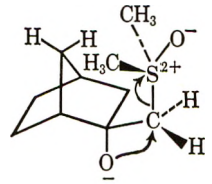


In the case of dissymmetric bicyclic ketones, such as **1**, **5**, and **13**, two modes of reaction are possible. With norcamphor (**13**) the observed ratio of *exo*/*endo* attack is 9.0:1.0 (Chart II) and probably reflects the fact that not only is *exo* attack sterically more favorable than *endo*, *e.g.*, $(k_1)_{exo} > (k_1)_{endo}$, but that, because of repulsions between the methyl groups and the *endo* hydrogens at C-5 and C-6, the *endo*-betaine **14** is less favorably



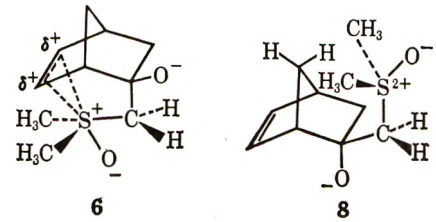
14

oriented for displacement of dimethyl sulfoxide than is the *exo*-betaine **16**, *i.e.*, $(k_2)_{exo} > (k_2)_{endo}$.



16

With dehydronorcamphor (**5**) *exo*/*endo* attack occurs in the ratio of 5.8:14 or 0.24:1.0 (Chart II). It is suspected that this greatly enhanced preference for *endo* (axial) attack may be due to π-electron participation[3] by the reactive double bond of the ketone which increases both $(k_1/k_{-1})_{endo}$ with respect to $(k_1/k_{-1})_{exo}$ by stabilizing the increased positive charge on sulfur in the *endo*-transition state and intermediate *endo*-betaine **6**[3] of eq 1, and $(k_2)_{endo}$ with respect to $(k_2)_{exo}$ by fixing the *endo*-betaine **6** in the most favorable conformation for intramolecular displacement of dimethyl sulfoxide, eq 2.



6 **8**

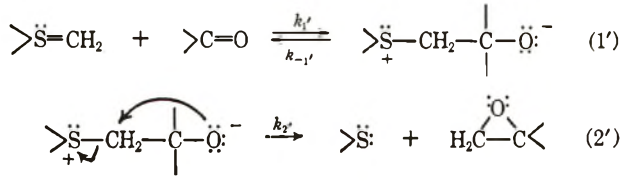
It is doubtful that this preference for methylene transfer from **2** to the *endo* side of dehydronorcamphor (**5**) could derive from steric effects alone. Not only does this ketone exhibit a strong kinetic preference for *exo* attack by other nucleophiles (Table I), but there is apparently little difference in the thermodynamic stability of most *exo*- or *endo*-5-substituted norbor-

nenes.[17] Hence, in the absence of π-electron participation by the double bond, it is unlikely that a strong bias for reversible *exo* attack in eq 1 would be overridden by an even greater tendency for irreversible *endo*-methylene product formation in eq 2.

Nor is it believed that the effect of the double bond can be predominantly inductive in nature. Brown and Muzzio[15] have clearly demonstrated that with respect to norcamphor (**13**) *exo* attack by borohydride ion is enhanced in dehydronorcamphor (**5**) while *endo* attack is suppressed (Chart II). They have suggested that the electron-withdrawing inductive effect of the double bond is responsible for the enhanced "*exo* reactivity" of **5**. Assuming that their explanation is correct, it is clearly not possible to attribute both the enhanced *exo* reactivity of **5** toward the nucleophile borohydride and its enhanced "*endo* reactivity" toward the nucleophile dimethyloxosulfonium methylide (**2**) to this same inductive effect.[18]

In the case of norbornen-7-one (**1**) the preference for methylene transfer from **2** to the side of the double bond is even more pronounced, *i.e.*, >100:1. Here too, the effect of the double bond is to decrease the rate of *syn* attack by borohydride ion while apparently increasing the *syn* reactivity of **1** toward attack by the oxosulfonium ylide **2** (Chart II). Again we suspect that the latter reaction is accompanied by π-electron participation whose effect is to increase the forward rates of both steps by stabilizing the developing positive charge on sulfur and holding the intermediate *syn*-betaine **3** in the best conformation for the internal displacement of dimethyl sulfoxide. Since **1** is extremely reactive toward nucleophiles,[2,11] and since *syn* attack is also the sterically as well as the electronically favored process (Table I), the over-all reaction is quite rapid and highly stereospecific.

The reaction of dimethylsulfonium methylide (**12**) with a ketone may probably, in analogy to dimethyloxosulfonium methylide (**2**), be considered as a two-step reaction,[16] *viz.*



(1′)

(2′)

However, since **12** is considerably more reactive than **2**,[7] the first step of the reaction (1′) is likely to be less reversible, *i.e.*, $k_{-1}'/k_2' << k_{-1}/k_2$, so that with a dissymmetric ketone the proportion of *exo*/*endo* oxide will be approximately determined by $(k_1')_{exo}/(k_1')_{endo}$. Also because of its higher reactivity the course of the reaction of the sulfonium ylide **12** with a ketone is less likely to be influenced by small differences in the stabilities of the intermediate betaines. In other words, the transition state of **1** will be reached earlier in the reaction than that of **1**, and hence will be less susceptible to the effect of π-electron participation.[19] Under the circumstances it is probably not surprising that the sulfonium ylide reacts by the sterically favored process in each case, *e.g.*, transfers methylene from the *exo* side of both **5** and **13** and from the *syn* side of **1** (Table I).

Experimental Section[20]

Dehydronorcamphor (5).—Although dehydronorcamphor has been known for many years[21a] the authors believe that the following preparation is generally superior to any of the published methods[21] because it proceeds in 35% over-all yield in two steps from commercially available starting materials.

Forty grams (0.16 mol) of aluminum *t*-butoxide was added in one portion to a warm solution of 23.2 g (0.168 mol) of norborn-5-en-2-yl formates[22] and 40 g (0.37 mol) of *p*-benzoquinone in 350 ml of dry benzene. The mixture was refluxed for 24 hr with stirring and then cooled to room temperature. Hydrochloric acid (3 *N*, 100 ml) was added, and, after filtration through a Celite mat, the aqueous layer was discarded. The benzene layer was washed successively with six 200-ml portions of 3 *N* hydrochloric acid, six 200-ml portions of aqueous 5% sodium hydroxide, and finally two 100-ml portions of saturated sodium chloride solution. The benzene was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure to yield 11.2 g (0.104 mol, 62%) of ketone, bp 55–57° (10 mm). A glpc analysis of the distillate on the 8-ft UCON column[20] (column temp, 100°; helium flow, 85 ml/min) showed it to be greater than 98% pure; its infrared and nmr spectra are identical with those of authentic dehydronorcamphor prepared in the usual manner.[21c]

5-Methylnorborn-2-en-*exo*- and -*endo*-5-ol (10 and 11, Respectively).—To a solution of methylmagnesium iodide, prepared in the usual manner from 2.0 g (0.082 g-atom) of magnesium turnings and 12.7 g (0.0883 mol) of methyl iodide in 100 ml of anhydrous ether, was slowly added a solution of 2.0 g (0.019 mol) of dehydronorcamphor (**5**) in 25 ml of anhydrous ether. After the addition was complete, the reaction mixture was heated at gentle reflux for 1 hr and cooled the complex was decomposed by the addition of water and wet sodium sulfate. The precipitated salts were removed by filtration, and the ethereal solution was dried over anhydrous sodium sulfate and concentrated. The residue was distilled through a short-path distillation apparatus to yield 1.40 g (0.0113 mol, 60%) of the tertiary alcohols. Analysis of the distillate by glpc on the 8-ft UCON column[20] (column temp, 100°; helium flow, 120 ml/min) showed two components. The first (retention time, 4.3 min; rel abundance, 97%) has an ir spectrum (CCl_4) identical with that of *exo*-5-methylnorborn-2-en-*endo*-5-ol.[9b] Its nmr spectrum (CCl_4) has resonances at δ 6.42–5.99, octet (2 $-CH{=}CH-$); 2.88–2.67, broad singlet (1 $\geqslant C-H$, bridgehead); 2.67–2.49, broad singlet (1 $\geqslant C-H$, bridgehead); 1.92–1.73, perturbed doublet (1 $>CHH$); 1.73–1.57, perturbed doublet (2 $>CHH$); 1.57–1.46, perturbed, concentration dependent singlet (1 $\geqslant C-OH$); 1.42, singlet (3 $-CH_3$); 1.27–0.90, perturbed doublet (1 $>CHH$). In dilute

(17) (a) A. C. Cope, E. Ciganek, and N. A. Le Bel, *J. Amer. Chem. Soc.*, **81**, 2799 (1959); (b) J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4083 (1959).

(18) *E.g.*, since the steric factors in *exo* addition (eq 1) to either **5** or **13** are essentially identical (*cf.* **8** and **16**), the electron-withdrawing inductive effect of the double bond could only increase the absolute rate of *exo*-nucleophilic attack upon **5** with respect to a similar attack upon **13**.

(19) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(20) Melting and boiling points are uncorrected. Microanalyses were performed by either Bernhardt Mikroanalitisches Laboratorium, Mülheim, Germany, or Galbraith Laboratories, Inc., Knoxville, Tenn. The mass spectral analysis was performed by the Morgan-Schaffer Corp., Montreal. The infrared spectra were determined on a Perkin-Elmer grating spectrophotometer Model 337, except for the high-dilution spectra which were run on a Perkin-Elmer Model 521 using 1-cm quartz cells. The nmr spectra were determined on a Varian A-60 spectrophotometer at ~35° using tetramethylsilane (δ 0.00) and/or chloroform (δ 7.31) as internal standards in carbon tetrachloride. The glpc analyses, which were not corrected for differences in thermal conductivity of the components, were carried out on an F & M Model 500 linear temperature-programmed gas chromatograph using an 8 ft × 0.25 in. coiled copper tube packed with 20% water-insoluble UCON on 60–80 mesh Chromosorb P, or 12 ft × 0.25 in. copper tubes packed with 20% of a 2:1 mixture of Quadrol/SAIB[8] on 60–80 mesh, nonacid-washed Chromosorb P or with 20% diethyleneglycol succinate (DEGS) on nonacid-washed Chromosorb P. The preparative glpc's were carried out on an Aerograph Autoprep Model 600 using a 10 ft × 0.375 in. coiled aluminum tube packed with 20% Quadrol/SAIB (2:1)[8] on 60–80 mesh, nonacid-washed Chromosorb P.

(21) (a) K. Alder and H. Rickert, *Ann. Chim.*, **543**, 19 (1940); (b) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956); (c) S. J. Cristol and P. K. Freeman, *ibid.*, **83**, 4427 (1961); (d) H. Krieger, *Suomen Kemistilehti, B*, **38**, 68 (1965).

(22) Prepared in 65% yield, as described by Alder and Rickert,[21a] from freshly cracked cyclopentadiene and vinyl formate (Columbia Organic Chemical Co.).

solution (CCl_4), its ir spectrum exhibits an absorption at 3595 cm^{-1} (π- - - H–O) (lit.[23] 3591 cm^{-1}). The second (retention time, 5.6 min; rel abundance, 3%) has an infrared spectrum (CCl_4) in good agreement with the published spectrum of *endo*-5-methylnorborn-2-en-*exo*-5-ol (10)[9b] and shows resonances in the nmr (CCl_4) at δ 6.06, multiplet (2 –C*H*=C*H*–); 2.92–2.50, broad singlet (1 >C–*H*, bridgehead) superimposed on a singlet at 2.85 whose position is concentration dependent (1 >C–O*H*); 2.60–2.13, broad singlet (1 >C–*H*, bridgehead); 2.13–0.93, broad complex multiplet superimposed on a sharp singlet at 1.21 (4 >C*HH* + 3 –CH_3), and exhibits a nonbonded O–H stretch at 3612 cm^{-1} (lit.[23] 3611 cm^{-1}) in its high-dilution (CCl_4) infrared spectrum.

The Reaction of Dehydronorcamphor (5) with Dimethyloxosulfonium Methylide (2).[7]—Trimethyloxosulfonium iodide[24] (11 g, 0.051 mol) was added to a dry-nitrogen-blanketed, stirred suspension of 1.20 g (0.0500 mol) of sodium hydride (available as a 53% dispersion in mineral oil from Metal Hydrides, Inc.) in 40 ml of dimethyl sulfoxide (DMSO). When the evolution of hydrogen had ceased, a solution of 5.40 g (0.0500 mol) of dehydronorcamphor (5) in 20 ml of DMSO was added dropwise over a period of 15 min with cooling. The reaction mixture was stirred at room temperature for 2 hr, at 50–60° for 1 hr, cooled, diluted with 100 ml of water, and extracted with three 50-ml portions of pentane. The pentane extracts were combined, washed with water, dried over anhydrous sodium sulfate, concentrated, and distilled under reduced pressure to yield 4.33 g of product, bp 46.5–49° (8.75 mm).

A glpc analysis on the 12-ft Quadrol/SAIB column[8,20] (column temp, 115°; helium flow, 100 ml/min) revealed the presence of three cleanly separated components[25] which were collected individually and identified as follows. The **first** component (retention time, 19.5 mm; relative abundance, 65%) shows infrared bands (CCl_4) at 3152, 3071, 726, 707 (–CH=CH–); 3045, 1465, 1452, 549, 520 (>C–CH_2–O?); and 1022, 918, 905 cm^{-1} (C–O?); and nmr resonances (CCl_4) at δ 6.14, octet (1 –C*H*=CH– + 1 –CH=C*H*–); 3.05–2.76, broad singlet (1 >C–*H*, bridgehead); 2.63, singlet (2 >C–CH_2–O); 2.32–2.09, broad singlet (1 >C–*H*, bridgehead); 1.92–1.07, complex multiplet (2 >C*HH*); 1.66–1.48, complex multiplet (2 >C*HH*).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.79; H, 8.40.

The authors believed this component to be a spiro[norborn-2-ene-5,2′-oxacyclopropane]. To test this a 95-mg (0.78 mmol) sample was reduced with a stirred slurry of 45 mg (1.2 mmol) of lithium aluminum hydride in 2 ml of anhydrous ether. After 6 hr at reflux, the cooled reaction mixture was hydrolyzed with 15% aqueous sodium hydroxide.[26] The precipitated salts were removed by filtration, and the ethereal solution was dried over sodium sulfate and evaporated to dryness at reduced pressure. Sublimation of the residue at 60° (90 mm) gave 21 mg (0.17 mmol, 22%) of white needles, mp 51–53° (lit.[9b] mp 54.8–55.8°). The retention time of this material on the 8-ft UCON column[20] (column temp, 100°; helium flow, 75 ml/min) and its infrared and nmr spectra are identical with those of the authentic *endo*-5-methylnorborn-2-en-*exo*-5-ol (10). We conclude that this **first** component is spiro[norborn-2-en-*exo*-5,2′-oxacyclopropane] (7).

The **second** component (retention time, 25.1 min; rel abundance, 27%) exhibits infrared bands (CCl_4) at 3140, 3066, 719, 711 (–CH=CH–); 3038, 1466, 1448, 559, 505 (>C–CH_2–O?); 1026, 885, 851 cm^{-1} (C–O?); and nmr resonances (CCl_4) at δ 6.73–6.06, complex multiplet (2 –C*H*=C*H*–); 3.09–2.90, broad singlet (1 >C–*H*, bridgehead); 2.84, singlet (2 >C–CH_2–O); 2.53–2.34, broad singlet (1 >C–*H*, bridgehead); 2.20–1.80, quartet (1 >C*H*H); 1.80–1.58, multiplet (2 >C*HH*); 1.42–1.00, perturbed doublet (1 >C*H*H).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.81; H, 8.25.

It was believed that this second component was also a spiro[norborn-2-en-5,2′-oxacyclopropane], and hence of *endo* configuration (9). This was confirmed by reduction of a 15-mg (0.12 mmol) sample with 12 mg (0.32 mmol) of lithium aluminum hydride as before. The 3.3 mg (0.024 mmol, 20%) of collected product (8-ft UCON column) was identical in every respect with the authentic *exo*-5-methylnorborn-2-en-*endo*-5-ol (11).

The retention time and the infrared and nmr spectra of the third component (retention time, 29.9 min; rel abundance, 8%) are identical with those of authentic dehydronorcamphor (5).

Samples of the two oxides (components 1 and 2) were collected for the reduction and rearrangement studies from the 10-ft Quadrol/SAIB column[20] (column temp, 125°; helium flow, 210 ml/min) on an Autoprep. Neither was rearranged under these conditions.[25]

The Reaction of Dehydronorcamphor (5) with Dimethylsulfonium Methylide (12).[7]—A suspension of 1.44 g (0.060 mol) of dry-nitrogen-blanketed sodium hydride in 30 ml of DMSO was heated at 70–75° for 45 min. The solution was cooled to room temperature, diluted with an equal volume of dry tetrahydrofuran (to prevent freezing), and then cooled in an ice–salt bath. With stirring, a solution of 12.2 g (0.0617 mol) of trimethylsulfonium iodide[7] in 50 ml of DMSO was added over a period of about 3 min. The reaction mixture was stirred for another minute before adding neat 5.04 g (0.0466 mol) of dehydronorcamphor (5). Stirring was continued at ice–salt temperature for 7 min and then for an additional 60 min with no further external cooling. The reaction mixture was then diluted with an equal volume of water (*CAUTION!*), and the product was extracted with four 50-ml portions of pentane. The combined extract was washed with water, dried over anhydrous sodium sulfate, concentrated at atmospheric pressure, and distilled under vacuum to yield 3.48 g of product, bp 50–53° (9 mm), which, by glpc analysis, consists of 6% spiro[norborn-2-en-*exo*-5,2′-oxacyclopropane] (7) and 94% spiro[norborn-2-en-*endo*-5,2′-oxacyclopropane] (9). No unreacted ketone 5 could be detected.

The Reaction of Norborn-2-en-7-one (1) with Dimethylsulfonium Methylide (12).—In the manner described previously, 6.1 g (0.031 mol) of trimethylsulfonium iodide[7] was treated with 0.72 g (0.030 mol) of sodium hydride followed by 2.70 g (0.0250 mol) of norborn-2-en-7-one (1) to yield 1.10 g of distilled product which glpc on the 12-ft Quadrol/SAIB column[20] (column temp, 115°; helium flow, 110 ml/min) revealed to consist of 21% spiro[norborn-2-en-*anti*-7,2′-oxacyclopropane] (4) and 79% unreacted ketone. The spectra of the collected oxide were identical with those described previously.[2] No unsaturated *syn* oxide could be detected.

Spiro[norbornan-*exo*-2,2′-oxacyclopropane] (15).—A solution of 212 mg (1.74 mmol) of spiro[norborn-2-en-*exo*-5,2′-oxacyclopropane] (7) in 15 ml of ethyl acetate was hydrogenated at atmospheric pressure using 16 mg of 5% palladium on carbon as a catalyst. The first 1.03 equiv (44.0 ml, 1.80 mmol) of hydrogen was absorbed in 30 min, after which time the rate of hydrogen uptake decreased sharply. The reaction was stopped at this point, the catalyst was removed by filtration, and the solvent was stripped by distillation at atmospheric pressure through a 0.5 × 15 cm wire-spiral-packed column. Distillation of the residue at 10 mm in a short-path still (bath temp, 85°) yielded 163 mg (1.32 mmol, 76%) of the colorless liquid, saturated *exo* oxide 15. Its infrared spectrum (CCl_4) shows no bands attributable to a double bond or a hydroxyl group but has absorptions at 3046, 1468, 1450, 528 (>C–CH_2–O?), 943 cm^{-1} (C–O?); nmr (CCl_4), δ 2.61, singlet (2 >C–CH_2–O); 2.50–2.24, broad singlet (1 >C–*H*, bridgehead); 1.86–1.00, complex multiplet (1 >C–*H*, bridgehead + 8 >C*HH*).

Anal. Calcd for $C_8H_{12}O$: C, 77.34; H, 9.74. Found: C, 77.01; H, 9.68.

Spiro[norbornan-*endo*-2,2′-oxacyclopropane] (17).—A 160-mg (1.31 mmol) sample of spiro[norborn-2-en-*endo*-5,2′-oxacyclopropane] (9) was hydrogenated in the same manner to yield 105 mg (0.846 mmol, 65%) of distilled (bath temp, 75°; pressure, 14 mm) saturated *endo* oxide 17: infrared (CCl_4) 3045, 1468, 1455, 517 (>C–CH_2–O?); 1060, 961, 951 cm^{-1} (C–O?); nmr, (CCl_4) δ 2.72, asymmetric doublet (1 >C–C$H_A$$H_B$–O); 2.54, asymmetric doublet (1 >C–C$H_A$$H_B$–O)—taken together these two doublets constitute a typical AB-type quartet,[10] J_{AB} = 5.8 cps, centered at δ 2.63; 2.46–2.17, broad singlet (1 >C–*H*, bridgehead); complex multiplet (1 >C–*H*, bridgehead + 8 >C*HH*).

(23) P. Hirsjarvi and K. Salo, *Suomen Kemistilehti, B*, **32**, 280 (1959).
(24) R. Kuhn and H. Trischmann, *Ann. Chim.*, **611**, 117 (1958).
(25) We have observed that an accumulation of acidic residues in the injection port of the gas chromatograph can cause the epoxides to rearrange to aldehyde. In order to obtain reproducible analytical results it was necessary to wash the injection port with base prior to the analysis of this mixture.
(26) V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

Anal. Calcd for $C_8H_{12}O$: C, 77.34; H, 9.74. Found: C, 76.88; H, 10.11;[27] mol wt (by mass spectrometry)[20] 124.

The Reaction of Norcamphor (13) with Dimethyloxosulfonium Methylide (2).[7]—In the manner described previously a 5.30-g (0.0482 mol) sample of norcamphor (**13**) was allowed to react with an ~10% excess of dimethyloxosulfonium methylide in DMSO. Distillation of the product, bp 59–59.5° (14 mm), gave 4.00 g of clear liquid which was shown by glpc on the 12-ft Quadrol/SAIB column[20] (column temp, 125°; helium flow, 90 ml/min) to consist of at least two components. The **first** peak (retention time, 10.2 min; rel abundance, >98%) was shown by analysis of its infrared and nmr spectra (see Results) to be due to a 1:10 mixture of the saturated spiro[norbornan-*exo*- and -*endo*-2,2′-oxacyclopropanes] (**15** and **17**), respectively, while the **second** component (retention time, 17.4 min; relative abundance, <2%) was identical in all respects with the starting ketone **13**.

The Reaction of Norcamphor (13) with Dimethylsulfonium Methylide (12).—A 5.50-g (0.0500 mol) sample of norcamphor (**13**) was allowed to react in the manner described previously with a solution of the ylide generated from 1.2 g (0.050 mol) of sodium hydride and 11.3 g (0.0571 mol) of trimethylsulfonium iodide[7] in DMSO. The 4.1 g of distilled product was shown by glpc on the 12-ft Quadrol/SAIB column[20] (column temp, 125°; helium flow, 90 ml/min) to consist of at least two components. The **first** component (retention time, 10.2 min; relative abundance, 43%) was shown by nmr to consist of 95% spiro[norbornan-*endo*-2,2′-oxacyclopropane] (**17**) and 5% spiro[norbornan-*exo*-2,2′-oxacyclopropane] (**15**). The **second** peak (retention time, 17.4 min; relative abundance, 57%) was identified as unreacted starting material (**13**) by its retention time and its infrared and nmr spectra.

Competitive Reaction Rates. A. Of Dimethyloxosulfonium Methylide (2) with Norcamphor (13) and Dehydronorcamphor (5).—A solution of 0.025 mol of ylide in 20 ml of DMSO was prepared as described previously and allowed to come to thermal equilibrium in an oil bath at 25.0°. A similarly thermostated solution containing 0.044 mol of ketone [42.8% dehydronorcamphor (**5**), 57.2% norcamphor (**13**) by glpc] in 10 ml of DMSO was added to the solution of ylide over a 10-min period. After the addition had been completed, the mixture was stirred for 1 additional hr, decomposed by the addition of 50 ml of water, and extracted with three 25-ml portions of pentane. The combined extract was washed with water, dried over anhydrous sodium sulfate, and concentrated by distillation of the solvent at atmospheric pressure through a 15-cm, wire-spiral-packed column. The concentrate was analyzed by glpc on the 12-ft Quadrol/SAIB column[20,25] (injection port temp 155°;[28] column temp, 115°; helium flow, 90 ml/min). The mixture contained 2.9 parts spiro[norbornan-2,2′-oxacyclopropanes] [10% *exo* (**15**) to 90% *endo* (**17**) *vide supra*], 3.2 parts spiro[norborn-2-en-5,2′-oxacyclopropanes] [71% *exo* (**7**) to 29% *endo* (**9**), *vide supra*], 1.0 part dehydronorcamphor (**5**), and 3.0 parts norcamphor (**13**). The relative reactivities calculated[14] from these data are shown in Chart II.

B. Of Dimethyloxosulfonium Methylide (2) with Norbornen-7-one (1) and Dehydronorcamphor (5).—The product concentrate from a similar experiment using a mixture of 62.4% norbornen-7-one (**1**) and 37.6% dehydronorcamphor (**5**) consisted of 22.6 parts spiro[norbornen-*anti*-7,2′-oxacyclopropane] (**4**), 1.0 part spiro[norborn-2-en-5,2′-oxacyclopropanes] (71% **7**, 29% **9** as before), 3.9 parts norbornen-7-one (**1**),[28] and 23.0 parts dehydronorcamphor (**5**). The calculated[14] relative reactivities are shown in Chart II.

C. Of Dimethyloxosulfonium Methylide (2) with Norbornen-7-one (1) and Norbornan-7-one (18).—In a similar manner a solution of 1.08 g (0.0100 mol) of norbornene-7-one (**1**) and 1.10 g (0.0100 mol) of norbornan-7-one (**18**) in 30 ml of DMSO was added to a solution of ylide prepared by the reaction of 0.24 g (0.010 mol) of sodium hydride and 2.2 g (0.0095 mol) of trimethyloxosulfonium iodide in 10 ml of DMSO. The reaction mixture was stirred overnight before being diluted with 70 ml of water. The resulting white sulfur-containing precipitate, after being washed with water and several portions of pentane, amounted to 0.562 g.[12]

The aqueous filtrate was extracted with five 20-ml portions of pentane which were combined with the previous pentane washings, washed further with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to 5 ml as before. A glpc analysis of the concentrate, *vide supra*, revealed the presence of 78.6 parts spiro[norborn-2-en-*anti*-7,2′-oxacyclopropane] (**4**), 5.2 parts norbornen-7-one (**1**), 9.6 parts spiro[norbornan-7,2′-oxacyclopropane], and 6.6 parts norbornan-7-one (**18**). The approximate relative reactivity of the two ketones is shown in Chart II.[11]

Registry No.—**7**, 16282-08-9; **9**, 16282-09-0; **10**, 3212-13-3; **11**, 3212-14-4; **15**, 16282-10-3; **17**, 16282-11-4.

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(27) Considerable difficulty was experienced in obtaining good analytical data on this material. The mean of seven carbon–hydrogen determinations carried out by two different laboratories[20] over a 27-month period is C, 76.67 ± 0.28; H, 9.90 ± 0.33. The value reported in the text is the best of these individual determinations. We suspect that the difficulty arises from the demonstrably facile rearrangement of the epoxide to norbornancarboxaldehyde which is partially oxidized and/or hydrated prior to weighing.

(28) Norbornen-7-one does not decarbonylate under these glpc conditions.

Intramolecular Nucleophilic Participation. VII. The Role of the *o*-Carbomethoxy Group in the Solvolysis of Ring-Substituted Benzyl Halides and Their α-Methyl Derivatives

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Rate constants (k_s) for the solvolysis of 1-(2- and 4-carbomethoxyphenyl)ethyl bromides in 80 vol. % aqueous dioxane have been determined. In this medium at ordinary temperatures the 2-carbomethoxy derivative hydrolyzes more rapidly than its 4-carbomethoxy isomer. The k_s values have been compared with those for reactions under comparable conditions of structurally related carbomethoxy and dicarbomethoxy derivatives of benzyl and 1-phenylethyl bromides, and the role of the *o*-CO_2CH_3 group as an internal nucleophile in promoting solvolytic reactions of substituted benzyl halides and their α-methyl derivatives has been reevaluated. The contribution of this substituent as a participant in hydrolytic processes appears to increase with changes in structure of the reacting halide in the order *o*-$CH_3OOCC_6H_4CH_2X$ < *o*-$CH_3OOCC_6H_4CH(CH_3)X$ < *o*-$CH_3OOCC_6H_4C(CH_3)_2X$. This series is discussed in terms of the orientation of the bonds to α carbon relative to the ring plane in the activated complexes for hydrolysis of such compounds.

The fact that *o*-carbophenoxybenzhydryl bromide hydrolyzes considerably more rapidly than its *para* isomer has been ascribed to the capacity of the *o*-CO_2R group to participate as a nucleophile in the polar rupture of the carbon–bromine bond.[1] The solvolysis rates of *o*-carbomethoxybenzyl bromide and the *o*-carbomethoxy derivative of phenyldimethylcarbinyl chloride (*t*-cumyl chloride) are somewhat larger than those of their *para* isomers, but the differences in reactivity are not so great as those observed for the substituted benzhydryl halides. It was, therefore, concluded that the ring substituent does not function very effectively as a participant in the reactions of the *o*-carbomethoxy derivatives of either the benzyl or cumyl halide.[1,2] In the case of the reaction of the benzyl halide it is reasoned that, for maximum stabilization of the activated complex, the bonds to carbon at the reaction center must lie in the plane of the aromatic nucleus. This provides for maximum overlap of the ring π electrons with the vacant, or partially vacant, p orbital which develops as halide ion departs. This is a conformation which is not favorable for the involvement of the *ortho* substituent. A similar explanation has been considered in discussing the *t*-cumyl chloride results, and alternatively it has been suggested that an activated complex which is akin to a carbonium ion generated from a tertiary halide might not derive much additional stabilization through electron release by *o*-CO_2CH_3 even if the geometric situation were favorable.[3]

The 1-(2- and 4-carbomethoxyphenyl)ethyl bromides have now been prepared, and their solvolysis rates in 80 vol. % aqueous dioxane have been investigated. The results of a comparative study of the hydrolysis rates of the 1-(2,4- and 2,6-dicarbomethoxyphenyl)ethyl bromides have also become available recently.[4] With this new information at hand it is appropriate to reevaluate the contribution of the carbomethoxy group as a participant in polar reactions of *o*-carbomethoxybenzyl halides and their α-methyl derivatives.

Results and Discussion

Table I is presented to review briefly the relative influences of nonparticipating *ortho* and *para* substituents on the solvolysis rates of benzyl halides and their α-methyl and α,α-dimethyl derivatives. The *ortho*-substituted compounds are less reactive than their *para* isomers, even in those cases in which the opposite order is predicted if only the inductive effects of the substituents are taken into consideration [as, for example, for *o*- and *p*-$CH_3C_6H_4C(CH_3)_2Cl$].[5] The factor which is dominant in controlling the relative reactivities of the pairs of isomers must, therefore, be the steric hindrance provided by the *ortho*-ring substituents to stabilization of the activated complex through solvation and through delocalization of ring π electrons.[6-8]

TABLE I

SOLVOLYSIS RATE CONSTANT RATIOS [k_s (*ortho*)/k_s (*para*)] FOR ISOMERIC MONOSUBSTITUTED BENZYL, 1-PHENYLETHYL, OR *t*-CUMYL HALIDES

Compounds	Solvent	Temp, °C	k_s (*ortho*)/k_s (*para*)	Ref
o- and *p*-$ClC_6H_4CH_2Cl$	50% aq acetone	50	0.52	*a*
o- and *p*-$CH_3C_6H_4CH_2Cl$	50% aq acetone	50	0.48	*a*
o- and *p*-$CH_3C_6H_4CH(CH_3)Cl$	100% ethanol	34.8	0.41	*b*
o- and *p*-$ClC_6H_4C(CH_3)_2Cl$	90% aq acetone	25	0.026	*c*
o- and *p*-$CH_3C_6H_4C(CH_3)_2Cl$	90% aq acetone	25	0.14	*d*

[a] S. C. J. Olivier, *Rec. Trav. Chim.*, **49**, 697 (1930). [b] See ref 6. [c] H. C. Brown, Y. Okamoto, and G. Ham, *J. Amer. Chem. Soc.*, **79**, 1906 (1957). [d] See ref 5.

In Table II a summary is presented of rate runs which have been made in studying the hydrolysis of the 1-(2- and 4-carbomethoxyphenyl)ethyl bromides, later designated as compounds VII and VIII. In Table III a comparison is made of the solvolysis rate constants of these two compounds in 80 vol. % aqueous dioxane at 70.7° relative to those of 1-phenylethyl bromide and two of its dicarbomethoxy derivatives and with those of benzyl bromide and certain of its mono- and dicarbomethoxy derivatives.

Although no other substituent (*e.g.*, CH_3 or Cl) can

(1) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **84**, 1179 (1962).

(2) J. L. Cotter, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **28**, 1917 (1963).

(3) E. A. Jeffery, R. K. Bansal, L. J. Andrews, and R. M. Keefer, *ibid.*, **29**, 3365 (1964).

(4) M. J. Strauss, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, in press.

(5) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *ibid.*, **79**, 1897 (1957).

(6) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 850 (1956).

(7) G. Baddeley, J. Chadwick, and H. T. Taylor, *ibid.*, 2405 (1954).

(8) S. Winstein and B. K. Morse, *J. Amer. Chem. Soc.*, **74**, 1133 (1952).

TABLE II

RATE CONSTANTS FOR HYDROLYSIS OF THE 1-(2- AND 4-CARBOMETHOXYPHENYL)ETHYL BROMIDES, $CH_3CH(Br)C_6H_4CO_2CH_3$, IN 80% AQUEOUS DIOXANE

Isomer	Range[a] of [RBr]$_i$, mol/l.	Temp, °C	$10^5 k_s$,[b] sec^{-1}
2-CO_2CH_3	0.039–0.075	70.7	12.2 ± 1.0
4-CO_2CH_3	0.026–0.041	70.7	1.59 ± 0.05
2-CO_2CH_3	0.054–0.123	45.4	0.87 ± 0.02
4-CO_2CH_3	0.026–0.060	45.4	0.123 ± 0.01

[a] Three runs at differing initial reactant concentration were made with each isomer at the two temperatures. [b] Activation parameters have been calculated using the rate constants reported at the two temperatures. For the 2-CO_2CH_3 derivative values of E_a = 22.0 ± 0.2 kcal and $\Delta S^{\ddagger}$ = −13.1 ± 0.6 eu have been obtained and for the 4-CO_2CH_3 derivative, E_a = 21.3 ± 0.2 kcal and $\Delta S^{\ddagger}$ = −18.9 ± 0.6 eu.

serve as a totally adequate model for the carbomethoxy group, it is concluded on the basis of the results summarized in Table I that, if *o*-CO_2CH_3 were nonparticipating in reactions of the type under consideration, *p*-carbomethoxy-substituted benzyl and related halides should be more reactive than their *ortho* isomers. Actually the reverse is true, as is revealed in various ways in Table III.

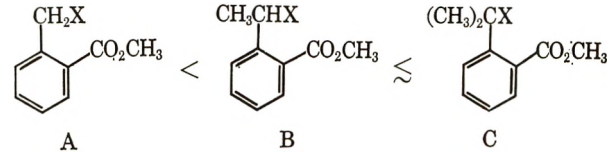
The introduction of a carbomethoxy substituent *para* to the reaction center of benzyl bromide and also of 1-phenylethyl bromide results in diminished reactivity, much more so in the latter case than in the former (*cf.* compounds I and III and VI and VIII). Even if there were no accompanying steric effects, it might normally be anticipated that the rate repression produced by *p*-CO_2CH_3, which is electronic in nature, would be more strongly manifested if the substituents were moved from *para* to *ortho* positions; yet the rate constant for 1-(2-carbomethoxyphenyl)ethyl bromide (VII), though substantially less than that of the parent bromide (VI), is almost eight times that of its *para* isomer (VIII), and *o*-carbomethoxybenzyl bromide (II) hydrolyzes almost four times as readily as its *para* isomer (III) and is even somewhat more reactive than benzyl bromide itself.

The rate-lowering effect of *p*-CO_2CH_3 can also be observed by comparing the relative rate constants of the *o*-carbomethoxy-substituted benzyl and 1-phenylethyl bromides with those of the corresponding 2,4-dicarbomethoxy-substituted bromides. On this basis V is only about one-third as reactive as II, and X about one-fourth as reactive as VII. On the other hand, a slightly enhanced reactivity results when *o*-CO_2CH_3 is introduced as a second substituent in a bromide which is already substituted with *p*-CO_2CH_3 (*cf.* III and V and also VIII and X).

In the case of the hydrolysis of 1-(2,6-dicarbomethoxyphenyl)ethyl bromide (IX) the conditions for forced participation of the two CO_2CH_3 groups which flank the reaction center are ideal.[4] In the activated complex the bonds to the carbon at the reaction center must lie in or near a plane perpendicular to the ring because of the severe steric barrier to the attainment of other conformational arrangements which is created by the *ortho* substituents. This places the p orbital at the α carbon in a highly favorable position to accept electrons from either *o*-CO_2CH_3 group. Compound IX has a k_s value over four times that for its 2,4 isomer (X), while the solvolysis rate constants ratios for the chlorine analogs of IX and X (in which CO_2CH_3 groups are replaced by Cl) is about 0.06;[4] that is, the reactivity ratio of IX to X is about 70 times as large as would be predicted on the basis of the behavior of the dichlorophenylethyl bromides. The fact that the 2,4- and 2,6-dicarbomethoxybenzyl bromides (IV and V) are comparable in reactivity is considered to indicate that there is little, if any, steric opposition to a coplanar orientation of the ring and the bonds to trigonal carbon in the activated complex for hydrolysis of IV. This conclusion can be confirmed by the use of molecular models.

It now seems safe to state without qualification that the hydrolysis of *o*-carbomethoxybenzyl bromide (II) as well as of 1-(2-carbomethoxyphenyl)ethyl bromide (VII) is subject to rate enhancement to some degree through release of electrons in the activation process from CO_2CH_3 to the carbon undergoing positive polarization. This statement should be generally applicable to any of the compounds in Table III which have *o*-carbomethoxy substituents.

The influence of the carbomethoxy group as a participant in the reactions of II and VII is considered to be much less than in the reaction of IX since the *ortho*/*para* isomer rate constant ratios for benzyl and phenylethyl bromides which bear nonparticipating substituents are much larger than the corresponding ratios of the chlorine substituted analogs of IX and X (see Table I). The k_s ratio for the *o*- and *p*-carbomethoxy derivatives of *t*-cumyl chloride[2] is of the order of 2.5:1 in 70% aqueous acetone at 25°. By taking this figure and the appropriate data from Tables I and II into consideration, it has been concluded that the influence of *o*-carbomethoxy as a participant on substrate reactivity in solvolytic processes becomes increasingly more important in the order



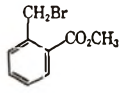
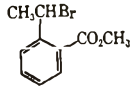
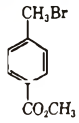
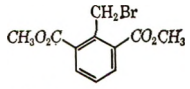
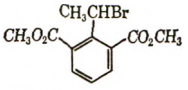
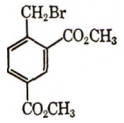
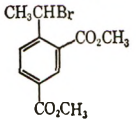
A B C

It seems reasonably safe to say that the hydrolysis of the *t*-cumyl halide derivative is at least as strongly influenced by the *o*-CO_2CH_3 group (functioning as a neighboring nucleophile) as is the reaction of the 1-phenylethyl halide. A more quantitative comparison is not justified because of the difficulties in choosing k_s (*ortho*)/k_s (*para*) ratios (Table II) which would correctly reflect the relative reactivities of the pairs of isomers if *ortho*-substituent participation did not occur and because of differences in reaction conditions employed in studying A, B, and C (*e.g.*, solvent, temperature, and the identity of X).

The above series runs parallel to the relative stability series for the benzyl, 1-phenylethyl, and *t*-cumyl cations. Since these cations are respectively primary, secondary, and tertiary, it seems likely that the importance of bonding interactions between the ring and the reacton center in providing for stabilization of the activated complexes for hydrolysis of the halides in question should diminish in that same order; that is, the energy sacrificed in moving the bonds to trigonal carbon out of the ring plane of the activated complexes should

TABLE III

RELATIVE SOLVOLYSIS RATE CONSTANTS OF CARBOMETHOXY AND DICARBOMETHOXY DERIVATIVES OF BENZYL AND 1-PHENYLETHYL BROMIDES [80 VOL. % AQUEOUS DIOXANE, 70.7°][a]

No.	Compound	Rel reactivity	k_s (*ortho*)/k_s (*para*)	No.	Compound	Rel reactivity	k_s (*ortho*)/k_s (*para*)
I		1.00		VI		64.5	
II		1.4	3.5	VII		6.9	7.8
III		0.40		VIII		0.89	
IV		0.30	0.55[b]	IX		7.9	4.4[b]
V		0.55		X		1.8	

[a] The k_s values for compounds I, II, and III were calculated from data presented by A. Singh, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, 84, 1179 (1962); the values for compounds IV, V, IX, and X are from M. J. Strauss, L. J. Andrews, and R. M. Keefer, *ibid.*, in press; and that for VI was calculated from data of A. H. Fainberg and S. Winstein, *ibid.*, 79, 1602 (1957). [b] The ratio of k_s values for the 2,6- and 2,4-disubstituted compounds.

drop off in this order, and this should be increasingly favorable for the effective release of electrons from the carbomethoxy group to the vacant p orbital of the α carbon. In the case of the *o*-carbomethoxy-substituted *t*-cumyl cation there is no doubt significant steric opposition to the attainment of a coplanar orientation of the ring and the bonds to trigonal carbon.

It is conceivable that, in the reactions of the *o*-carbomethoxy derivatives of the benzyl as well as of the 1-phenylethyl and *t*-cumyl halides, the activated complexes might assume conformations which provide for maximum *ortho*-substituent participation. Under these circumstances the thermodynamic disadvantages of a complete sacrifice of bonding interactions of the reaction center and the ring presumably would be fully offset through involvement of CO_2CH_3. Particularly for the benzyl halide reaction, in which the rate enhancement associated with participation by *o*-CO_2CH_3 is rather subtle, it is considered improbable that the activated complex actually is so structured. Rather it is considered likely that the plane of the trigonal carbon lies in a position somewhere between the ring plane and its perpendicular bisector. Presumably as ring-electron delocalization makes a diminishingly important contribution in providing for stabilization of the activated complex (as the reacting halide changes from primary to secondary to tertiary), the plane of the trigonal carbon shifts progressively toward a position most favorable for involvement of the *ortho* nucleophile. The unusual effectiveness of *o*-$COOC_6H_5$ in promoting the hydrolysis of *o*-carbophenoxybenzhydryl bromide is thought to result because the geometry of the activated complex is favorable for acceptance by the trigonal carbon of electrons both from the unsubstituted ring and from the substituent on the other ring.

Since the process of substituent participation has some of the characteristics of an Sn2 reaction, hydrolysis of the tertiary halide (C in the series A–B–C) conceivably might have been found to be less susceptible to the influence of the *ortho* nucleophile than the hydrolysis of the secondary halide (B). Though this does not seem to be the case, it will be recalled in this connection that the *o*-carbophenoxy group is apparently a much less effective participant in the hydrolysis of a substituted 1,1-diphenylethyl halide than of a substituted benzhydryl halide.[3]

From the thermodynamic standpoint the solvolysis rate constant for 1-(2-carbomethoxyphenyl)ethyl bromide (VII) is higher than that for 1-(4-carbomethoxyphenyl)ethyl bromide (VIII) because the activation entropy for reaction of VII is much less negative than that for VIII; the activation energy for VII is actually slightly greater than that for VIII (see Table II). In this instance the entropy loss associated with participation appears to be substantially less than that connected with the incorporation of solvent in the activated complex when the carbomethoxy group is *para* to the reaction center. The fact that *o*-carbomethoxybenzyl bromide hydrolyzes faster than its *para* isomer at normal temperatures is similarly explained.[1] In the case of the carbomethoxy derivatives of *t*-cumyl chloride, however, the *ortho* isomer has the lower activation energy (by about 3 kcal) and more negative entropy of activation (by about 9 eu); these figures apply to reaction in 70% aqueous acetone.[2,9] This reversal is explained on the grounds that the activated complex for solvolysis of the *para*-substituted *t*-cumyl halide is less extensively solvated than that for the corresponding

(9) Activation entropies in solvolytic processes are frequently considerably less negative for reactions which occur with than for those which take place without neighboring group participation. Such differences in activation energies have been used in a diagnostic sense, as for example in establishing which aryl groups provide anchimeric assistance in the solvolysis of 2-aryl benzenesulfonates; *cf.* S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4803 (1956).

α-phenylethyl halide. The differences in activation parameters for the reactions of the *ortho*- and *para*-substituted *t*-cumyl chlorides are, in fact, directionally like those predicted if the contribution of solvent in providing for stabilization of the activated complex is ignored.

Experimental Section

1-(4-Carbomethoxyphenyl)ethyl Bromide.—A sample of 4-iodo-1-ethylbenzene was prepared by treatment of the diazonium salt of *p*-ethylaniline (K & K Laboratories) with potassium iodide.[10] The Grignard reagent prepared from the iodo compound was carbonated to obtain a crude sample of *p*-ethylbenzoic acid, mp 106–109° (lit.[11] mp 112°). This was converted into its acid chloride by heating with thionyl chloride, and the aroyl halide was esterified with methanol to obtain methyl *p*-ethylbenzoate, bp 80–82° (2 mm) [lit.[11] bp 121–123° (20 mm)]. A mixture of 6.5 g of the ester, 7.2 g of N-bromosuccinimide, and 0.1 g of benzoyl peroxide in 120 ml of carbon tetrachloride was irradiated with ultraviolet light and heated at reflux for 0.5 hr. After removal of the succinimide and the solvent, 1-(4-carbomethoxyphenyl)ethyl bromide was obtained as a pale yellow oil. This was crystallized from ligroin to provide 7.0 g (66% yield) of colorless needles, mp 29° [lit.[11] bp 135–138° (1 mm)]; no melting point has been reported previously.

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.38; H, 4.58; Br, 32.90.

The nmr spectrum of this material in carbon tetrachloride shows a doublet at τ 8.02 (side chain CH_3), a singlet at 6.70 ($-COOCH_3$), a quartet centered at 4.92 (benzylic H), and two doublets at 2.61 and 2.08 (the aromatic A_2B_2 system).

1-(2-Carbomethoxyphenyl)ethyl Bromide.—The same general procedures which were applied in the synthetic sequence described above were used to convert *o*-ethylaniline (Eastman Organic Chemicals) to 1-ethyl-2-iodobenzene[12] and the iodo compound to *o*-ethylbenzoic acid, mp 62–64° (lit.[13] mp 65–65.5°). The acid was converted by way of the acid chloride to its methyl ester,[14] bp 75° (1 mm). A mixture of 10 g of the methyl *o*-ethylbenzoate, 11.1 g of N-bromosuccinimide, and 0.1 g of benzoyl peroxide in 200 ml of carbon tetrachloride was heated at reflux and irradiated with ultraviolet light for 20 min. After removal of succinimide and the solvent, various unsuccessful attempts were made to induce crystallization of the oily product. It was finally dissolved in ligroin, and the solution was treated with decolorizing carbon. The ligroin was then removed under reduced pressure, leaving 11 g (74% yield) of pale yellow 1-(2-carbomethoxyphenyl)ethyl bromide.

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 48.86; H, 3.81; Br, 33.02.

Distillation of this material was not attempted since the structurally similar compounds, *e.g.*, *o*-carbomethoxybenzyl bromide, decompose to give phthalide under such conditions.[1]

Although the product was not analytically pure its nmr spectrum in carbon tetrachloride showed only peaks characteristic of 1-(2-carbomethoxyphenyl)ethyl bromide; these included a doublet at τ 8.34 (side-chain CH_3), a singlet at 6.50 ($-COOCH_3$), a quartet centered at 3.80 (benzylic H), and a multiplet at 2.3–3.3 (aromatic H).

Kinetic Experiments.—The method of purification of the dioxane used in the rate studies has been described previously.[1] In all runs 80 vol. % aqueous dioxane prepared by mixing 20 vol. of water and 80 vol. of purified dioxane at room temperature was used as the solvent. The changes in hydrogen bromide content of the rate mixtures which took place during hydrolysis of the organic bromides were determined by observing the accompanying downfield shifts of the hydroxylic proton nmr peak of the reaction medium. The use of this method in studying the kinetics of hydrolysis of organic halides has been described in detail previously.[4] The rate constants, k_s, which are reported are defined by the equation, $k_s = 2.303/t \ (\log [RBr]_i/[RBr]_t)$, in which the subscripts i and t relate to initial time and time t.

Products of Hydrolysis of the Isomeric 1-(Carbomethoxyphenyl)ethyl Bromides.—A small sample of each of the two bromides was hydrolyzed in aqueous dioxane at 70.7° under conditions comparable to those of the rate runs. The reaction was allowed to proceed for at least 8 half-lives. The solvent was then removed under vacuum at room temperature. The residue was extracted with ether, and the dried extract was concentrated to dryness to obtain the reaction product. The material isolated from the reaction of 1-(2-carbomethoxyphenyl)ethyl bromide was 1-oxo-3-methylphthalan.[15] Because only a small quantity of the liquid product was obtained distillation was not attempted. Its elemental analysis and spectral properties were sufficient to identify it.

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.04; H, 5.33.

The nmr spectrum of the neat liquid showed a doublet at τ 8.78 (side-chain CH_3), a quartet at 4.78 (benzylic H), and a complex multiplet at 2.7 (aromatic H). The infrared spectrum of the liquid showed a strong carbonyl stretch at 1765 cm^{-1}.

Phthalide has been isolated from the products of hydrolysis of *o*-carboxybenzyl bromide,[1] and phthalan derivatives have been obtained from the 2,4- and 2,6-dicarbomethoxybenzyl bromides and the 1-(2,4- and 2,6-dicarbomethoxyphenyl)ethyl bromides.[4] It is not certain whether these are produced directly from the hydrolysis of the bromides or whether they are generated from substituted benzyl alcohols or 1-phenylethanol derivatives which possibly may form as reaction intermediates. This matter has not been further investigated since satisfactory procedures for preparing samples of *o*-carbomethoxybenzyl alcohol and structurally related alcohols have not been discovered.

No pure product could be isolated from the hydrolysis of 1-(4-carbomethoxyphenyl)ethyl bromide. The material recovered was presumably a mixture of 1-(4-carbomethoxyphenyl)ethanol and 1-(4-carboxyphenyl)ethanol. The nmr spectrum of the mixture (in CCl_4) showed a doublet at τ 8.65 (side-chain CH_3), a singlet at 6.23 ($-CO_2CH_3$), a quartet at 5.2 (benzylic H), and two doublets at 2.7 and 2.2 (the A_2B_2 aromatic system). The infrared spectrum of the crude product showed absorption at 3600 cm^{-1} (OH stretch) and a broad carbonyl band at 1700–1725 cm^{-1}.

Registry No.—I, 100-39-0; II, 2417-73-4; III, 2417-72-3; IV, 16281-93-9; V, 16281-94-0; VI, 585-71-7; VII, 16281-95-1; VIII, 16281-97-3; IX, 16281-98-4; X, 16281-99-5.

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(10) C. Willgerodt and W. Bergdolt, *Ann. Chim.*, **327**, 287 (1903).

(11) E. D. Bergman and J. Blum, *J. Org. Chem.*, **24**, 549 (1959).

(12) F. Weygand, H. Weber, E. Makawa, and G. Eberhard, *Chem. Ber.*, **89**, 1994 (1956).

(13) C. R. Hauser and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **76**, 1264 (1954).

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Chemistry of Cyclopropanols. VII. Pyrolysis of Cyclopropyl Acetates

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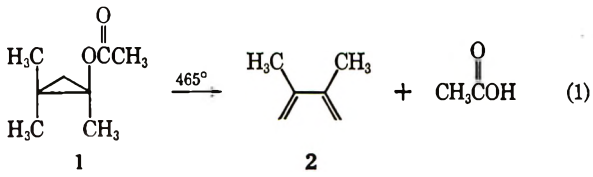
On pyrolysis at 485° cyclopropyl acetate, 1-methylcyclopropyl acetate, and 1,2,2-trimethylcyclopropyl acetate undergo a smooth rearrangement to allylacetates or their pyrolysis products. 1- and 2-arylcyclopropyl acetates, by contrast, give rise to numerous products including methylphenylacetylene, propiophenone, and indene derivatives. The products of both groups of compounds are suggested to arise by cyclopropane-bond homolysis.

In line with our earlier interest in the pyrolysis of cyclic esters,[1] we have subjected a variety of cyclopropyl esters[2] to the normal conditions for these elimination reactions. These studies have uncovered a new cyclopropyl rearrangement and shed some light on the mechanism of the pyrolyses of cyclopropane compounds in general.

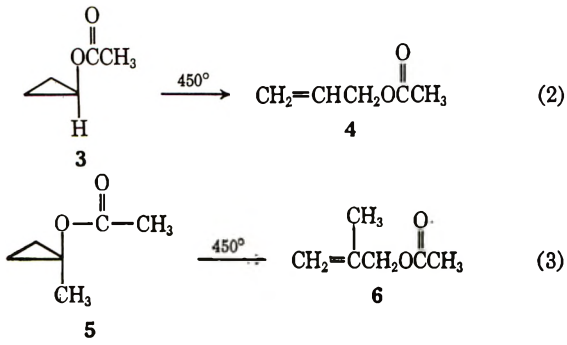
We first examined the pyrolysis of the easily obtained[3] 1,2,2-trimethylcyclopropyl acetate. During pyrolysis by dropping through a helices-packed tube at 465°[4] 1 molar equiv of acetic acid was smoothly eliminated, and the cyclopropyl acetate was quantitatively converted into 2,3-dimethylbutadiene (eq 1). Various



(1)

1 2

mechanisms can be written to account for this transformation, but many can be ruled out by our subsequent observation that cyclopropyl and 1-methylcyclopropyl acetate were converted into allyl and 2-methylallyl acetate, respectively, under essentially the same conditions (eq 2 and 3). Obviously a similar rearrangement of the trimethyl acetate would lead to the formation of an allyl acetate which would undergo pyrolytic elimination under the reaction conditions.



(2)

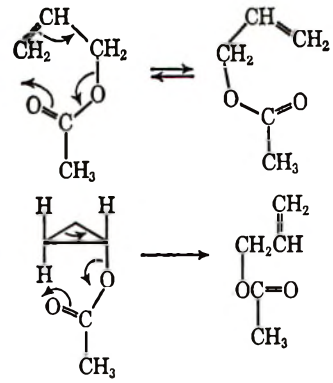
3 4

(3)

5 6

Our initial inclination was to consider this to be a cyclopropyl analog of the well-known Cope rearrangement of allyl esters[5] in which a new C–O bond is formed, the ring opens and the old C–O bond is broken simultaneously (Scheme I). While such a highly concerted

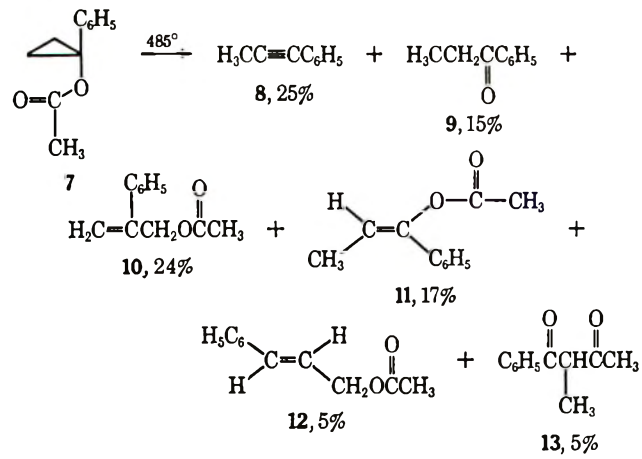
Scheme I



reaction might appear attractive, subsequent work has made it unlikely.

Whereas the alkyl-substituted cyclopropyl acetates lead cleanly to a single product upon pyrolysis, aryl cyclopropyl acetates give rise to complex mixtures of products. In the case of 1-phenylcyclopropyl acetate we have attempted a reasonably complete analysis of the compounds formed (Scheme II). The percentages given for the products of this pyrolysis are based on complete conversion of the starting acetate.

Scheme II



7 8, 25% 9, 15%

10, 24% 11, 17%

12, 5% 13, 5%

The drastic change in products obtained with phenyl substitution is understandable if the pyrolysis is assumed to proceed by homolytic bond cleavage to a 1,3-trimethylene diradical. Such a cleavage is expected to occur at these temperatures, since they are in the region where 1,2-dideuteriocyclopropane undergoes *cis–trans* isomerization.[6] The diradical could be trapped by the carbonyl group of the acetate, leading eventually to rearrangement.

(1) C. H. DePuy, R. W. King, and D. H. Froemsdorf, *Tetrahedron*, **7**, 123 (1959).

(2) C. H. DePuy, G. M. Dappen, and R. A. Klein, *J. Org. Chem.*, **27**, 3742 (1962).

(3) J. P. Freeman, *ibid.*, **29**, 1379 (1964).

(4) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(5) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, **21**, 328 (1956).

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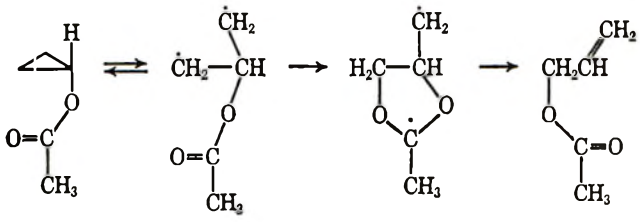
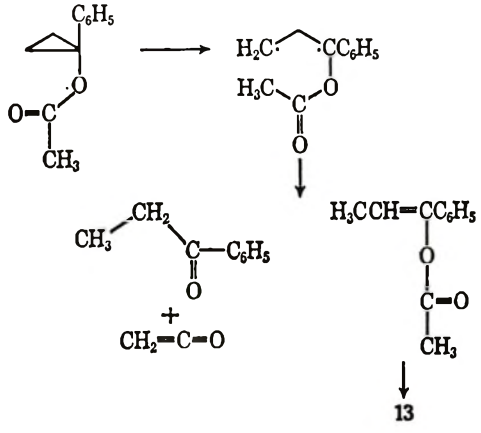
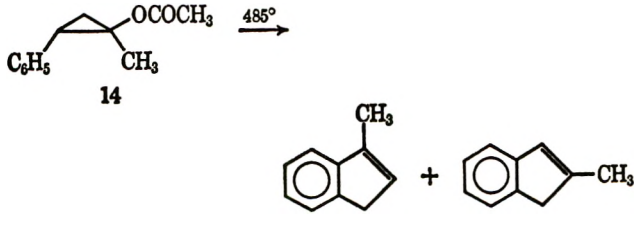


In the case of 1-phenylcyclopropyl acetate pyrolysis, 1,2 cleavage is vastly superior to the 2,3 cleavage needed for this type of rearrangement. As a consequence, a whole new set of products arise and the 2-phenylallyl acetate is only one of a number of products formed (Scheme III). The origin of the methylphenylacetylene is still obscure, and additional experiments are needed to determine its mode of formation. Elimination to phenylcyclopropene and rearrangement of this intermediate is one possibility.

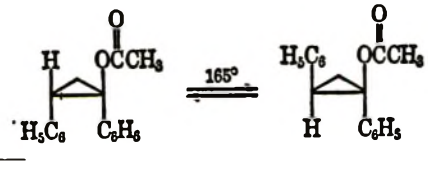
SCHEME III



Further evidence for the intermediacy of diradicals is found in the products from the pyrolysis of 1-methyl-2-phenylcyclopropyl acetate. In this case the major products at 450° are the isomeric methylindenes, presumably formed by cyclization of the diradical into the *ortho* position of the benzene ring.



Taken together, the data are best accommodated by the view that a 1,3 diradical is formed reversibly, and that subsequent reactions determine the particular product ratios formed. This is consistent with an earlier observation that 1,2-diphenylcyclopropyl acetates undergo *cis–trans* isomerization faster than any other reaction.[7] We cannot rule out completely a competing concerted rearrangement, but, since the results do not demand such a process, and molecular models do not reveal that it would be particularly favorable, we see no compelling need to invoke it.



(7) C. H. DePuy and L. B. Rodewald, *Tetrahedron Lett.*, 2951 (1964).

Experimental Section

All melting points and boiling points are uncorrected. Analytical vapor phase chromatography (vpc) separations were performed on a Model 500 instrument of F & M Scientific Co., and preparative separations were done with an Aerograph Model A90P instrument. The liquid phases employed were Ucon LB550X, LAC 446, or β,β'-oxydipropionitrile (ODPN) as indicated for the individual separations.

Cyclopropyl acetate (3) was prepared from peroxytrifluoroacetic acid and methyl cyclopropyl ketone by the method of Emmons and Lucas.[8]

1-Phenylcyclopropyl acetate (7) was prepared *via* a modification of the procedure of Smith and Bryant.[9] To a mixture of 8.5 g (63 mmol) of 1-phenylcyclopropanol (prepared as described previously[2]), 25 ml of pyridine, and 150 ml of benzene cooled with an ice–salt bath was slowly added 15.4 g of freshly distilled acetyl chloride. The reaction mixture was then allowed to warm to room temperature and stand for 40 hr. Water (100 ml) was then cautiously added and the aqueous layer was separated and extracted with two 50-ml portions of ether. The combined organic extracts were washed several times with dilute sulfuric acid, followed by successive washings with saturated sodium bicarbonate and water, and finally dried over $MgSO_4$. Solvents were removed under reduced pressure; the product (8.7 g, 78%) was distilled through a short Vigreux column, bp 45–48° (0.12 mm).

1-Methylcyclopropyl Acetate (5).—The 1-methylcyclopropanol, prepared as described previously,[10] was acetylated in the manner described for 7. The product was purified by distillation, bp 111–113° (lit.[10] bp 112.5–113°).

1,2,2-Trimethylcyclopropyl acetate (1) was prepared by the method of Freeman.[3]

trans-**2-Phenylcyclopropyl acetate** was synthesized as described previously.[10]

trans-**Cinnamyl Acetate** (12).—Acetylation[9] of *trans*-cinnamyl alcohol gave 91% of the desired acetate, bp 74–75° (0.15 mm) [lit.[11] bp 139–140° (10 mm)].

2-Phenylprop-2-enyl acetate (10) was prepared by selenium dioxide oxidation of 2-phenylpropene in acetic acid solution.[12]

1-Acetoxy-1-phenylpropene (11) was prepared from propiophenone as described previously;[13] the product was distilled at 86–90° (0.8 mm) [lit.[13] bp 133–136° (17 mm)].

1-Phenyl-2-methyl-1,3-butanedione (13).—Treatment of 1-phenyl-1,3-butanedione with sodium methoxide and methyl iodide as described previously[14] afforded the crude product which distilled at 71–73° (0.08 mm) [lit.[14] bp 150–152° (20 mm)].

Pyrolysis of Cyclopropyl Acetate (3).—The pyrolysis apparatus has been described previously.[1] The acetate (0.4 ml) was added dropwise from a syringe to the vertically mounted apparatus maintained at 480°. The pyrolysate was collected in a Dry Ice–acetone cooled trap and then passed through the apparatus a second time. Analysis of the second pyrolysate by vpc indicated that it contained 55% unreacted **3**, 44% a second compound, and less than 1% volatile materials (acetic acid was not present). The 44% component was isolated by preparative vpc and identified as allyl acetate by comparison with an authentic sample.

Pyrolysis of 1-Methylcyclopropyl Acetate (5).—A 1.0-ml sample of the acetate was pyrolyzed in the manner described for **3**. The pyrolysate contained 48% unreacted starting material, *ca.* 52% of a single product, and trace amounts of volatile materials. The major component was separated by preparative vpc on a UCON column and identified as 2-methylallyl acetate by comparison with an authentic sample.

(8) W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

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(12) L. F. Hatch and T. L. Patton, *J. Amer. Chem. Soc.*, **76**, 2705 (1954).

(13) P. Z. Bedoukian, *ibid.*, **67**, 1430 (1945).

(14) W. Dieckmann, *Chem. Ber.*, **45**, 2685 (1912).

Pyrolysis of 1,2,2-Trimethylcyclopropyl Acetate (1).—The pyrolysis of 20.0 g of this acetate was accomplished at 515° in the usual manner. Analysis of the pyrolysate by vpc indicated complete conversion of the ester; the mixture was washed with saturated sodium bicarbonate solution and dried over Na_2SO_4. Distillation of the organic material afforded a hydrocarbon which was identified as 2,3-dimethyl-1,3-butadiene (2) by comparison with an authentic sample.

Pyrolysis of 1 at several different temperatures indicated little conversion into product at 350°, about 50% conversion at 395°, and essentially complete reaction above 465°.

Pyrolysis of 1-Phenylcyclopropyl Acetate (7).—A 3.0-ml sample of this compound was pyrolyzed at 485° as described for **3**. Analysis of the pyrolysate by vpc on an LAC column indicated the presence of 11 compounds in addition to unreacted starting material. The components of the mixture were separated by preparative vpc and six were identified by comparison with authentic samples in each case. These compounds and their relative percentages are as follows: 1-phenylpropyne (8), 12.4%; propiophenone (9), 7.6%; phenallyl acetate (10), 11.4%; 1-acetoxy-1-phenylpropene (11), 8.7%; *trans*-cinnamyl acetate (12), *ca.* 2%; and 1-phenyl-2-methyl-1,3-butanedione (13), *ca.* 2–4%. Unreacted 7 accounted for 52% of the pyrolysate; the five unidentified components accounted for the remaining *ca.* 6%.

Pyrolysis of *trans*-2-Phenylcyclopropyl Acetate.—Reaction of a 1.0-ml sample of this compound in the usual manner at 465° produced a complex mixture as indicated by vpc analysis on a UCON column. The major product, comprising 50% of the mixture, was identified as *trans*-cinnamyl acetate by comparison with an authentic sample. Unreacted starting material accounted for a further 18% of the mixture and the remaining 32% contained a mixture of at least 13 additional compounds, none of which has been identified.

Pyrolysis of *cis*-2-Phenylcyclopropyl Acetate.—At 450°, 0.25 ml of this compound was pyrolyzed as described previously. Analysis of the pyrolysate by vpc on a UCON column indicated a mixture as complex as that produced from the corresponding *trans* compound; the major component again was shown to be *trans*-cinnamyl acetate.

Pyrolysis of 1-Methyl-*trans*-2-phenylcyclopropyl Acetate (14).—The acetate, 4.0 g, was pyrolyzed in the usual manner at 515°. The pyrolysate was diluted with pentane and extracted with saturated sodium bicarbonate. After drying over $MgSO_4$ and removal of pentane, the mixture was distilled at reduced pressure. In addition to starting material and a number of lesser components which have not been identified, distillation provided 0.8 g of a mixture of 2- and 3-methylindene (two-thirds and one-third, respectively, by analysis on an ODPN column). The latter compound was identified by comparison with a sample prepared by an independent route;[15] the 2-methyl derivative was identified by comparison of its nmr spectral properties with those previously reported.[16]

Registry No.—**1**, 16526-20-8; **3**, 4606-06-8; **5**, 16526-22-0; **7**, 16031-49-5; **14**, 16526-24-2; *cis*-2-phenylcyclopropyl acetate, 16526-25-3; *trans*-2-phenylcyclopropyl acetate, 16526-26-4.

Acknowledgment.—The authors are indebted to the National Science Foundation for support of this work.

(15) Prepared by reaction of indanone with methylmagnesium iodide and subsequent acid-catalyzed dehydration of the indanol derivative.

(16) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 590 (1963).

Substituent Effects on the Photoaddition of Diphenylacetylene to 1,4-Naphthoquinones

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The photoaddition of diphenylacetylene to 1,4-naphthoquinone and the corresponding 2-methoxyl and acetoxyl derivatives was investigated. In all cases, cyclobutene formation occurred to varying extents depending on the 2 substituent, thereby establishing this process as a useful synthetic method. In addition, the work provides the first examples of simultaneous C_4 and C_3O cycloaddition of alkynes to quinones and, in the case of 1,4-naphthoquinone, a particularly attractive system for studying the effects of reaction variables on the competing modes of addition.

Relative to the number of olefin and 1,3-diene photoadditions to *p*-quinones,[1] few reports on alkyne addition have appeared. Of these, only methoxy-*p*-benzoquinone undergoes C_4 cycloaddition[2] and affords 1-methoxybicyclo[4.2.0]octa-3,7-diene-2,5-diones of general structure I.[3] Both *p*-benzoquinone[4] and the tetrachloro derivative[5] photoadd diphenylacetylene to afford compounds II (X = H and Cl, respectively), presumably, by C_3O cycloaddition[2] *via* the unstable oxetenes III.[4] In contrast to olefins,[6] alkynes have not been observed to undergo concurrent C_4 and C_3O cycloaddition to quinones, a potentially attractive situation for determining the effects of solvent, temperature, and concentration changes on the competing modes of addition. The findings that tetrachloro-*p*-benzoquinone undergoes different modes of addition with cyclooctene[7] and diphenylacetylene[5] indicate clearly that ene and yne additions are not necessarily analogous and merit independent study. In addition, the varying extents to which energy transfer may occur between excited quinones and unsaturated compounds must be considered.

The photoaddition of alkynes to *p*-quinones has been of interest to us, primarily, as a synthetic route to the new class of compounds, represented by I, which are desirable for chemical studies and also as potential precursors of the cyclobutadiene derivatives IV. Consequently, our short-range objective was to extend the scope of this process with particular emphasis on varying the bridgehead substituents. For the long run, we hoped to uncover a system which provides both C_4 and C_3O cycloaddition products for mechanistic studies.

(1) For a current review, see J. M. Bruce, *Quart. Rev.* (London), **21**, 405 (1967).

(2) The terms C_4 and C_3O cycloadditions are adopted from C. H. Krauch, W. Metzner, and G. O. Schenck, *Ber.*, **99**, 1723 (1966).

(3) S. P. Pappas and B. C. Pappas, *Tetrahedron Lett.*, 1597 (1967).

(4) H. E. Zimmerman and L. Craft, *ibid.*, 2131 (1964); D. Bryce-Smith, G. I. Fray, and A. Gilbert, *ibid.*, 2137 (1964).

(5) J. A. Barltrop and B. Hesp, *J. Chem. Soc., Sect. C*, 1625 (1967).

(6) For example, see C. H. Krauch and S. Farid, *Tetrahedron Lett.*, 4783 (1966).

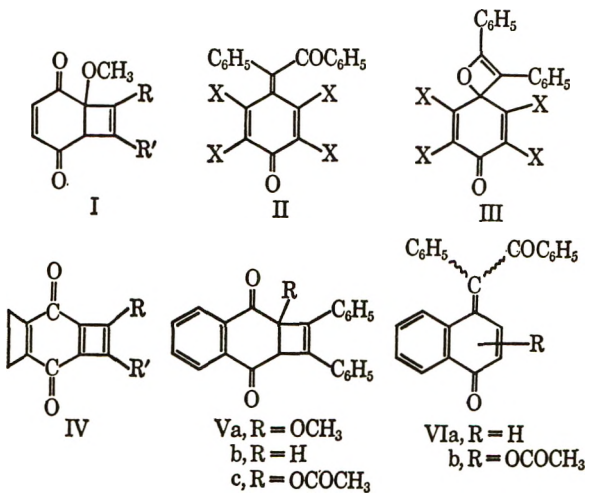
(7) D. Bryce-Smith and A. Gilbert, *Proc. Chem. Soc.* (London), 87 (1964); *Tetrahedron Lett.*, 3417 (1964).

In attempting to fulfill these objectives, we decided to examine the course of photoaddition of alkynes in the naphthoquinone series for two major reasons. First, for chemical studies it was desirable to incorporate the reactive 3,4-carbon–carbon double bond of structure I into an aromatic system; and secondly, the prospect of achieving simultaneous C_4 and C_3O cycloaddition appeared more favorable in this series, since alkenes afford both oxetanes and cyclobutanes with 1,4-naphthoquinone,[6] and only oxetanes with *p*-benzoquinone.[8]

Herein we report the results of our studies on the photoreactions of diphenylacetylene with 1,4-naphthoquinone as well as 2-methoxy- and 2-acetoxy-1,4-naphthoquinone.

Results

Photoreaction of diphenylacetylene (42.6 mmol) and 2-methoxy-1,4-naphthoquinone (11.7 mmol) was conducted in acetonitrile solution (200 ml) and monitored by infrared spectroscopy. The reaction was over in about 2.5 hr and resulted in the appearance of new carbonyl absorption at 5.92 μ. There was no significant absorption in the 6-μ region, characteristic of the products of C_3O cycloaddition.[4] A single photoadduct was isolated in 60% yield, after chromatography and recrystallization from benzene–hexane, and assigned the structure Va on the basis of spectral evidence. Thus, in addition to a multiplet of aromatic hydrogen resonances (14 H's), the nmr spectrum[9] of the adduct consisted of singlets at τ 5.50 (1 H) and 6.50



(3 H's), representing the methine and methoxyl hydrogens, respectively. The carbonyl absorption and ultraviolet spectrum of the adduct, which appear in Table I, are consistent with this formulation.

This result, which parallels that of methoxy-*p*-benzoquinone,[3] indicates that the methoxyl group specifically directs C_4 cycloaddition to the apparent exclusion of the C_3O process. Since there is evidence that the latter mode of addition proceeds *via* the n,π^* state of *p*-benzoquinone,[4,8] we investigated the course of photoaddition of diphenylacetylene to 2-methoxy-1,4-naphthoquinone with light of wavelengths longer than 400 mμ,[10] thereby severely limiting direct excitation to π,π^* singlets.[11] Under these conditions, photoaddition proceeded two to three times slower relative to reaction with unfiltered light,[12] the formation of products derived from C_3O cycloaddition could not be detected by infrared or nmr spectra, and adduct Va was isolated in 76% yield.

Table I

Absorption Spectra of the Adducts

Adduct	$\nu_{C=O}$, μ[a]	λ_{max}, mμ (log ϵ)[b]
Va	5.92	355 (3.37),[c] 288 (4.10),[c] 255 (4.25), 225 (4.55)
Vb	5.92	352 (3.36),[c] 290 (4.13), 257 (4.47), 228 (4.67)
Vc	5.73, 5.89	355 (3.47),[c] 290 (4.11),[c] 262 (4.28), 228 (4.62)
VIa	6.03, 6.06	350 (4.16), 301 (4.21), 286 (4.23), 252 (4.28)
VIb	5.63, 6.00	
	6.04, 6.06	388 (4.29), 300 (4.19), 290 (4.27), 252 (4.51)

[a] Obtained in chloroform solution on a Perkin-Elmer 257 spectrophotometer. [b] Obtained in 95% ethanol solution on a Cary 14 spectrophotometer. [c] Shoulder.

In contrast diphenylacetylene underwent photoaddition to 1,4-naphthoquinone, under similar conditions, by both C_4 and C_3O processes as evidenced by infrared spectra. The reaction was considerably slower, remaining incomplete after 9 hr.

Chromatography provided two adducts which were purified by repeated recrystallizations from benzene–hexane mixtures and assigned the structures Vb and VIa. The adducts were shown to be isomeric by elemental analysis. Ultraviolet spectra and relevant carbonyl absorption bands in the infrared, which appear in Table I, as well as nmr spectra are in complete accord with the assignments. Thus, in addition to aromatic hydrogen resonances (7 H's), Vb displayed a singlet at τ 5.50 (1 H), assigned to the methine hydrogens, while VIa exhibited four broad singlets in the vinyl region (1 H). Of added interest, nmr spectra of VIa, taken at various stages of recrystallization, indicated the presence of two isomers. Thus, while once-recrystallized material, obtained from the chromatography, exhibited four peaks in the vinyl region of approximately equal weight, two further recrystallizations resulted in substantial dimunition of the resonances at τ 3.65 and 3.47 relative to those at 3.54 and 3.37. Apparently, the two possible geometric isomers of VIa are produced in approximately equal amounts, and splitting between the nonequivalent vinyl hydrogens is not significant.

In anticipation of utilizing this system for mechanistic studies, nmr spectra were obtained on aliquots removed from the reaction at various time intervals. The spectra indicated that (1) the two modes of addition proceed cleanly, and (2) chemical shifts of the nonaromatic hydrogens in starting quinone and each of the photoadducts are sufficiently distinct for ready analysis by integration. Consequently, we have determined that the ratio of C_4 to C_3O cycloaddition products is 1 to 4 under the indicated conditions,[13] and are investigating solvent effects in this system.

(8) D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *J. Chem. Soc., Sect. C*, 383 (1967).

(9) The nmr spectra were obtained in deuteriochloroform solution on a Varian A-60 spectrometer with TMS as an internal reference.

(10) See ref 8 for the preparation of this filter solution.

(11) The lowest π,π^* absorption band of 2-methoxy-1,4-naphthoquinone exhibits a maximum at 330 mμ (log ϵ 3.44) in acetonitrile. No longer wavelength maxima or shoulders are observed. Apparently, n,π^* absorption is masked by the long wavelength tail of the π,π^* band.

(12) Approximate relative rates were determined by comparison of infrared spectra of aliquots from the reactions with those exhibited by standard mixtures of starting quinone and adduct Va.

(13) See Experimental Section for details.

The photoaddition of diphenylacetylene and 2-acetoxy-1,4-naphthoquinone was investigated in order to assess the effect of the acetoxyl group on the course of addition, and with the hope of thereby producing the corresponding cyclobutene adduct for pyrolysis studies. This was found to be the least reactive system examined. After 31 hr, unreacted quinone and both C_4 and C_3O cycloaddition products were in evidence from infrared spectra. Work-up as before resulted in the isolation of two isomeric adducts in about equal amounts, which were confidently assigned the gross structures Vc and VIb. Carbonyl absorptions and characteristic ultraviolet spectra are shown in Table I. The nmr spectra are in complete accord with the assignments. Thus, Vc exhibits, in addition to aromatic hydrogen resonances (14 H's), singlets at τ 5.65 (1 H) and τ 7.80 (3 H's) attributable to the methine and acetoxyl hydrogens, respectively. Strikingly, for VIb, the nmr spectra of once-recrystallized material, obtained from the chromatography, consisted simply of a single sharp peak at τ 7.67 (3 H's) and a multiplet in the aromatic region (15 H's), which apparently includes the vinyl hydrogen. The supernatant exhibited the same spectrum with additional, weak resonances in the acetoxyl and aromatic regions. Since it is unlikely that the acetoxyl hydrogens of the two possible structural isomers of VIb would exhibit the same chemical shift, it appears that one of these isomers is a major product. In addition, since the two geometric isomers of adduct VIa were clearly differentiated by nmr spectra, there is the intriguing possibility that the acetoxyl group directs not only the site of reaction, but also ring opening of the oxetene intermediate. Attempts to fully characterize this adduct have, as yet, been unsuccessful.

Discussion

The results allow little doubt that a variety of 1,4-naphthoquinones will undergo C_4 cycloaddition of alkynes, thereby establishing a convenient synthetic route to the corresponding tricyclo[6.4.0.0^{3,6}]dodeca-4,8-10,12-tetraene-2,7-dione adducts.[14]

The substituent effects on the mode of cycloaddition are quite striking and worthy of comment. Of particular interest would be a correlation of structure with reactivity, based on some measurable or predictable properties of the reactants. Although the data is limited, there is a definite trend in this series of diminishing C_3O cycloaddition and increasing cyclobutene formation which accompanies enhanced electron-releasing ability of the substituent. This pattern of reactivity appears to conform to the suggestion that C_3O and C_4 cycloadditions may occur *via* n,π^* and π,π^* triplet states, respectively.[5]

Experimental Section[15]

Irradiation and Work-Up.—A "Black Light" source (G. E. H100SP 38-4) was utilized and placed about 10 cm from the reaction vessel (a Pyrex-jacketed beaker), which was fitted with a rubber stopper with two serum-capped openings for N_2 entry and exhaust, and aliquot removal. Nitrogen was passed through the solutions, around which tap water or filter solution[10] was circulated (recycled in the latter case), for 20 min prior to and during the irradiations, which were conducted at about 20°. The crude product from each reaction was absorbed on a minimum amount of Mallinckrodt SilicAr, which was applied to a SilicAr column, 2.5 × 10 cm, with hexane. Solvent mixtures employed consecutively were hexane, hexane–benzene, benzene, benzene–ether, and ether. In each case, diphenylacetylene, C_4 cycloadduct, and C_3O product were eluted in that order. Most of the fractions were crystalline or crystallized on trituration with ether. The fractions were distinguished and combined on the basis of infrared spectra, and the products were purified by recrystallizations from benzene–hexane mixtures. In each case, greater than 80% of the reacted quinone was accounted for by the indicated products. However, the reported yields, which represent the per cent of theory of each product isolated in analytically pure form based on reacted quinone, are considerably lower when more than one adduct is formed as a result of our emphasis on ease of purification rather than recovery. Carbonyl absorption bands and ultraviolet spectra of the adducts appear in Table I.

3-Methoxy-4,5-diphenyltricyclo[6.4.0.0^{3,6}]dodeca-4,8,10,12-tetraene-2,7-dione (Va).—Irradiation of an acetonitrile solution (200 ml) of diphenylacetylene (7.59 g, 0.213 *M*) and 2-methoxy-1,4-naphthoquinone[16] (2.20 g, 0.0585 *M*) for 2.5 hr, followed by the general work-up procedure, afforded a 60% yield of adduct Va: mp 128–129°; nmr spectrum, aromatic hydrogen multiplet and singlets at τ 5.50 (methine H) and 6.50 (methoxyl H's).

Anal. Calcd for $C_{25}H_{18}O_3$: C, 82.0; H, 5.0. Found: C, 81.8; H, 4.8.

4,5-Diphenyltricyclo[6.4.0.0^{3,6}]dodeca-4,8,10,12-tetraene-2,7-dione (Vb), mp 180°, was isolated in 5% yield from the irradiation of diphenylacetylene (8.45 g, 0.380 *M*) and 1,4-naphthoquinone[17] (1.50 g, 0.0760 *M*) in acetonitrile (125 ml) for 9 hr. In this case several recrystallizations were required to separate the adduct from starting quinone. The nmr spectrum consisted of a multiplet of aromatic hydrogen resonances and a singlet at τ 5.50 (methine H's).

Anal. Calcd for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.5; H, 5.0.

5-(α-Benzoyl)benzylidenebicyclo[4.4.0]deca-3,6,8,10-tetraene-2-one (VIa).—The above irradiation provided this adduct, mp 165–172°, as a mixture of isomers in 25% yield. The variation of nmr spectra with recrystallization indicated that each isomer exhibits two broad singlets in the vinyl region at τ 3.65 and 3.47 and at 3.54 and 3.37, respectively. No efforts were made to separate the isomers.

Anal. Calcd for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.8; H, 4.8.

3-Acetoxy-4,5-diphenyltricyclo[6.4.0.0.0^{3,6}]dodeca-4,8,10,12-tetraene-2,7-dione (Vc).—Irradiation of diphenylacetylene (6.24 g, 0.233 *M*) and 2-acetoxy-1,4-naphthoquinone[18] (2.0 g, 0.0653 *M*) in acetonitrile (150 ml) for 31 hr, followed by the general work-up procedure, provided this adduct in 20% yield: mp 209–211°; nmr spectrum, aromatic hydrogen multiplet and singlets at τ 5.65 (methine H) and 7.80 (acetoxyl H's).

Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.2; H, 4.6. Found: C, 79.2; H, 4.7.

5-(α-Benzoyl)benzylidene-3(or -4-)acetoxybicyclo[4.4.0]deca-3,6,8,10-tetraene-2-one (VIb), mp 225–256°, was isolated from the above irradiation in 20% yield, after two recrystallizations of chromatographed product. The nmr spectrum consisted of a single sharp peak at τ 7.67 (acetoxyl H's) and a multiplet in the aromatic region which includes the vinyl hydrogen, as determined by integration.

(14) Preliminary results indicate that 2,3-dichloro-1,4-naphthoquinone undergoes C_4 cycloaddition of diphenylacetylene, as well, thereby extending this generalization.

(15) Acetonitrile was distilled from phosphorus pentoxide prior to use. Diphenylacetylene, purchased from Aldrich Chemicals, was used directly without further purification. Elemental analyses were carried out by Spang, Ann Arbor, Mich.

(16) This quinone was conveniently prepared from 2-hydroxy-1,4-naphthoquinone, purchased from Aldrich Chemicals, by treatment with methanol and sulfuric acid as described for the preparation of 4-methoxy-2,5-toluquinone: R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952). For an alternative synthesis, see E. Bernatek and F. Christenssen, *Acta Chem. Scand.*, **19**, 2009 (1965).

(17) Commercial material from Eastman Chemicals was sublimed prior to use.

(18) J. Thiele and E. Winter, *Ann.*, **311**, 341 (1900).

Anal. Calcd for $C_{25}H_{18}O_4$: C, 79.2; H, 4.6. Found: C, 79.6; H, 4.4.

Registry No.—Va, 16526-86-6; Vb, 16526-87-7; Vc, 16526-88-8; VIa, 16526-89-9; diphenylacetylene, 501-65-5.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Institutes of Health (GM 1394) for partial support of this research.

Factors Governing the Reaction of the Benzyl Grignard Reagent. III. The Formation of *ortho* and *para* Products in Reactions with Alkyl Sulfates *via* Triene Intermediates

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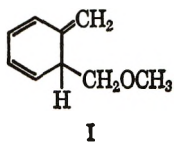
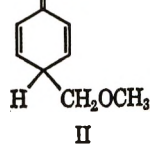
Benzylmagnesium chloride was treated with dimethyl, diethyl, and di-*n*-propyl sulfate as well as *n*-propyl tosylate under standardized conditions. In all cases the principal product was an alkylbenzene accompanied by smaller amounts of *both ortho*- and *para*-substituted toluenes. Under identical conditions the same Grignard reagent reacts with methyl iodide to form only ethylbenzene, but at a much slower rate. Likewise, benzyllithium forms only *n*-butylbenzene with di-*n*-propyl sulfate in a tetrahydrofuran solvent. When benzylmagnesium chloride is treated with diethyl sulfate and the reaction mixture hydrolyzed with deuterium chloride in deuterium oxide, the *o*- and *p*-ethyltoluenes produced contain a large percentage of molecules with one deuterium atom incorporated in the methyl group attached to the ring. This is rationalized in terms of triene intermediates which are aromatized during hydrolysis. Attention is directed to the fact that *para*-substituted products are formed in displacement reactions of the benzyl Grignard but usually not in carbonyl additions. Contrary to earlier literature reports, no *para* products were found when benzylmagnesium chloride reacts with either ethyl chlorocarbonate or ethyl formate.

It was recently disclosed[1] that, in displacement reactions between the benzyl Grignard reagent and chloromethyl methyl ether, triene intermediates like I, and probably II, exist in the reaction mixture prior to hydrolysis. Such intermediates are protonated by strong acids during hydrolysis to form, in this instance, *o*- and *p*-methylbenzyl methyl ether.



I



II

It seemed reasonable that intermediates like I and II should be formed in other displacement reactions also in which the benzyl Grignard participates. To this end we turned our attention to the preparation of *n*-propylbenzene from the reaction of the benzyl Grignard with diethyl sulfate.[2] It had been pointed out[3] that this preparation produced *p*-ethyltoluene as a by-product, but no *o*-ethyltoluene could be detected. When we repeated this reaction, it was found that *both* *o*- and *p*-ethyltoluene are indeed produced in this case as shown in Table I. Likewise, when our study was extended to dimethyl and di-*n*-propyl sulfate, small amounts of both the *ortho*- and *para*-substituted toluenes were again produced (Table I). This was also true when *n*-propyl *p*-toluenesulfonate was substituted for di-*n*-propyl sulfate as the alkylating agent. Of interest was the observation that no ring-substituted products were produced in the reaction between benzyllithium and di-*n*-propyl sulfate or between the benzyl Grignard and methyl iodide. A summary of all of these results is in Table I.

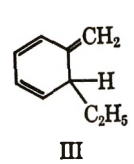
TABLE I

REACTION OF BENZYLMAGNESIUM CHLORIDE AND BENZYLLITHIUM WITH VARIOUS ALKYLATING AGENTS[a]

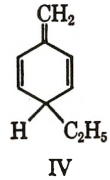
Run	Organometallic[c]	Alkylating agent	Products, %[b] $C_6H_5CH_2R$	o-$CH_3C_6H_4R$	p-$CH_3C_6H_4R$
1	$PhCH_2MgCl$	$(CH_3)_2SO_4$	74[d]	0.5	0.3
2	$PhCH_2MgCl$	$(C_2H_5)_2SO_4$	71[e]	7	2.3
3	$PhCH_2MgCl$	$(n\text{-}C_3H_7)_2SO_4$	77[f]	8	0.8
4	$PhCH_2MgCl$	$n\text{-}C_3H_7OTs$	77[g]	1	0.8
5	$PhCH_2Li$	$(n\text{-}C_3H_7)_2SO_4$	72[h]	...	...
6	$PhCH_2MgCl$	CH_3I	49[i]	...	...

[a] In all cases the initial concentration of the organometallic was 0.4 *M*. The benzyllithium reaction (run 5) was carried out in tetrahydrofuran; all others were in diethyl ether. [b] These values represent the percentage distribution of product in the distilled fraction and in most cases are the average of two runs. [c] In every case (except run 6) the reaction mixture was stirred at room temperature for 1 hr after the alkylating agent had been added. [d] There was an average of 9% toluene also isolated in this run. [e] About 15% toluene was also isolated. [f] There was also isolated in this run about 2% isobutylbenzene, 1% each of *o*- and *p*-cymene, and 5% toluene. [g] Also 5% toluene was isolated. [h] About 27% toluene was also recovered along with 1% isobutylbenzene. [i] This reaction was carried out for 3 days. In addition to ethylbenzene, 26% toluene was also obtained.

To demonstrate the existence of intermediates like III and IV in the reaction with diethyl sulfate, a reaction mixture was divided into two equal parts just prior to hydrolysis. One of the parts was hydrolyzed with aqueous hydrochloric acid and the other part with saturated ammonium chloride solution. The latter



III

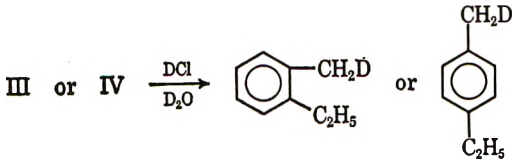


IV

(1) R. A. Benkeser and W. DeTalvo, *J. Amer. Chem. Soc.*, **89**, 2141 (1967).
(2) H. Gilman and W. E. Catlin, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 471.
(3) J. G. Burtle and R. L. Shriner, *J. Amer. Chem. Soc.*, **69**, 2059 (1947).

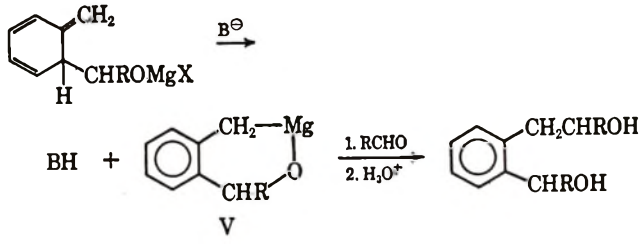
portion produced only half as much of the *o*- and *p*-ethyltoluenes as the portion hydrolyzed with the hydrochloric acid. This was identical with our findings with chloromethylmethyl ether and can be rationalized in the same way.[1] Apparently intermediates like I–IV are aromatized by mineral acids during hydrolysis, but are much less reactive toward weaker acids like ammonium chloride. In the latter instance they survive the hydrolysis step only to be destroyed during distillation.

Much more positive evidence for the existence of intermediates III and IV was obtained by hydrolyzing another reaction mixture with DCl in D_2O. Analysis of the *o*- and *p*-ethyltoluenes thus produced by nmr confirmed the presence of considerable deuterium in the methyl groups bonded to the aromatic ring. Mass spectral analysis of the same material established the incorporation of only one deuterium atom at this position and gave values of 48–55% deuterium enrichment. Clearly, a considerable portion of the *o*- and *p*-ethyltoluenes produced in this reaction is arising during hydrolysis and can best be rationalized in terms of intermediates like III and IV.



In a blank experiment it was shown that this uptake of deuterium was not the result of any exchange between the alkyltoluenes and the DCl during hydrolysis. When *p*-ethyltoluene in ether was stirred with DCl in D_2O to simulate hydrolysis conditions, no deuterium exchange occurred.

There is still another way to rationalize the incorporation of deuterium during hydrolysis. It has been amply demonstrated that in certain carbonyl addition reactions of the benzyl Grignard reagent[4] as well as in certain other displacement reactions,[1] bis products often result from reaction of 1 equiv of the organometallic with 2 equiv of the alkylating or carbonyl reagent. In the case of the carbonyl reactions, such products have been explained[4b,5] by a reaction sequence as follows.



In essence, a base (B^-) which could conceivably be another molecule of benzyl Grignard abstracts an allylic proton to form a new organometallic, V, which reacts in conventional fashion with more carbonyl reagent to form biscarbinols. It is conceivable that in our system intermediates like III and IV might react with more Grignard reagent (by allylic hydrogen abstraction) to form new organometallic intermediates, which, upon reaction with DCl would result in deuterium incorporation. We do not consider such a sequence likely in our case because no trace of either *o*- or *p*-ethyl-*n*-propylbenzene could be detected in our reaction products. It certainly seems that the same organometallic intermediate which is capable of deuteration with DCl should also be capable of reaction with diethyl sulfate to form products like *o*- or *p*-ethyl-*n*-propylbenzene. Hence, we believe the monodeuterated products we observed came about by reaction of intermediates III and IV with DCl.

Discussion of Results

Certain comments are in order with regard to the data in Table I. In the first four entries there are some differences to be noted with regard to the *ortho* and *para* isomers obtained. For example, these so-called "abnormal" products seem less in the case of the dimethyl sulfate reaction (entry 1) and the *n*-propyl tosylate (entry 4). However, since the differences are small, we prefer to reserve comment at this time as to their possible significance. That the alkylating agent probably plays a role, however, in determining whether such "abnormal" products are formed is indicated by the methyl iodide reaction (entry 6). While this reaction is very slow (requiring 3 days), it seems significant that no *o*- or *p*-ethyltoluene is formed in this case.

The reaction with di-*n*-propyl sulfate (entry 3, Table I) proved interesting in that small amounts of isobutylbenzene as well as *o*- and *p*-cymene were detected among the products. While conclusive proof is lacking, we feel that our *n*-propyl sulfate, although prepared by well-established reactions, was probably contaminated with small amounts of the isopropyl isomer produced during the multistep preparative sequence employed.[6] These branched-chain impurities did not show up when *n*-propyl tosylate was substituted for the *n*-propyl sulfate (entry 4) suggesting that they were caused by impurities in the sulfate. It is also noteworthy that 1% isobutylbenzene again appeared when this same sample of *n*-propyl sulfate was treated with benzyllithium (entry 5), suggesting again that the sulfate was slightly impure.

Again, it will be noted that the "abnormal" *ortho* and *para* products were eliminated when benzyllithium was used (entry 5). Some caution must be exerted in comparing this result with the others in Table I since tetrahydrofuran was used as the solvent rather than the usual diethyl ether. However, it was our previous[1] experience, also, that benzyllithium reacts almost exclusively at the α position during such displacements.

When the data in Table I are considered in conjunction with the existing literature[7] on the subject, it becomes apparent that *para*-substituted products result almost exclusively from displacement reactions of the benzyl Grignard reagent. When the latter reacts with carbonyl reagents, *para* products almost never are formed. There seemed to be possibly two exceptions

(4) (a) J. Schmidlin and A. Garcia-Banus, *Ber.*, **45**, 3193 (1912); (b) W. G. Young and S. Siegel, *J. Amer. Chem. Soc.*, **66**, 354 (1944); (c) S. Siegel, S. K. Coburn, and D. R. Levering, *ibid.*, **73**, 3163 (1951); (d) R. A. Benkeser and T. E. Johnston, *ibid.*, **88**, 2220 (1966).

(5) S. Siegel, W. M. Boyer, and R. R. Jay, *ibid.*, **73**, 3237 (1951).

(6) There was no isopropyl alcohol in the n-propyl alcohol we used as the starting material in this reaction sequence.

(7) See M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 1134, for pertinent references.

to this statement, namely the reaction between benzylmagnesium chloride and ethyl chlorocarbonate and ethyl formate[8] wherein small amounts of *para* products were found. Using an excess of carbonyl compound,[9] we found neither of these reactions to be particularly clean-cut. Numerous products were produced in addition to considerable amounts of polymeric material, especially in the case of ethyl formate. Most significant, however, was our inability to detect any *para*-substitution products in either the crude or distilled reaction mixtures. This was true even when oxidation of the crude products was attempted with permanganate followed by subsequent conversion of the acids to esters with diazomethane. Analysis of these esters by vpc disclosed no trace of dimethyl terephthalate.

Hence, the generalization seems to be evolving that *para*, *ortho*, and normal products are formed in displacement reactions of the benzyl[10] Grignard reagent. Carbonyl addition reactions of this reagent result in normal and *ortho* products only.

Experimental Section

o-(n-Propyl)ethylbenzene.—A solution of *o*-ethylphenylmagnesium bromide was prepared in 200 ml of dry tetrahydrofuran from 8 g (0.33 g-atom) of magnesium and 55.5 g (0.3 mol) of *o*-ethylbromobenzene (Eastman). To this solution was added 51.0 g (0.3 mol) of *n*-propyl iodide. The mixture was refluxed for 3 hr and hydrolyzed with 100 ml of 3 *N* hydrochloric acid. After the customary work-up, the product was distilled through a short Vigreux column and 8.4 g (18%) of product was collected boiling at 200–204°. An analytical sample (n^{20}D 1.4970) was collected by vpc (20 ft, 20% dibutyl tetrachlorophthalate on Chromosorb P, 60–80 mesh, at 140°).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.37; H, 11.07.

Reaction of Benzylmagnesium Chloride with Various Alkyl Sulfates and Sulfonates.—Since the conditions employed in these reactions were nearly identical, the directions given below for methyl sulfate can be considered typical for all. The results of all these runs are in Table I.

A. Methyl Sulfate.—To a three-necked flask equipped with a mercury-sealed stirrer, pressure-equalizing dropping funnel with nitrogen inlet, and reflux condenser was added 313 ml of an ethereal solution of benzylmagnesium chloride containing 0.3 mol of the organometallic. Then 437 ml of anhydrous ether was added to produce 750 ml of a 0.4 *M* solution. To this solution was added dropwise 75.6 g (0.6 mol) of methyl sulfate in 50 ml of ether over a 40-min period. After stirring for 1 hr, the mixture was hydrolyzed with 3 *N* hydrochloric acid. The aqueous layer was washed twice with ether, and the ethereal solutions were combined. Most of the solvent was removed, and the residue was refluxed with 50 ml of a 30% potassium hydroxide solution for 1 hr. After the usual work-up, the product was distilled and 25.6 g was collected boiling at 90–145°. Analysis by vpc (see Table I) using a 20 ft × 0.125 in. column of 2.5% dibutyltetrachlorophthalate +2.5% Bentone 34 on Chromosorb W, 80–100 mesh, at 100° showed no trace of the *o*- or *p*-ethyltoluenes.

B. Ethyl Sulfate.—There was obtained 25.9 g of product boiling at 140–155°. Analysis by vpc (see Table I) using the same column as was used for methyl sulfate showed no trace of either *o*- or *p*-(*n*-propyl)ethylbenzene.[11] Authentic samples of the latter compound, as well as *o*-[12] and *p*-ethyltoluene,[12b] were at hand for a comparison of retention times.

C. n-Propyl Sulfate.[13]—There was obtained 12.6 g of material boiling at 80–200°. Complete separation of the products of this reaction [toluene, isobutylbenzene, *n*-butylbenzene, *o*- and *p*-cymene, and *o*-[14] and *p*-(*n*-propyl)toluene] was achieved using a Golay capillary column of Squalene at 80° and a hydrogen pressure of 14 psi.

D. n-Propyl p-Toluenesulfonate.[15]—Conditions for this reaction were essentially the same as those described for the methyl sulfate case except that 0.1 mol of Grignard was used and 0.2 mol of the sulfonate. There was obtained 11.0 g of product which contained only toluene, *n*-butylbenzene, and *o*- and *p*-(*n*-propyl)-toluene.

Benzyllithium with n-Propyl Sulfate.—To 193 ml of tetrahydrofuran containing 0.0772 mol of benzyllithium[16] was added dropwise 60.0 g (0.33 mol) of *n*-propyl sulfate in 50 ml of dry tetrahydrofuran over a period of 40 min. After stirring at room temperature for 1 hr, the mixture was hydrolyzed with 3 *N* hydrochloric acid and then worked up in the customary manner. Distillation yielded 12.4 g of material boiling at 80–200°. See Table I for results.

Benzylmagnesium Chloride with Methyl Iodide.—To 750 ml of ether containing 0.3 mol of benzylmagnesium chloride was added dropwise 44.9 g (0.3 mol) of methyl iodide in 50 ml of ether over a 40-min period. The mixture was stirred for 3 days before it was hydrolyzed and worked up in the customary fashion. Distillation afforded 22.7 g of product boiling at 90–140°, which contained 49% ethylbenzene and 26% toluene (analysis by vpc).

Benzylmagnesium Chloride with Diethyl Sulfate. Hydrolysis with Saturated Ammonium Chloride and Aqueous Hydrochloric Acid.—To a solution (0.4 *M*) of 0.3 mol of benzylmagnesium chloride in 750 ml of anhydrous ether was added 46.2 g (0.3 mol) of diethyl sulfate in 100 ml of ether in a 20-min period. After stirring at room temperature for 1 hr, the mixture was divided into two parts. One portion was hydrolyzed with 50 ml of 15% HCl solution and 50 ml of water, the other portion with 50 ml of saturated ammonium chloride solution and 50 ml of water. Both portions were worked up in the usual manner, distilled, and analyzed by vpc (12 ft × 0.25 in. stainless steel column packed with Apiezon L on 60–80 mesh Chromosorb W at 130°). The portion hydrolyzed with hydrochloric acid contained 7% *o*-ethyltoluene and 6% *p*-ethyltoluene; that hydrolyzed with ammonium chloride contained 3% each of these two compounds.

None of the bis-substituted products (*e.g.*, the *n*-propylethylbenzenes) could be detected.

Benzylmagnesium Chloride with Diethyl Sulfate. Hydrolysis with DCl in D_2O.—A reaction was carried out under identical conditions to those described directly above. A portion (150 ml) of the reaction mixture was hydrolyzed with 20 ml of 10% DCl in D_2O and 20 ml of D_2O.[17] After the customary work-up, a sample of the *ortho*-substituted compound (*i.e.*, partially deuterated *o*-ethyltoluene) was collected by vpc (same column and conditions as above). Analysis of this sample for deuterium by mass spectroscopy indicated there was 55% of *o*-$DCH_2C_6H_4C_2H_5$ and 45% of the protium analog.[18] A pure sample of the *para* compound was collected by gc by reinjecting an initially collected[19] sample. Mass spectral analysis of this sample showed 48% deuterium enrichment.

Attempted Deuterium Exchange of p-Ethyltoluene with DCl in D_2O.—In a 200-ml flask was placed 2 g of *p*-ethyltoluene in 50 ml of ether. To the flask was added 5 ml of 20% DCl in D_2O and 5 ml of D_2O followed by 10 ml of D_2O. The mixture was stirred for 15 min.

The aqueous layer was separated and washed several times with Et_2O. The washings and organic layer were combined and dried over Drierite. The solvent was distilled by using a 12-in. Vigreux column. A sample of *p*-ethyltoluene was collected by vpc using a 4 ft × 0.25 in. stainless steel column packed with Apiezon L on 60–80 mesh Chromosorb W.

(8) H. Gilman and J. E. Kirby, *J. Amer. Chem. Soc.*, **54**, 345 (1932).

(9) Apparently this condition was employed originally[8] to minimize carbinol formation which is known to occur if the Grignard is in excess; see P. R. Austin and J. R. Johnson, *ibid.*, **54**, 647 (1932).

(10) It should be noted that this statement is made in connection with the *unsubstituted* benzylic Grignard. Additional research will be needed to ascertain whether substituents in the aromatic ring or on the side chain play a role in determining orientation.

(11) V. N. Ipatiev, N. A. Orlov, and A. D. Petrov, *Compt. Rend. Acad. Sci., URSS, Ser. A*, 255 (1928).

(12) K. v. Auwers, *Ann. Chim.*, **419**, 109 (1919); (b) *ibid.*, **419**, 110 (1919).

(13) C. M. Suter and H. L. Gerhart, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 111.

(14) A. Claus and H. Hansen, *Ber.*, **13**, 897 (1880).

(15) F. L. Hahn and H. Walter, *ibid.*, **54**, 1541 (1921).

(16) H. Gilman, H. A. McNinch, and D. Wittenberg, *J. Org. Chem.*, **23**, 2044 (1958).

(17) The DCl was 99% isomerically pure and the D_2O was 99.5%.

(18) Analysis of the sample by nmr generally corroborated these results.

(19) The retention times of *n*-propylbenzene and the *para* compound are very close. A rough separation of these two materials was achieved by the first gc collection and final purification by the second.

Analysis of this sample for deuterium by nmr spectroscopy indicated that *no* deuterium exchange had occurred.

Benzylmagnesium Chloride and Ethyl Chlorocarbonate.—To ethyl chlorocarbonate (65.1 g, 0.6 mol) in 100 ml of anhydrous ether was added slowly 750 ml of a 0.4 *M* solution of benzylmagnesium chloride in ether. The temperature of the reaction mixture was kept at 0 to −5° by a Dry Ice–acetone bath. After this addition was completed, the mixture was stirred for 1 hr and then hydrolyzed with 100 ml of 15% hydrochloric acid followed by 100 ml of water. Following the usual work-up, the solvent was removed and the residue analyzed by vpc (4 ft × 0.25 in. stainless steel column packed with Apiezon L on 60–80 mesh Chromosorb W). The following products[20] were identified: ethyl phenylacetate (31%), tribenzylcarbinol (21%), ethyl *o*-toluate (12%), β,β-bis(benzyl)styrene (13%), and diethyl homophthalate (1%). Neither ethyl *p*-toluate nor diethyl homoterephthate could be detected by vpc.

To 3 g of the crude reaction product in 250 ml of boiling water containing 25 g of KOH was slowly added 13 g of finely powdered potassium permanganate. The mixture was refluxed 4 hr, and then the excess permanganate was destroyed by adding a small amount of ethanol. The heavy manganese dioxide precipitate was washed with a small amount of dilute alkali, and the filtrate and washings were combined and acidified with hydrochloric acid. The organic acids were extracted with ether and then esterified with diazomethane. Analysis by vpc (4 ft × 0.25 in. Apiezon L on Chromosorb W) showed the products to be methyl benzoate and dimethyl phthalate in that their nmr and infrared spectra matched those of an authentic sample. No dimethyl terephthalate could be detected.

Benzylmagnesium Chloride and Ethyl Formate.—The procedure was the same as that described for ethyl chlorocarbonate except that 44.4 g (0.6 mol) of ethyl formate was used. Analysis of the product was by vpc (5 ft × 0.25 in. column packed with 5% FFAP on 60–80 mesh Chromosorb W). Only phenylacetaldehyde was formed in any quantity (14%) in addition to considerable amounts of tar (25 g). The following materials were also identified: benzaldehyde (3%), benzyl formate (5%), β-phenylethyl formate (3%), benzyl alcohol (4%), and β-phenylethanol (1%).[21]

The crude mixture obtained from this reaction was oxidized by permanganate in essentially the same way as for ethyl chlorocarbonate. After work-up and esterification with diazomethane, the methyl esters were again analyzed by gc. Only methyl benzoate and dimethyl phthalate were found; no dimethyl terephthalate could be detected.

Registry No.—Benzylmagnesium chloride, 6921-34-2; benzyllithium, 766-04-1; *o*-(*n*-propyl)ethylbenzene, 16021-20-8.

Acknowledgment.—This research was supported by the U. S. Army Research Office (Durham) to whom the authors are deeply indebted.

(20) Each of these materials was isolated by gc and were identical in retention time, nmr, and infrared spectra with authentic samples. The percentages listed are yields based on benzylmagnesium chloride and were determined by vpc using ethyl benzoate as an internal standard.

(21) The yields given are based on benzylmagnesium chloride and were obtained by gc using *o*-bromotoluene as an internal standard.

Metal–Ammonia Reduction. III. Stepwise Transformation of Polycyclic Aromatic Hydrocarbons[1,2]

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Reduction of benz[*a*]anthracene to dodecahydrobenz[*a*]anthracene in controlled stages *via* di-, tetra-, hexa-, octa-, and decahydrobenz[*a*]anthracene is achieved by means of lithium dissolved in liquid ammonia or liquid amine solvents. Utilization of nuclear magnetic resonance spectra and mass spectra to distinguish isomeric hydroaromatic structures is described.

Although the reduction of aromatic ring systems by alkali metals dissolved in liquid ammonia was observed by LeBeau and Picon[3] in 1914, it was not until the elegant investigations of Birch[4] and his collaborators that the method achieved acceptance as a major synthetic tool. The state of current knowledge, summarized in an excellent comprehensive monograph by Smith,[5] is surprisingly deficient regarding substances other than monobenzenoid molecules. Naphthalene,[3,6,7] anthracene,[8−10] phenanthrene,[7,11] pyrene,[12] fluorene,[13] and acenaphthene[8] are apparently the only polycyclic aromatic hydrocarbons to be investigated. Precautions for the exclusion of impurities known to affect the course of such reactions (trace metals,[2,14] peroxides, oxygen[15]) are seldom mentioned in the earlier literature, and characterization of the hydroaromatic products is often unsatisfactory by modern standards. Extensive reduction, often accompanied by disproportionation of products, is common. Also, the stepwise reduction of compounds possessing three or more fused aromatic rings had not been described prior to our studies in this field.[2,16]

Since controlled transformation of polycyclic aromatic hydrocarbons would provide hydroaromatic substances of considerable interest as synthetic intermediates,[17] we undertook to reinvestigate the

(1) This investigation was supported in part by U. S. Public Health Service Research Grant CA-08674 from the National Cancer Institute. Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) Part II: R. G. Harvey and K. Urberg, *J. Org. Chem.*, **33**, 2571 (1968).

(3) P. LeBeau and M. Picon, *Compt. Rend.*, **158**, 1514 (1914).

(4) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

(5) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, part 2, John Wiley and Sons, Inc., New York, N. Y., 1963.

(6) C. B. Wooster and F. B. Smith, *J. Amer. Chem. Soc.*, **53**, 179 (1931); A. J. Birch, A. R. Murray and H. Smith, *J. Chem. Soc.*, 1945 (1951); W. Hückel and H. Schlee, *Ber.*, **88**, 346 (1955).

(7) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).

(8) P. LeBeau and M. Picon, *Compt. Rend.*, **159**, 70 (1914).

(9) H. F. Miller and G. B. Bachman, *J. Amer. Chem. Soc.*, **57**, 768 (1935).

(10) A. J. Birch, *et al.*, *J. Chem. Soc.*, 2209 (1963); J. Runge, *Z. Chem.*, **2**, 374 (1962); *J. Prakt. Chem.*, [4] **31**, 280 (1966).

(11) S. Mejer, *Bull. Acad. Polon. Sci., Chim.*, **9**, 773 (1961).

(12) O. Neunhoeffer and H. Woggon, *Ann.*, **600**, 34 (1956); O. Neunhoeffer, H. Woggon, and S. Dähne, *ibid.*, **612**, 98 (1958).

(13) W. Hückel and R. Schwen, *Ber.*, **89**, 481 (1956).

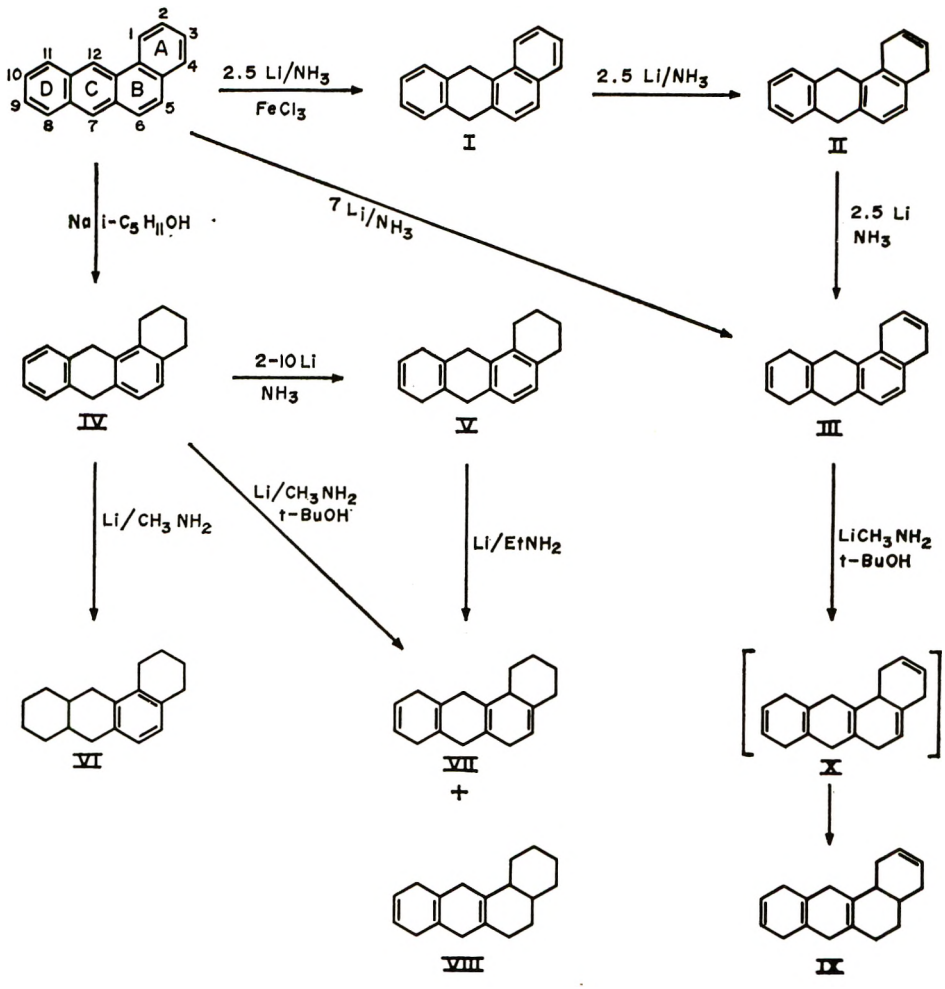
(14) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Celia, *J. Org. Chem.*, **26**, 3237 (1961).

(15) J. F. Eastham and D. R. Larkin, *J. Amer. Chem. Soc.*, **81**, 3652 (1959).

(16) R. G. Harvey, *J. Org. Chem.*, **32**, 238 (1967).

(17) For example, compounds with an internal double bond, such as V and VI, may serve as precursors to polycyclic hydrocarbons having a cyclopropyl ring fused along the ring juncture. Synthesis of several such unusual molecules will be reported shortly.

SCHEME I
STEPWISE REDUCTION OF BENZ[a]ANTHRACENE



addition of alkali metals to higher ring systems in ammonia and amine solvents. A preliminary paper described[16] reduction of 9,10-dihydroanthracene to the tetra and hexahydro stages by lithium in liquid ammonia and verified that conditions play a dominant role in the reduction of this polycyclic aromatic hydrocarbon.[18] Limitation of reduction to a single stage was favored, predictably, by low lithium–hydrocarbon ratios (optimum ~2.5) and by total solution of the aromatic compound. Also, it proved advantageous to withhold addition of the proton source (*i.e.*, alcohol) until late in the reaction period, then to add it rapidly.

The present paper reports stepwise conversion of the more complex polycyclic aromatic hydrocarbon, benz[*a*]anthracene, through the dodecahydro level. For the assignment of structural formulas to the derivatives, the techniques of nmr and mass spectroscopy were utilized extensively. Also, qualitative assessment of product distribution was achieved by charge-transfer chromatography[19] on thin layers of silica gel impregnated with *s*-trinitrobenzene.

Results

Treatment of benz[*a*]anthracene with lithium[20] in liquid ammonia under standard conditions led to 1,4,7,8,11,12-hexahydrobenz[*a*]anthracene (III) in separate consecutive reactions *via* 7,12-dihydrobenz[*a*]-anthracene (I) and 1,4,7,12-tetrahydrobenz[*a*]anthracene (II) (Scheme I). Each reaction proceeded in good yield (Table I). Owing to the enhanced resistance of III to further transformation, direct synthesis of III from benz[*a*]anthracene proved to be practicable, with 7–10 equiv of lithium being optimum.

The positions of the incoming hydrogens were accurately predicted through consideration of the relative stabilities of the intermediate radical anions and/or dianions. Qualitatively, these were assumed to be secondary > tertiary and benzyl > allyl > aliphatic. Quantitative predictions are theoretically possible; according to HMO theory, the protons may be expected to attach to the positions of highest electron density in the hydrocarbon dianion.[21] However, the coefficients of the lowest vacant molecular orbitals have not been calculated, except for benz[*a*]anthracene.[22]

Benz[*a*]anthracene is known to form a 7,12-dilithio adduct.[23] The nmr spectrum of I displayed a pair of doublets at τ 5.67 and 5.87 (J = 3 Hz) assigned to the

(18) However, the effect of variation of conditions may be different from that for monobenzenoid substances, owing to the probable importance of dianionic intermediates in more highly conjugated molecules.

(19) R. G. Harvey and M. Halonen, *J. Chromatog.*, **25**, 294 (1966).

(20) Preliminary tests indicated reactions of anthracene and benz[*a*]-anthracene to proceed more cleanly with lithium than with sodium.

(21) E. Hückel, International Conference on Physics, London, 1934, Vol. II, p 9.

(22) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 425.

(23) W. E. Bachmann, *J. Org. Chem.*, **1**, 347 (1936).

TABLE I

HYDROBENZ[a]ANTHRACENE COMPOUNDS

Compound	Formula	Mp, °C	Yield, %	$R_f \times 100$[a]	Calcd, % C	Calcd, % H	Found, % C	Found, % H
I	$C_{18}H_{14}$	111–112[b]	94	19				
II	$C_{18}H_{16}$	100.5–102	66	26	93.06	6.94	93.35	6.91
III	$C_{18}H_{18}$	141–42	82	32	92.26	7.74	92.44	7.77
IV	$C_{18}H_{18}$	69.5–70.3[c]	65	35				
V	$C_{18}H_{20}$	111–111.5	94	35	91.47	8.53	91.58	8.42
VI	$C_{18}H_{24}$	113.5–114.4	54	60	89.94	10.06	89.83	9.94
VII	$C_{18}H_{22}$	133.5–134	70	59	90.70	9.30	90.50	9.35

[a] R_f values are for chromatography on thin layers of silica gel impregnated with *s*-trinitrobenzene prepared as previously described[14] employing benzene–heptane 3:7 as the eluting solvent. [b] Lit.[21] mp 112–112.5°. [c] Lit.[25] mp 69.3–69.9°.

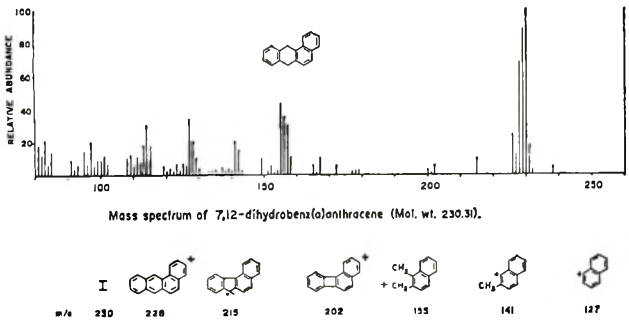


Figure 1.

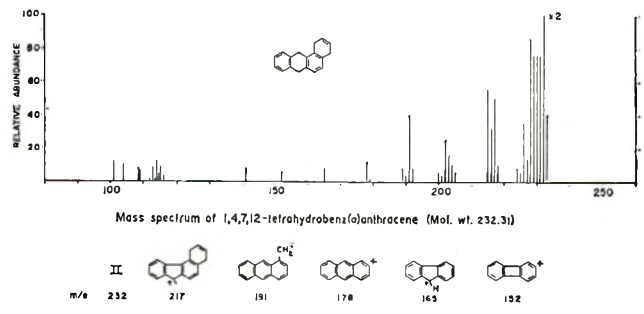


Figure 2.

C-12 and C-7 benzylic protons, respectively, on the basis of the greater downfield shift of the methyl protons of 1-methylnaphthalene (τ 7.33) relative to those of the 2 isomer (τ 7.52).

At the second stage, the least substituted ring (A in Scheme I) of the more reactive naphthalene portion of I may be expected to be most susceptible to attack. Compare the resulting 1,4 dianion (benzylic–allylic) with the alternative intermediates formed by attack at ring B (5,12a dianion having a negative charge at a ring juncture) or at ring D (diallylic 8,11 dianion). In agreement with the predicted structure, II, there occurred in the nmr region a broad singlet at τ 3.97 (two vinylic protons), a doublet at τ 2.87 (J = 3.5 Hz), an apparent singlet at τ 2.78 (aromatic protons at C-5,6, and C-8–11, respectively), and singlets at τ 7.10 and 7.57 (benzylic protons at C-7,12 and C-1,4, respectively). Assignment of the τ 7.10 peak to the C-7,12 protons is based on the identity of this value with that observed for the benzylic protons of 9,10-dihydroanthracene.[16] The least substituted of the two aromatic rings of II should provide greatest stabilization for a 1,4 radical anion. Assignment of structure III to the third stage product was supported in the nmr spectrum by apparent singlets at τ 4.10 and 4.20 (vinylic protons at C-2,3 and C-9,10, respectively; the latter is consistent with τ 4.20 and 4.27 for the related protons of 9,10-dihydroanthracene[16] and V, respectively) and by additional peaks for the appropriate numbers of protons at τ 7.33 (allylic), 2.90 (aromatic), and 6.73, 6.72, and 6.85 (benzylic at C-1,4, C-7, and C-12, respectively; the latter appeared as doublets, J = 7 Hz).

The resistance of III to further reduction necessitated employment of the more powerful lithium–amine system of Benkeser.[24] However, the strong tendency of this reagent toward extensive isomerization and reduction of double bonds indicated the desirability of short reaction time and careful control of other conditions. In order to devise satisfactory conditions, a series of test reactions were carried out with 1,2,3,4,7,12-hexahydrobenz[a]anthracene (IV), obtained from treatment of the parent aromatic hydrocarbon with sodium in refluxing isoamyl alcohol.[25] Delayed or slow addition (>5 min) of alcohol to a solution of IV and lithium in methylamine favored formation of 1,2,3,4,7,7a,8,9,10,11,11a,12-dodecahydrobenz[a]anthracene (VI) or further reduction products. Conversely, reduction in the presence of *t*-butyl alcohol furnished 1,2,3,4,6,7,8,11,12,12b-decahydrobenz[a]anthracene (VII) plus a lesser proportion of a further reduction product, VIII. It is likely that VI arises from the intermediate octahydro derivative, V, *via* base-catalyzed isomerization of the double bonds into conjugation followed by further reduction, rather than *via* direct reduction of the unsaturated bonds,[24] a kinetically unfavorable process. V was most efficiently synthesized directly from IV with lithium in ammonia. The structure of V was supported by peaks at τ 4.20 (two vinylic protons), 3.08 (two aromatic protons), 7.33 (four allylic protons), 8.20 (four aliphatic protons as a quintet, J = 3 Hz), and a broad absorption at τ 6.84 (benzylic protons) in the nmr spectrum.

Lithium–methylamine (or ethylamine) reduction of V furnished VII and VIII accompanied by traces of minor products. Finally, treatment of III with lithium and *t*-butyl alcohol in methylamine provided 1,4,4a,5,6,7,8,11,12,12b-decahydrobenz[a]anthracene (IX) rather than the expected octahydro derivative, X.

The tendency toward isomerization and polyreduction in amine solvents necessitated caution in assigning structures VI–IX. The extent of reduction was determined with high accuracy from the mass spectra. The parent peak of VII and IX appeared at m/e 238 cor-

(24) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963).

(25) L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **59**, 2502 (1937).

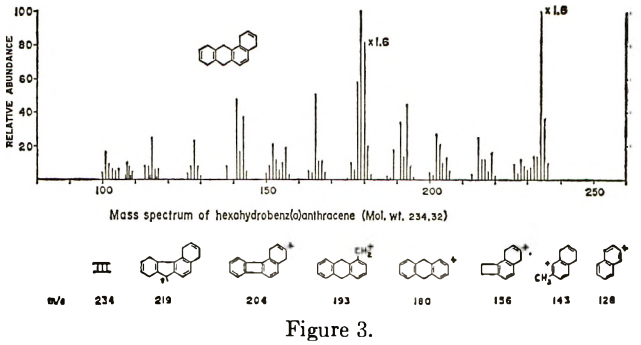


Figure 3.

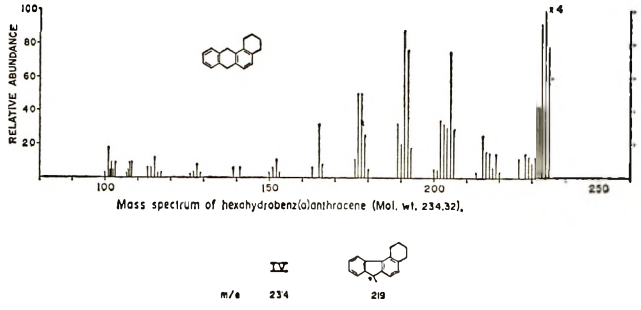


Figure 4.

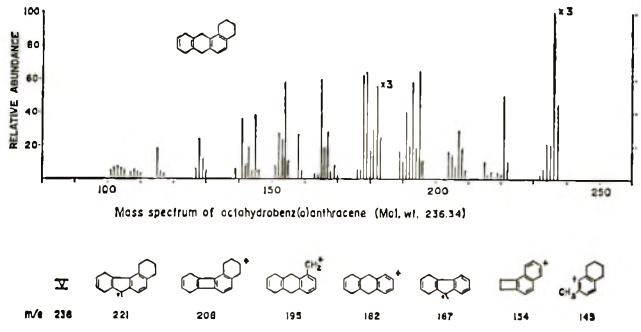


Figure 5.

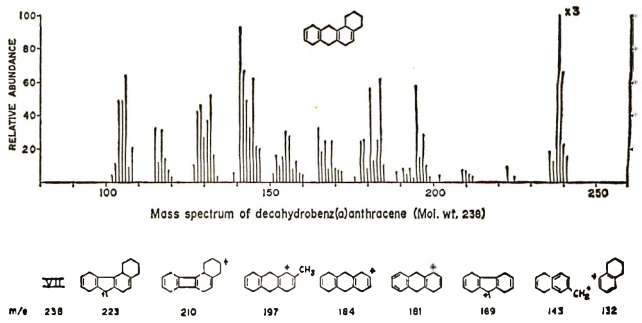


Figure 6.

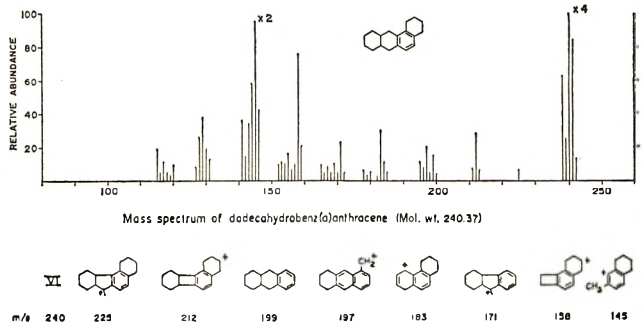


Figure 7.

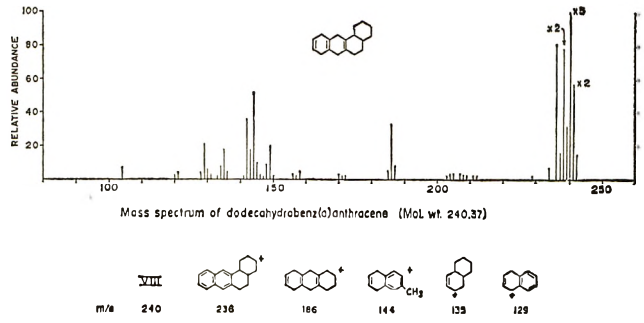
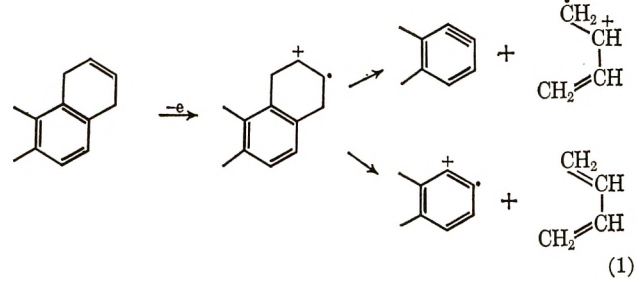


Figure 8.

responding to $C_{18}H_{22}$ (decahydro), while those of VI and VIII were found at *m/e* 240 corresponding to $C_{18}H_{24}$ (dodecahydro). Positions of the double bonds were deduced by analysis of nmr and mass spectral data.

Observed cleavage patterns, generally consistent with current knowledge of the behavior of cyclic olefins under electron beam bombardment,[26] were distinguished by a high proportion of peaks of relatively large mass (Figures 1–8). Also evident is a strong tendency toward aromatization. Associated with each major fragment are a series of peaks identified as arising *via* successive loss of allylic hydrogen until the fully aromatic ion is attained. Loss of methylene accounts for a series of commonly observed minor peaks (*e.g.*, *m/e* 165, 215, and 217 in Figure 2). Double loss of methylene with formation of biphenylene derivatives also appears to take place (*e.g.*, *m/e* 202 in Figure 1). The position, or positions, from which such loss occurs may be ascertained with decreasing certainty as the number of possibilities increases (*i.e.*, with increasing extent of reduction). The suggested probable structures indicated below the figures[27] should be viewed in this light. Finally, cyclic olefins may be expected to decompose *via* the well-known retro Diels–Alder pathway.[26,28,29] Indeed, the spectrum of IX, the only compound in the series I–IX to contain a suitable cyclohexene ring, exhibits a major peak (*m/e* 184) indicative of loss of a butadiene fragment. Analogous decomposition of the nonconjugated cyclohexadiene structures of III, V, and VII–IX with release of an acetylenic component was not detected. This process appears, therefore, to be relatively unfavorable. On the other hand, the presence of fused aromatic rings on one or both of the double bonds of 1,4-cyclohexadiene generally leads to fragments which may be rationalized as arising from reversal of the Diels–Alder reaction. Formation of benzyne may be involved (eq 1).



(1)

(26) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(27) The benzylic cations in these figures may exist partially or even exclusively as the corresponding tropylium ions; see S. Meyerson and P. N. Rylander, *J. Chem. Phys.*, **27**, 901 (1957).

(28) K. Biemann, *Angew. Chem.*, **74**, 102 (1962).

(29) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).

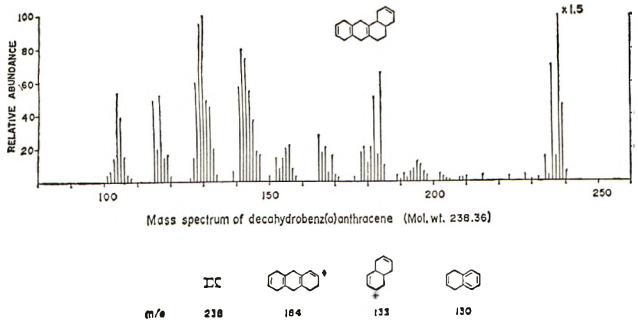
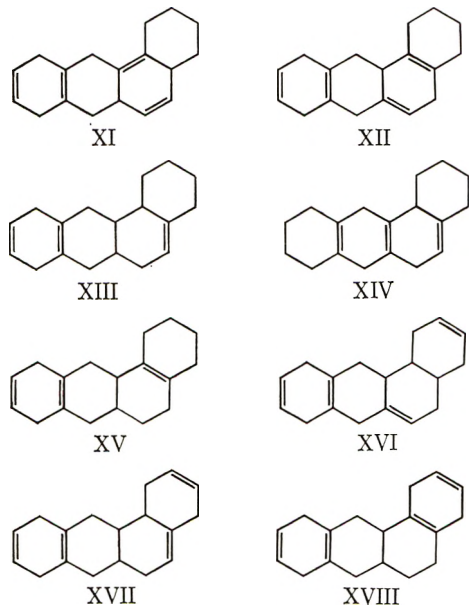


Figure 9.

The mass spectral data proved to be a valuable supplement to the nmr data in ruling out certain possible isomeric structures. Thus, the alternative structure XI for the decahydrobenz[*a*]anthracene (VII) obtained from treatment of IV or V with lithium in methylamine is inconsistent with the presence of three vinylic protons in the nmr region, appearing as a singlet at τ 4.25 (2 H at C-9,10) and a broad band at τ 4.62 (1 H at C-5) (Chart I). A second alternative formula, XII, may not be rejected on the basis of proton resonance data alone, owing to the broad overlapping nature of the singly allylic and aliphatic bands. However, the absence of a fragment in the *m/e* 210 region of the mass spectrum (corresponding to reverse Diels–Alder reaction in the cyclohexene ring) argues strongly against XII.

CHART I



Similarly, VIII was established as the formula of the triolefin obtained from the same reaction. Alternative structures XIII and XIV failed to satisfy the nmr absorption pattern which displayed bands at τ 4.30 (2 H), 7.45 (4 H), and 7.55 (4 H) due to vinylic, outer ring allylic and adjacent ring allylic protons, respectively. The final reasonably probable structure, XV, was most convincingly excluded by the absence of any significant peaks in the *m/e* 212 region of the mass spectrum, corresponding to loss of ethylene from ring A.

The second dodecahydro compound was identified as VI on the basis of chemical probability, nmr spectrum (two aromatic protons at τ 3.17), and mass spectral cracking pattern.

For the remaining decahydro compound, three structures (XVI–XVIII) must be considered in addition to the assigned structure, IX. XVI and XVII may be rejected as incompatible with the nmr data (four vinylic hydrogens, τ 4.30). The major peak at *m/e* 184 in the mass spectrum, while not readily explicable in terms of XVIII, is simply interpreted as resulting from the retro Diels–Alder reaction in IX (as discussed earlier).

The structures of the hydroaromatic products I–V conform closely to prediction based on consideration of the relative stabilities of the intermediate charged precursors. It is less obvious why reduction of the B ring of V should furnish VII rather than XII. Both structures place a charge on a tertiary position in the intermediate, and should be favored in preference to XI which would necessitate charge at two tertiary carbon atoms. Models indicate VII to be free to adopt a relatively unstrained conformation bent in the C ring, whereas XII is considerably more rigid and strained. The origin of VIII and IX is presumably *via* isomerization of the appropriate double bond of VII and X into conjugation, followed by subsequent rapid reduction.

Finally, it should be pointed out that the hydrobenz[*a*]anthracene compounds reported herein represent only a small fraction of many conceivable isomeric structures. Other isomers may be made available by combination of the metal–ammonia technique with other methods of hydrogenation.[30]

Experimental Section

Physical Data.—Melting points were taken on a Leitz Kofler hot-stage microscope and are corrected. Proton nmr spectra were obtained on a Varian Model A-60 spectrophotometer with chemical shifts reported relative to tetramethylsilane in deuteriochloroform. For mass spectral analysis an A.E.I MS9 double-focusing mass spectrometer was employed with the source set at 200° and the electron beam energy at 70 eV.

Material and Methods.—Ammonia, monomethylamine, and monoethylamine (Matheson Co.) were distilled into the reaction vessel through a column of barium oxide (10–12 mesh) except where otherwise indicated. Benz[*a*]anthracene (Terra Chemicals, Inc.) was dissolved in hot ethanol, filtered, and recrystallized (mp 160–162°). 1,2,3,4,7,12-Hexahydrobenz[*a*]anthracene (IV) was prepared by reduction of benz[*a*]anthracene with sodium and isoamyl alcohol, according to the method of Fieser and Hershberg.[25] Tetrahydrofuran (THF) was purified by distillation from $LiAH_4$ and stored over CaH_2 under nitrogen. Lithium wire (Lithium Corp. of America) was wiped free of oil and washed with hexane before use. Thin layer plates of silica gel impregnated with *s*-trinitrobenzene were prepared by the method previously described.[15] Silica gel for column chromatography (Davison, Grade 950, mesh 60–200) was activated by heating overnight at 100°.

All reductions in ammonia were carried out employing the conditions reported earlier[2,16] unless specific variations are cited. Precautions for the exclusion of atmospheric oxygen and moisture were scrupulously followed; all reductions were carried out under helium (preferable to nitrogen owing to the ease of lithium nitride formation).

7,12-Dihydrobenz[*a*]anthracene (I).—A solution of benz[*a*]anthracene (1.14 g, 5 mmol) in 75 ml of dry THF was added to a flask containing 150 ml of liquid ammonia and 40 mg of ferric chloride. To the resulting solution at reflux temperature was added lithium wire (85 mg, 12 mg-atoms). The blue color of the

(30) For example, catalytic hydrogenation of benz[*a*]anthracene[25] yields 8,9,10,11-tetrahydrobenz[*a*]anthracene, the lithium–ammonia reduction of which should lead to a different series of hydrobenz[*a*]anthracene derivatives than reported herein.

solution was discharged after 2 hr by rapid addition of alcohol. After evaporation of the ammonia and dilution with water, the product was obtained by filtration. It was taken up in acetone and filtered to remove a residue; the solvent was removed *in vacuo* to provide I (1.08 g, mp 111–112°).

1,2,7,12-Tetrahydrobenz[*a*]anthracene (II).—A similar procedure was followed for the reduction of I, except that ferric chloride was omitted. The oily yellow solid obtained was purified by chromatography on silica gel to give II as white flakes, mp 96–98°.

1,4,7,8,11,12-Hexahydrobenz[*a*]anthracene (III) was obtained both directly from II and from benz[*a*]anthracene, in both cases employing a method analogous to that employed for preparation of II. With benz[*a*]anthracene as the starting material, 7–10 equiv of lithium/mol of benz[*a*]anthracene provided optimum yield (Table I); greater excess led to increasing quantity of minor side products (detected on thin layers of trinitrobenzene on silica gel). These substances are suspected to arise from isomerization of double bonds into conjugation, followed by their reduction, rather than from hydrogenation of the B ring.

1,2,3,4,7,8,11,12-Octahydrobenz[*a*]anthracene (V).—To a solution of IV (1.17 g, 5 mmol) in 75 ml of THF and 150 ml of liquid ammonia was added lithium (694 mg, 100 g-atoms). The stirred solution was maintained at gentle reflux for 3 hr; then 20 ml of ethanol in 30 ml ether was added from a dropping funnel over a 45-min period. After evaporation of the ammonia, the solution was partitioned between ether and water. The ether phase was dried over magnesium sulfate and evaporated to dryness. Recrystallization of the resulting white solid from ethanol gave pure V (Table I).

Reduction of IV with Lithium in Methylamine.—IV (1.17 g, 5 mmol) was added to a solution of lithium (347 mg, 50 g-atoms) in 250 ml of liquid methylamine at reflux; 30 sec later 5 ml of *t*-butyl alcohol was added as rapidly as practicable. When the intense blue color of the solution disappeared (8 min), ethanol (5 ml) and water (10 ml) were added. Removal of the amine by evaporation, followed by partition of the product between ether and water, gave the crude product, recrystallization of which from ethanol furnished pure VII (Table I).

The mother liquors were evaporated to dryness and chromatographed on a column of silica gel prepared in petroleum ether (bp 30–60°). Elution with hexane gave the dodecahydro compound VI (42 mg) followed by an oily solid (445 mg), identified as the isomer VIII. Recrystallization from ethanol–methanol at 4° furnished pure VIII (Table I), a compound which appeared to be especially sensitive to autooxidation.

An analogous reaction in which the *t*-butyl alcohol was added 15 min after the lithium (243 mg, 7 g-atoms) over a 5-min period furnished VI as the major product. Recrystallization from ethanol gave the analytical sample of VI (mp 113.5–114.5°, white needles). Thin layer chromatography of the mother liquor showed a major spot of higher R_f value (probably, therefore, a tetradecahydro derivative) which was not investigated further.

Reduction of III with Lithium in Methylamine.—Lithium (208 mg, 6 g-atoms) was added to a solution of 3 ml of *t*-butyl alcohol in 250 ml of methylamine at reflux. Then 2 min later III (1.17 g, 5 mmol) was added, followed by 15 ml THF in order to bring into solution the incompletely dissolved hydrocarbon. The blue color disappeared within 10 min. Work-up in the usual manner gave an oil (1.12 g), revealed by thin layer chromatography to contain two principal components. Chromatography on silica gel with elution by hexane furnished IX (716 mg) as a viscous oil.

Registry No.—I, 16434-59-6; II, 16434-60-9; III, 16434-61-0; IV, 16434-62-1; V, 16434-55-2; VI, 16452-37-2; VII, 16434-56-3; VIII, 16434-57-4; IX, 16434-58-5.

A Method for the Addition of the Elements of Ketene to Some Selected Dienes in Diels–Alder Fashion

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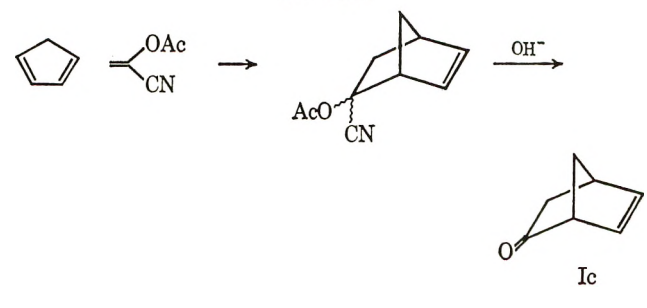
Received November 14, 1967

New and improved syntheses for dehydronorcamphor, bicyclo[2.2.2]oct-2-en-5-one, and tetracyclo[4.3.0.-$0^{2,4}.0^{3,7}$]nonan-8-one and the syntheses of tricyclo[4.2.2.$0^{2,5}$]deca-3,7-dien-9-one and tricyclo[3.2.2.$0^{2,4}$]non-6-en-8-one are described. These syntheses consist of Diels–Alder or homo Diels–Alder addition of acrylonitrile, chlorination of the nitrile adduct with phosphorus pentachloride, followed by hydrolysis of the resulting α-chloronitrile with potassium hydroxide in aqueous dimethyl sulfoxide.

The addition of ketenes to dienes yields products in which a cyclobutanone moiety is produced by cycloaddition of the ketene to a single double bond.[1] This mode of reaction is distinguished from normal Diels–Alder addition in which a double bond adds 1,4 across a conjugated system. The alternative routes available for achieving the syntheses of addition products, which conceptually are the result of Diels–Alder addition of ketene, have been complicated by two factors. Dienophiles capable of forming adducts which are easily convertible to ketones, such as vinyl acetate, will not add easily to the less reactive dienes. On the other hand, dienophiles that do add easily to most dienes such as acrylonitrile or acrylate esters are not easily convertible to the corresponding ketone. Bartlett and Tate[2] suggested an elegant solution to this problem in their synthesis of dehydronorcamphor (Ic) from α-acetoxyacrylonitrile and cyclopentadiene (Scheme I). This method suffers principally from the commercial unavailability of α-acetoxyacrylonitrile.[3]

SCHEME I

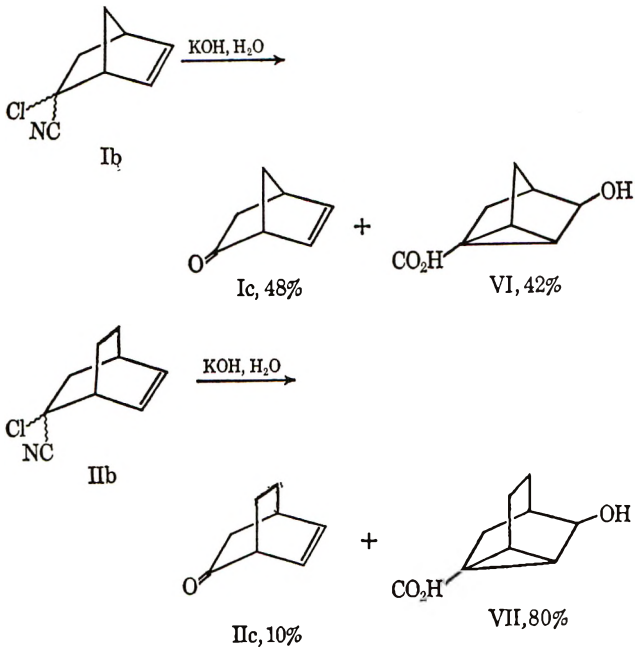


Ic

In more recent studies Paasivirta and Krieger[4] prepared dehydronorcamphor (Ic) and bicyclo[2.2.2]-oct-2-en-5-one (IIc) from chloronitriles, which were obtained by adding α-chloroacrylonitrile to cyclo-

(1) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 2 (1962).
(2) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).
(3) R. M. Nowak, *J. Org. Chem.*, **28**, 1182 (1963).
(4) J. Paasivirta and H. Krieger, *Suomen Kemstilehti, B*, **38**, 182 (1965); J. Paasivirta, *Suomen Kemstilehti, A*, **39**, 120 (1966); see also H. Krieger and S. E. Masar, *ibid.*, **39**, 119 (1966).

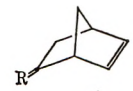
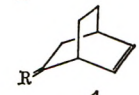
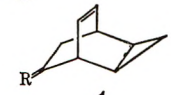
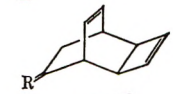
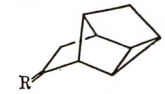
SCHEME II



pentadiene and 1,3-cyclohexadiene (Scheme II). Although α-chloroacrylonitrile is readily available, it has been our experience that it gives polymeric tars when heated with less reactive dienes at temperatures exceeding 140–160°.

We have developed a more generally applicable procedure for the syntheses of ketene Diels–Alder addition products, based on the conversion of readily obtainable Diels–Alder acrylonitrile adducts to α-chloronitriles. Our chlorination method is adapted from a procedure reported by Stevens and Coffield[5] for halogenation of secondary nitriles with phosphorus pentachloride or phosphorus pentabromide. The chief differences are in the use of solvent to moderate the reaction and in the addition of pyridine in order that the chlorination can be performed in the presence of a double bond. In the second step of the procedure the α-chloronitrile adducts are converted to ketones by treatment with potassium hydroxide in dimethyl sulfoxide (DMSO). As starting dienes cyclopentadiene and 1,3-cyclohexadiene were selected to illustrate completely standard reactions; cyclooctatetraene[6,7] and cycloheptatriene[8–16] were chosen as interesting examples of substrates which react and apparently react by way of their valence tautomers, 2,4,7-bicyclo[4.2.0]octatriene and norcaradiene; and norbornadiene was used to illustrate a synthesis *via* an initial homo Diels–Alder reaction. Table I lists the ring systems synthesized and the yields obtained. (Ring structure numerals are assigned letters to indicate substituents: a for R = H, CN; b for R = Cl, CN; and c for R = O.)

TABLE I
SUMMARY OF YIELD DATA

		Yield, %[a] Chloronitrile R = Cl, CN	Yield, %[a] Ketone R = O
I		89	79
II		61	68
III		80	49
IV		Not isolated	50[b]
V		76	73

[a] Yields are based on immediate precursor. [b] Yield is based on nitrile IVa.

This method gives an improvement in both yield and simplicity over previous methods for making ketones Ic,[2,4,17] IIc,[4,18] and Vc.[19] Structural confirmation for these three known ketones was provided by comparison of the spectral data obtained with an infrared spectrum of Ic,[17] nmr and infrared spectra of ketone Vc,[19] and with the reported infrared absorptions of ketone IIc.[18]

Ketones IIIc and IVc have not previously been reported and their structural assignments are based on infrared and nmr spectra (see Experimental Section) and on the known proclivity of these ring systems, synthesized *via* Diels–Alder reactions, to have the cyclopropyl or cyclobutenyl rings *syn* to the double bond.[7,11,12]

It is instructive to compare the results of Paasivirta and Krieger[4] with those presented here. The conditions used by these workers (aqueous potassium hydroxide) for the conversion of α-chloronitrile to ketone would be expected to favor a larger SN1/SN2 ratio than under our conditions (DMSO–potassium hydroxide), which should favor a bimolecular displacement of chloride by hydroxide. This argument is based on the known ability of DMSO to enhance the nucleophilicity of anions, relative to reactions in protic solvents,[20] and is borne out by the isolation of hydroxy acids VI and VII by Paasivirta and Krieger and by the high yields obtained for ketones Ic and IIc in this work.

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(19) (a) Synthesis of ketone Vc has been briefly described in a preliminary communication: P. K. Freeman and D. M. Balls, *Tetrahedron Lett.*, No. 5, 437 (1967). (b) H. K. Hall, Jr. [*J. Org. Chem.*, **25**, 42 (1960)], prepared this ketone in less than 1% yield from nitrile Va.
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Experimental Section

Melting points are uncorrected. The nmr spectra were recorded with a Varian Associates A-60 nmr spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were recorded with a Perkin-Elmer Model 137 infrared spectrophotometer (except as noted in Table II) and were calibrated with a polystyrene spike at 1601.4 cm^{-1}. Vapor phase chromatographic analyses were performed on an F & M Model 609 chromatograph equipped with a flame ionization detector. Two columns were used: column A, 14 ft × 0.25 in., 15% Carbowax 20M on 70–80 mesh Anakrom AS; column B, 18 ft × 0.25 in., 12% SE 30 on 110–120 mesh Anakrom AS. A Parr Instrument Co., Series 4500, pressure reaction apparatus was used for Diels–Alder reactions except as noted. Elemental analyses were performed by Max Bernhardt, Microanalytisches Laboratorium, Max-Planck Institute, Mülheim, Germany. The acrylonitrile, α-chloroacrylonitrile, and olefins used were all practical grade and were distilled just before they were used. Dimethyl sulfoxide was practical grade (mp 18°). Chloroform was distilled from phosphorus pentachloride prior to using in chlorination of the nitriles.

TABLE II

A COMPARISON OF INFRARED STRETCHING FREQUENCIES OF RELATED NITRILES AND α-CHLORONITRILES

Ring system	Nitrile,[a] cm^{-1}	Chloronitrile,[a] cm^{-1}
I	2238.8	2240.0
II	2238.8	2240.4
III	2238.2	2244.3
IV	2239.4	
V	2236.9	2242.4

[a] The absorption frequencies reported in this table were obtained by measurements with a Perkin-Elmer Model 621, equipped with a frequency marker, on dilute CCl_4 solutions, and are averages of two determinations. Indene was used for calibration and the values reported are believed to be accurate to better than 0.5 cm^{-1}.

Synthesis of Dehydronorcamphor (Ic).—5-Chloro-5-cyanobicyclo[2.2.1]hept-2-ene (Ib) was prepared by mixing cyclopentadiene and 2-chloroacrylonitrile at 70–80° according to the method of Krieger:[21] yield 89%; bp 54–56° (1.8 mm); mp 47–48° (lit. mp 45–47°). A 68.6-g (0.446 mol) sample of α-chloronitrile Ib was dissolved in 400 ml of DMSO in a 1-l. flask fitted with mechanical stirrer and internal thermometer. A solution of 75 g of 85% potassium hydroxide (1.14 mol) in 25 g of water was prepared by mixing and heating until dissolved. The hot alkali was poured into the stirred DMSO–chloronitrile solution. After 24–36 hr the dark reaction mixture was subjected to steam distillation until the distillate no longer had a strong odor of product. The distillate was extracted three times with ether, and the combined ether extracts were dried. Distillation on an 18-in. semimicro spinning-band column gave 35.1 g (78.6%) of ketone Ic, bp 80–81° (45 mm), mp 22–23° (lit.[4] mp 22–23°). The infrared spectrum was identical with that of an authentic sample.[17]

Preparation of 5-Chloro-5-cyanobicyclo[2.2.2]oct-2-ene (IIb).—Using the Diels–Alder addition of 1,3-cyclohexadiene and α-chloroacrylonitrile to prepare chloronitrile IIb[4] resulted in yields of only 17%. The following procedure gives a considerable improvement in over-all yield. 5-Cyanobicyclo[2.2.2]oct-2-ene (88.2 g, 0.65 mol) prepared in 88.7% yield as previously described[22] was added slowly, with stirring, to a solution of pyridine (106 g, 1.33 mol) and phosphorous pentachloride (207 g, 0.994 mol) in 1500 ml of dry chloroform. After refluxing for 16 hr, the mixture was poured onto 2 kg of ice. After the ice had melted, the layers were separated and the aqueous phase was washed twice with ether. The organic extracts were combined and washed once with saturated aqueous sodium chloride and once with 10% aqueous sodium carbonate. Removal of solvent and distillation gave 67.2 g (60.8%) of chloronitrile, mp 88–90°. The nmr and infrared spectra of the chloronitriles prepared by the two methods were essentially identical. Vapor phase chromatographic analyses of the chloronitriles prepared by the two methods on column B (180°) showed two peaks in the ratios 74:26 for the cyclohexadiene–α-chloroacrylonitrile adduct and 70:30 for the product obtained from chlorination of IIb.

Preparation of Bicyclo[2.2.2]oct-2-en-5-one (IIc).—A hot solution of 106 g (1.61 mol) of 85% potassium hydroxide in 30 ml of water was added to a solution of 66.7 g (0.40 mol) of chloronitrile IIb in 600 ml of DMSO. There was a gradual darkening of color from yellow to black and a mild increase in temperature to 50–60°. After 12 hr, vpc analysis (column B, 170°) revealed that no more chloronitrile was present and that a new peak corresponding to ketone IIc had appeared. The reaction mixture was added to 1 kg of ice–water and extracted five times with petroleum ether (bp 30–60°). Drying over magnesium sulfate and distilling off the solvent left a semisolid mass which was sublimed to give 33.0 g (68%) of ketone, mp 84–86° (lit.[4] mp 84–86°).

Preparation of 8-Cyanotricyclo[3.2.2.0^{2,4}]non-6-ene (IIIa).—Cycloheptatriene (276 g, 3.00 mol), acrylonitrile (212 g, 4.00 mol), and 4-*t*-butylcatechol were placed in a Parr, Series 4500, pressure reaction apparatus. The vessel was heated, with stirring to 180–200° for 36–40 hr. Distillation of the contents after cooling on an 18-in. semimicro spinning-band column gave 302.0 g (70.2%) of nitrile, bp 70–76° (0.1–0.2 mm). The ir had ν_{max} at 3070 (cyclopropyl and vinyl C—H) and 2238 cm^{-1} (—C≡N). The 1600–1700-cm^{-1} region showed very weak absorptions. The nmr spectrum had complex patterns in the regions τ 4.1–4.45 (2 H), 6.8–9.3 (7 H), and 9.65–10.00 (2 H).

Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found: C, 82.58; H, 7.81.

Preparation of 8-Chloro-8-cyanotricyclo[3.2.2.0^{2,4}]non-6-ene (IIIb).—Nitrile IIIa (145 g, 1.00 mol) was added to a solution of phosphorus pentachloride (313.1 g, 1.50 mol), pyridine (160 g, 2.00 mol), and 1500 ml of dry chloroform. The mixture was refluxed with stirring for 72 hr under a nitrogen atmosphere. Work-up of the reaction mixture was similar to that described for chloronitrile IIb except that the product distilled at 84–92° (0.9–1.0 mm), 141 g (80%). The nmr spectrum exhibited absorptions at τ 3.9–4.6, complex multiplet (2 H); 6.50–6.88 and 6.88–7.22, broad multiplets (1 H each); 7.2–8.2 and 8.4–9.1, complex absorptions (2 H each); and 9.4–10.0, complex multiplet (2 H). The ir spectrum exhibited ν_{max} 2244 (C≡N stretch) and 3040 cm^{-1} (vinyl C—H stretch). More accurate determination of the C≡N stretching frequencies in the infrared for each pair of nitriles, revealed, as in this case, that substitution of chlorine α to the nitrile group causes a shift to higher frequencies of 1.2–6.1 cm^{-1} (Table II).

Anal. Calcd for $C_{10}H_{10}NCl$: C, 66.86; H, 5.61. Found: C, 67.03; H, 5.64.

Preparation of Tricyclo[3.2.2.0^{2,4}]non-6-en-8-one (IIIc).—Chloronitrile IIIb (122.4 g, 0.69 mol) and 800 ml of DMSO were heated to 50°. A hot solution of 120 g of 85% potassium hydroxide in 40 g of water was poured into the stirred reaction mixture. After 48 hr at this temperature, the black mixture was subjected to steam distillation. The distillate was extracted three times with ether; the ether extracts were dried over magnesium sulfate. Distillation of the ether extracts yielded 44.2 g (49%) of ketone IIIc, bp 72–74° (0.9–1.0 mm). In another experiment where the chloronitrile was not distilled a 52% yield was obtained based on nitrile IIIa. The nmr spectrum showed complex patterns in the following ranges: τ 3.90–4.55, 6.73–7.18, 7.20–8.08, 8.53–9.10, 9.38–9.75. The areas of each set of peaks were all equal and therefore correspond to two protons each. The ir showed ν_{max} 3040, 2990, 1710, 1430, 1410, 1360, 1285, 1160, 1145, 1100, 1040, 964, 888, 845, 812, 763, 728, and 705 cm^{-1}.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.61; H, 7.55.

Preparation of Tricyclo[4.2.2.0^{2,5}]deca-3,7-diene-9-carbonitrile (IVa).—Cyclooctatetraene (60 g, 0.576 mol), acrylonitrile (53 g, 1.00 mol), and 0.5 g of *t*-butylcatechol were heated in a sealed glass tube to 180° for 18 hr. Distillation of the reaction mixture under 0.01–0.05-mm pressure until an internal flask temperature of 250° was reached gave 78.8 g (88%) of nitrile whose vapor phase chromatogram (column B, 190°) showed two peaks of almost equal area. The ir spectrum showed ν_{max} at 2245 (—C≡N stretch) and 3060 (vinyl C—H stretch) cm^{-1}. The nmr spectrum had peaks at τ 3.95–4.4, complex multiplet (4 H); 6.93, triplet (1 H); 7.1–7.7, complex multiplet (4 H);

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8.1–8.5, complex multiplet (2 H). Nitrile IVa gave $n^{25}D$ 1.5240 (lit.[23] $n^{25}D$ 1.5236).

Preparation of Tricyclo[4.2.2.0^{2,5}]deca-3,7-dien-9-one (IVc).—Pyridine (80 g, 1.0 mol) was slowly added to a solution of 121 g (0.58 mol) of phosphorus pentachloride in 700 ml of dry chloroform. To the resulting white suspension was added 64.8 g (0.388 mol) of nitrile IVa. Work-up after 36 hr of heating at reflux consisted of pouring onto ice, removing the aqueous layer, washing the aqueous phase twice with ether, washing the combined organic extracts with saturated sodium carbonate, and removing the solvent on a rotary evaporator. This treatment gives 88 g of dark liquid which was used without further purification. In a separate experiment, attempted distillation of the chloronitrile at 0.01 mm led to decomposition and loss of product. The 88 g of dark liquid described above was dissolved in 600 ml of DMSO, and to this was added a hot solution 66 g (1.0 mol) of 85% potassium hydroxide in 22 ml of water. After 24 hr the mixture was worked up as described for the purification of ketone IIc. After sublimation, 28.1 g (49.7% based on nitrile IVa) of ketone was obtained. The nmr spectrum exhibited bands at τ 3.80–4.42, complex multiplet (4 H); 6.9–7.5, broad absorption (4 H); 8.13 and 8.15, two doublets (1 H each). The ir showed absorptions at 1710 (C=O stretch) and 3060 cm^{-1} (vinyl C—H stretch).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.07; H, 6.96.

8-Cyanotetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (Va).—Nitrile Va was prepared from freshly dried and distilled norbornadiene [bp 86–87° (693 mm)] and acrylonitrile [bp 74–75° (693 mm)]. The method of Shrauzer and Glockner[24] or Shrauzer and Eichler[25] was scaled up to preparative proportions. The latter method is more convenient for large-scale preparations if the acrylonitrile is added slowly rather than all at once as described.[25] Yields were 85–93% using centigram quantities.

8-Cyano-8-chlorotetracylo[4.3.0.0^{2,4}.0^{3,7}]nonane (Vb).—A mixture of nitrile Va (494 g, 3.41 mol), 1000 ml of carbon tetrachloride, and phosphorus pentachloride (208 g, 1.00 mol) was heated at reflux in a vessel fitted with a stirrer, chlorine inlet, reflux condenser, and a gas bubbler. The chlorine inlet was placed between the flask and the condenser. There was a gradual evolution of hydrogen chloride, which after 24 hr becomes more sluggish. At this time chlorine gas was passed into the solution to convert phosphorus trichloride to the pentachloride. This process was continued until no more HCl was evolved (about 3 days). The completeness of reaction can be conveniently checked by vpc or nmr (by following the disappearance of the absorption corresponding to hydrogen α to nitrile). The cooled reaction mixture was poured onto 2.5 kg of ice and mixed until the ice melted. The two phases were allowed to separate (there may be an emulsion at this point which requires several hours to break up); the aqueous layer was extracted with carbon tetrachloride. The combined organic phases were washed once with water and then with 10% aqueous sodium carbonate until no more carbon dioxide was evolved. Simple distillation gives 463 g (76%) of oily chloronitrile: bp 89–94° (0.05–0.1 mm); ir, ν_{max} at 3060, 2245 cm^{-1}; nmr, multiplets at τ 7.65–7.82 (2 H), 7.82–8.0 (3 H), 8.27–8.44 (2 H), 8.44–8.62 (1 H), 8.68–8.87 (2 H).

Anal. Calcd for $C_{10}H_{10}ClN$: C, 66.85; H, 5.61; N, 7.80. Found: C, 66.92; H, 6.13; N, 8.16.

Preparation of Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-8-one (Vc).—Chloronitrile Vb (463 g, 2.58 mol) was dissolved in 2 l. of DMSO and the solution heated to 50°. A hot solution of 400 g of 85% potassium hydroxide in 120 g of water was slowly added. After stirring for 3 days at 50–60°, the dark reaction mixture was subjected to steam distillation. The distillate was saturated with sodium chloride and extracted with ether. The ether extracts were dried over magnesium sulfate, concentrated, and distilled to give 252 g (73%) of ketone, bp 69–70° (4 mm). In another experiment where the chloronitrile was not isolated the yield was 69.7% based on nitrile. The nmr spectrum showed multiplets centered at τ 7.48 (3 H), 7.78 (2 H), 8.40 (2 H), and a broad multiplet from 8.50 to 8.88 (3 H); ir had ν_{max} at 3060 (cyclopropyl C—H stretch) and 1756 cm^{-1} (carbonyl stretch). The ir and nmr spectra were identical with spectra of an authentic sample which were kindly supplied to us by Professor Alex Nickon.

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Registry No.—Ic, 694-98-4; IIb, 6962-73-8; IIc, 2220-40-8; IIIa, 16282-02-3; IIIb, 16282-03-4; IIIc, 16282-04-5; IVc, 16282-05-6; Vb, 16282-06-7; Vc, 16282-07-8.

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The Syntheses and Properties of Sterically Hindered Butadienes. A Modification of the Chugaev Reaction

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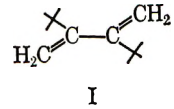
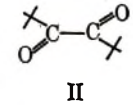
The synthesis of 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (IV) was accomplished *via* a double Wittig reaction with 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (III). The synthesis of 2,3-diisopropyl-1,3-butadiene (VIII) from 2,3-diisopropyl-1,4-butanediol (XI) was accomplished *via* a modification of the Chugaev reaction. The chemical and spectroscopic properties of 2,3-di-*t*-butyl-1,3-butadiene (I), of dienes IV and VIII, and of diketone III and dipivaloyl (II) are discussed. The heavily substituted butadienes I and IV are shown to be unusually unreactive.

Our interest in crowded molecules led to several unsuccessful attempts to synthesize 3,4-di-*t*-butylthiophene.[1] Ring-closure reactions of 2,3-di-*t*-butyl-1,3-butadiene (I), 2,3-di-*t*-butylsuccinnic acid derivatives, or dipivaloyl (II) with suitable reagents were unsuccessful.[1] The lack of reactivity of these α,β-di-*t*-butyl compounds in ring-closure reactions must be attributed to the bulky *t*-butyl groups. Spectroscopic evidence for an abnormal conformation in these α,β-di-*t*-butyl compounds was found for 2,3-di-*t*-butyl-1,3-butadiene (I).[2]



I



II

The ultraviolet absorption spectrum of the vapor of the butadiene I, taken at room temperature under

(1) Ae. de Groot, Ph.D. Thesis, Groningen, 1967.

(2) H. Wynberg, Ae. de Groot, and D. W. Davies, *Tetrahedron Lett.*, 1083 (1963).

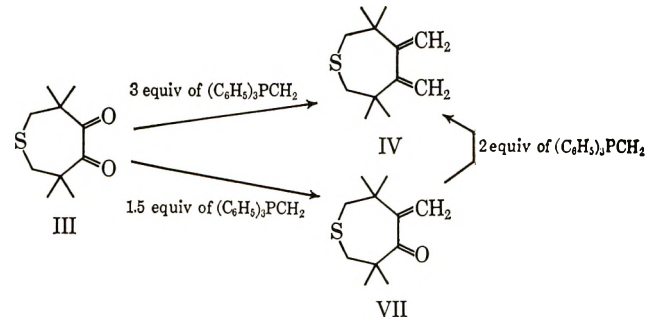
nitrogen, shows the absence of the typical dialkyldiene absorption maximum at 220 (vapor) ± 5 mμ.[3] Instead the spectrum of I shows a maximum near 185 mμ and a shoulder at 209 mμ which is characteristic of a substituted ethylene.[4] Molecular models show that a normal coplanar *cis* or *trans* conformation is sterically unlikely for diene I. An orthogonal conformation is clearly the favored one in this case. Leonard and Mader[5] studied the angle of twist about the intercarbonyl bond of α diketones and assigned an angle θ of 90–180° to dipivaloyl (II). An important difference between dipivaloyl and the butadiene I is the presence of the four vinyl protons in the butadiene. The hindrance between a proton at carbon atom 1 and the *t*-butyl group at carbon atom 3 prevents the coplanar *trans* conformation in the diene. This conformation is probably possible in the diketone.[6]

Bromination, hydrogenation, and ozonolysis reactions of I were investigated by Backer.[7] The latter[7] showed that diene I underwent no Diels–Alder reaction with sulfur dioxide or maleic anhydride. Our attempts to prepare 3,4-di-*t*-butylthiophene by heating the diene with sulfur were also unsuccessful. The relatively easy dealkylation of *t*-butylthiophene may well make any high-temperature route for the preparation of 3,4-di-*t*-butylthiophene impractical.[8,9] Huyser, Siegert, Sinnige, and Wynberg[10] showed that the diene I was unreactive in peroxide-induced free-radical reactions.

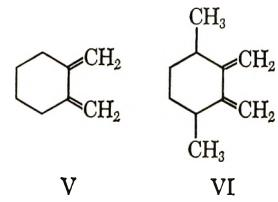
Dipivaloyl (II) does not react in ring-closure reactions. A Hinsberg thiophene synthesis with diethyl thiodiacetate was unsuccessful.[1] In the literature unsuccessful ring-closure attempts of dipivaloyl to form 2,3-di-*t*-butylquinoxaline[5] and 4,5-di-*t*-butylimidazole[11] are mentioned. We developed a successful route to the last two *o*-di-*t*-butyl heteroaromatics using the cyclic diketone III as starting material for the ring-closure reactions.[9] In diketone III the two potential *t*-butyl groups are part of a ring and thus the carbonyl functions are kept in a favorable position for ring-closure reactions. However, the angle of twist θ about the intercarbonyl bond in diketone III must also be about 90°,[5] as can be seen from molecular models of the diketone and from the longest wavelength absorption maximum in the ultraviolet spectrum [λ_{max} 333 mμ (ε 41.8)]. Comparison of the ultraviolet spectrum of diketone III with the spectra of the carbocyclic analogs of this diketone, prepared by Leonard and Mader,[5] shows that diketone III has the largest hypsochromic shift of the longest wavelength absorption maximum. This indicates that the interaction between the two carbonyl functions is minimal in diketone III, and the angle θ between the two carbonyl functions in III must be about 90°.

The successful ring-closure reactions of diketone III in comparison with the unreactivity of dipivaloyl in this type of reaction prompted us to compare the behavior of diene IV with that of 2,3-di-*t*-butyl-1,3-butadiene (I). Diene IV was prepared in 24–30% yield by reaction of diketone III with excess methylenetriphenylphosphorane in dimethyl sulfoxide as solvent[12] (Scheme I).

SCHEME I



Diene IV is a perfectly stable, clear liquid [bp 78° (1.9 mm), $n^{20}D$ 1.5135]. The ultraviolet absorption spectrum of diene IV shows no maximum above 185 mμ, clearly indicating that there is a complete lack of double-bond resonance in this diene. The angle of twist between the two double bonds must be about 90° (compare with diketone III). Thus the exocyclic diene IV and the open diene I show similar spectroscopic (and chemical, see below) behavior. However, the virtually fixed skew[2] conformation of diene I is clearly caused by steric interference between adjacent *t*-butyl groups and vinyl protons. A relatively rigid conformation of the seven-membered ring forces the two adjacent *exo*-methylene groups into an orthogonal position in diene IV, again causing the sharp hypsochromic shift in the absorption spectrum. 1,2-Dimethylenecyclohexane (V)[13] has abnormally low absorption in the ultraviolet spectrum [λ_{max} 220 mμ (ε 10,050)] and 3,6-dimethyl-1,2-dimethylenecyclohexane (VI) has an absorption maximum below 220 mμ.[14] Clearly the two



V VI

methyl groups in VI exhibit some influence on the coplanarity of the chromophore. The four methyl groups in 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (IV) cause even greater rigidity of the molecule, as is shown by the nmr spectrum. This nmr spectrum shows two singlets at τ 8.90 and 8.73 at room temperature for the methyl protons, an AB multiplet for the 2 and 7 methylene protons, and an AB multiplet for the exocyclic methylene protons.[15] When the sample was warmed, the two singlets collapsed at 92° and the AB multiplet for the 2 and 7

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(10) E. S. Huyser, F. W. Siegert, H. J. W. Sinnige, and H. Wynberg, *ibid.*, **31**, 2437 (1966).
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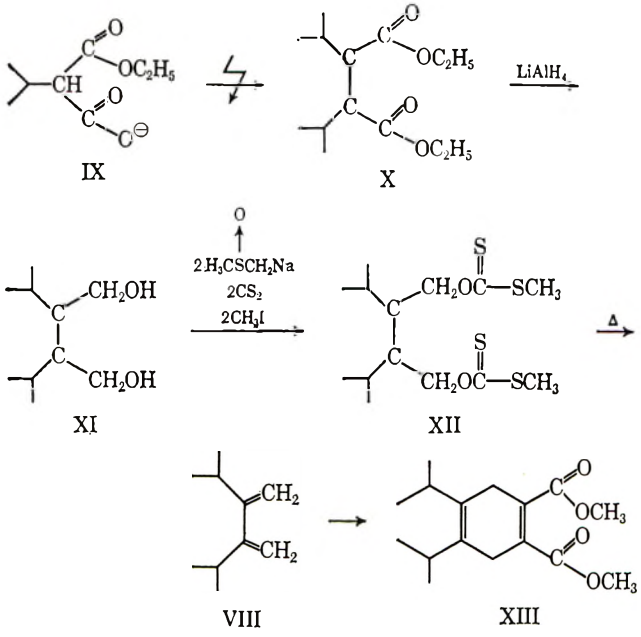
(13) W. J. Bailey and H. R. Golden, *J. Amer. Chem. Soc.*, **75**, 4780 (1953).
(14) W. J. Bailey and R. L. Hudson, *ibid.*, **78**, 2806 (1956).
(15) The nmr spectrum of diketone III shows a singlet for the methyl protons at τ 8.75 and a singlet for the 2 and 7 methylene protons at τ 7.43 at room temperature. The differences in the nmr spectra at room temperature also indicate that in these cyclic compounds III and IV the vinyl protons in diene IV cause considerably more steric hindrance than the free electrons of the carbonyl functions in diketone III[8] [compare diene I and dipivaloyl (II)].

methylene protons did the same at 112°. Since this molecule (IV) gives two coalescence temperatures, it is very simple to calculate the flipping barrier. This turned out to be 8.3 kcal/mol.[16]

Diene IV gives no Diels–Alder adduct upon reaction with ethylacetylene dicarboxylate, tetracyanoethylene, thiofluorenone, or benzyne. Thus both dienes (I and IV) show complete lack of reactivity in these Diels–Alder reactions.

A reaction of diketone III with 1.5 equiv of methylenetriphenylphosphorane gives the methylene ketone VII (60–70%) (Scheme I). Reaction of VII with more phosphorane yields diene IV. The ultraviolet absorption spectrum of VII shows only one maximum at λ 300 mμ (ε 40), again indicating the absence of resonance between the methylene and the carbonyl group. The ultraviolet spectra of the exocyclic cyclohexanedienes V and VI indicate diminished resonance between the double bonds but Diels–Alder adducts of these dienes can be obtained.[14] Since in the dienes I and IV there is a complete lack of resonance between the double bonds and no Diels–Alder adducts could be obtained, it appeared interesting to study the spectroscopic and chemical properties of 2,3-diisopropyl-1,3-butadiene (VIII). We expected that the steric hindrance in diene VIII would be intermediate between the hindrance in dienes V and VI, on the one hand, and dienes I and IV, on the other hand. Diene VIII was not known in the literature and several routes for its preparation were tried. A double Wittig reaction on 2,5-dimethyl-3,4-hexanedione analogous to the preparation of diene IV was unsuccessful.[17] 2,3-Diisopropyl-1,3-butadiene (VIII) was prepared *via* the route shown in Scheme II. Kolbe electrolysis of monoester

SCHEME II



IX gave 2,3-diisopropylsuccinnic acid diethyl ester (X).[18] Reduction of diester X with lithium aluminum hydride gave diol XI in 90% yield. The dehydration of this diol to diene VIII was accomplished by pyrolysis of the dixanthate XII (Chugaev reaction).[19]

The utility of the Chugaev reaction is dependent upon the ease of formation and purification of the xanthate. The most commonly encountered difficulty in the preparation of xanthates is formation of the metal salt of the alcohol.

Reaction of diol XI with potassium in xylene gave only 5–10% yield of the dixanthate XII in a slow, heterogenous reaction. A major improvement was made by using dimethyl sulfoxide as solvent and dimethyl sulfoxide carbanion as the stronger base. In an equilibrium reaction the bisalcoholate of diol XI is formed rapidly; the reaction remains homogeneous since the salt stays in solution.

Addition of carbon disulfide and methyl iodide results in the formation of the dixanthate XII in 50–60% yield.[20] The pyrolysis of dixanthate XII was performed in a normal distillation apparatus. At atmospheric pressure and 225-250° bath temperature, 2,3-diisopropyl-1,3-butadiene (VIII) was obtained in 60% yield. The ultraviolet spectrum of diene VIII shows a maximum at λ 223 mμ (ε 6180); this maximum occurs at slightly lower wavelength than predicted for a dialkyl-substituted butadiene (227 ± 5 mμ),[21] but the deviation is small. 2,3-Diisopropyl-1,3-butadiene (VIII) does give a Diels–Alder adduct with acetylenedicarboxylic acid dimethyl ester. These data indicate that the behavior of the diisopropylbutadiene VIII is more like that of a normal butadiene. Steric hindrance increases rapidly when *t*-butyl groups are substituted for isopropyl groups. From this work and from that of others[22] it is clear that substantial steric hindrance must be present before the chemical and physical properties of substituted butadienes are materially affected.

Experimental Section

Infrared spectra were determined in carbon tetrachloride, in potassium bromide disks or neat on a Perkin-Elmer Infracord Model 137 or on a Unicam SP 200. Ultraviolet spectra were recorded on a Zeiss spectrophotometer, Model P.M.Q. II, the solvents are indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as internal standard and are reported in τ values (parts per million). The solvents used are indicated. Melting points and boiling points are uncorrected. Microanalyses were performed by the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg.

3,3,6,6-Tetramethyl-4,5-dimethylene-1-thiacycloheptane (IV).—A dispersion of 7.2 g (0.15 mol) of sodium hydride (as a 50% dispersion in mineral oil) was washed twice with 25 ml of sodium-dried pentane in a nitrogen atmosphere to remove the mineral oil. Then 150 ml of dimethyl sulfoxide (dried and distilled from calcium hydride) was added *via* a syringe, and the mixture was heated at 70–75° for 45 min. The resultng solution was cooled to room temperature, and 54 g (0.15 mol) of methyltriphenylphosphonium bromide in 150 ml of dimethyl sulfoxide was added *via* a syringe. The dark red solution of the ylide was stirred at room temperature for 15 min and then 10 g (0.05 mol) of diketone III in 25 ml of dimethyl sulfoxide was added over a

(16) We thank Dr. S. van der Werf for the performance of the nmr experiments and calculations.

(17) 2,3-Di-*t*-butyl-1,3-butadiene (I) could not be prepared by a double Wittig reaction with dipivaloyl (II). A double Wittig reaction with benzil gave 2,3-diphenyl-1,3-butadiene in 15% yield. The double Wittig reaction is thus of limited use in the preparation of dienes from α diketones.

(18) L. Eberson, *Acta Chim. Scand.*, **13**, 40 (1959).

(19) R. Nace, *Org. Reactions*, **12**, 57 (1962).

(20) Cholesterol and *n*-octanol also gave the corresponding xanthates rapidly and in 90% yield. The general usefulness of this improved method for making xanthates is being investigated further.

(21) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 196.

(22) G. Vogel, *Chem. Ind.* (London), 1954 (1964).

period of 15 min. The reaction mixture was stirred at 45° for 20 hr and then poured into 300 ml of ice–water. The aqueous phase was filtered and extracted thoroughly with pentane. The pentane fractions were combined and washed with 100 ml of a 1:1 water–dimethyl sulfoxide solution and then with 200 ml of a saturated sodium chloride solution. The pentane solution was dried over sodium sulfate and then concentrated to a volume of about 20 ml. The solution was subjected to chromatography using 50 g of neutral aluminum oxide (activity grade 1) to remove all of the triphenylphosphine oxide. Elution with pentane and evaporation of the solvent gave a residue. Distillation gave 3.0 g (30%) of colorless diene IV: bp 78° (1.9 mm); n^{20}D 1.5135; ir spectrum (neat), absorptions at 3100 and 1620 cm^{-1}; nmr spectrum (20% in carbon tetrachloride), two singlets at τ 8.90 and 8.73 (methyl protons), AB multiplet centered on 7.64 (ring methylene protons), AB multiplet at 5.35 and 5.07 (vinyl protons).

Anal. Calcd for $C_{12}H_{20}S$ (196.35): C, 73.40; H, 10.26; S, 16.34. Found: C, 73.7, 73.7; H, 10.2, 10.2; S, 16.1, 16.1.

3,3,6,6-Tetramethyl-4-methylene-1-thiacycloheptane-5-on (VII).—To 0.1 mol of methylenetriphenylphosphorane in 200 ml of dimethyl sulfoxide was added 14.5 g (0.07 mol) of diketone III in 35 ml of dimethyl sulfoxide at room temperature (for details, see diene IV). The reaction mixture was stirred at 45° for 2.5 hr and then poured into 300 ml of ice–water. The reaction mixture was worked up as described for diene IV. The yield of methylene ketone VII was 9.2 g (63%): bp 60° (0.5 mm); mp 40.5–41°; ir spectrum (neat), absorptions at 1680 and 1610 cm^{-1}; nmr spectrum (10% in carbon tetrachloride), two singlets at τ 8.80 and 8.83 (methyl protons), two singlets at 7.53 and 7.47 (ring methylene protons), two singlets at 5.28 and 4.98 (vinyl protons); uv spectrum (in 96% ethanol), λ_{max} 300 mμ (ϵ 40).

Anal. Calcd for $C_{11}H_{18}OS$ (198.33): C, 66.61; H, 9.15; S, 16.16. Found: C, 66.7, 66.7; H, 9.2, 9.2; S, 16.2, 16.2.

2,3-Diphenyl-1,3-butadiene.—To 0.13 mol of methylene triphenylphosphorane in 225 ml of dimethyl sulfoxide was added 9.25 g (0.044 mol) of benzil in 30 ml of dimethyl sulfoxide in 10 min at room temperature. The reaction mixture was stirred for 3 hr in a nitrogen atmosphere at room temperature and then poured into 300 ml of ice–water. The reaction mixture was worked up as described for diene IV. The yield of 2,3-diphenyl-1,3-butadiene was 1.5 g (15%): mp 45–46° (lit.[23] mp 46–47°); nmr spectrum (20% in carbon tetrachloride), two doublets at τ 5.23 and 5.45 (vinyl protons), multiplet centered on 2.21 (aromatic protons).

α,α'-Diisopropylsuccinnic Acid Diethyl Ester (X).—A mixture of *d,l* and meso α,α'-diisopropylsuccinnic acid diethyl ester (X) was obtained as described by Eberson.[18] The yield of diester X, bp 134–136° (15 mm), n^{20}D 1.4345, was 60% [lit. bp 125–127° (11 mm), n^{20}D 1.4350[18]].

2,3-Diisopropyl-1,4-butanediol (XI).—A solution of 60 g (0.23 mol) of diester X in 200 ml of dry ether was added to a suspension of 11.4 g (0.30 mol) of lithium aluminum hydride in 200 ml of dry ether. The reaction mixture was refluxed for 1 hour after all the diester was added. The reaction products were hydrolyzed by careful addition of water and of a dilute solution of hydrochloric acid in water. The ether layer was separated, and the water layer was extracted with ether. The combined ether fractions were washed with water and dried over potassium carbonate. The ether was evaporated, and the residue was distilled *in vacuo*. The yield of diol XI, bp 109–110° (0.4 mm), was 36 g (90%). Analytically pure diol XI, mp 78–83°, was obtained by crystallization from petroleum ether (bp 60–80°): ir spectrum (neat), absorption at 3350 cm^{-1}; nmr spectrum (10% in deuteriomethanol), two doublets at τ 9.13 and 9.03 and at 9.07 and 8.95 (methyl protons), multiplet from 8.0 to 8.8 (tertiary protons), doublet at 6.38 and 6.32 (methylene protons).

Anal. Calcd for $C_{10}H_{22}O_2$ (174.18): C, 68.95; H, 12.68. Found: C, 69.2, 68.8; H, 12.4, 12.5.

Dixanthate of 2,3-Diisopropyl-1,4-butanediol (XII).—A solution of 5.3 g (0.11 mol) of methylsulfinylsodium in 150 ml of dimethyl sulfoxide was obtained as described for diene IV. To this solution was added at room temperature 8.7 g (0.05 mol) of diol XI in 25 ml of dimethyl sulfoxide. The reaction mixture was stirred for 1 hr and then 9.2 g (0.12 mol) of carbon disulfide in 25 ml of dimethyl sulfoxide was added. The temperature of the reaction mixture was kept below 45° by external cooling. After 1 hr 17 g (0.12 mol) of methyl iodide in 25 ml of dimethyl sulfoxide was added. The reaction mixture was stirred for 1 hr and then poured into 300 ml of ice–water. The water solution was extracted with pentane; the pentane fractions were washed with a small portion of water and dried over sodium sulfate. The pentane was evaporated, and the residue was crystallized from ethanol. The yield of dixanthate XII, mp 82–84°, was 8.8–10.6 g (50–60%): nmr spectrum (10% in carbon tetrachloride), two doublets at τ 8.90, 9.00 and 9.00, 9.10 (methyl protons), multiplet at 7.9–8.25 (tertiary protons), singlet at 7.45 (sulfur methyl protons), and a doublet at 5.40 and 5.32 (methylene protons).

Anal. Calcd for $C_{14}H_{26}O_2S_4$ (354.63): C, 47.41; H, 7.39; S, 36.17. Found: C, 47.9, 47.5; H, 7.5, 7.5; S, 35.3, 35.7.

2,3-Diisopropyl-1,3-butadiene (VIII).—In a Claisen flask 4.5 g (0.013 mol) of dixanthate XII was slowly heated to 230° (bath temperature). The bath temperature was kept at 230–250° until no more gas evolution was observed. The distillate was dissolved in pentane and treated with a dilute solution of mercuric chloride in ethanol. The alcoholic solution was filtered, and 100 ml of water was added. The water solution was extracted with pentane. The pentane solution was washed with water and dried over sodium sulfate. The solvent was evaporated, and the residue was distilled at atmospheric pressure. The yield of diene VIII, bp 140°, n^{20}D 1.4405, was 1.1 g (60%). An analytical sample was obtained by means of preparative glpc (F & M 810, 4 ft, 75°): ir spectrum (neat, 0.1-mm cell), absorptions at 3080, 1625, and 1600 cm^{-1}; nmr spectrum (10% in carbon tetrachloride), doublet at τ 9.00 and 8.90 (methyl protons), heptet centered on 7.63 (tertiary protons), two doublets at 5.08, 5.10 and 5.17, 5.19 (vinyl protons); uv spectrum (in isooctane), λ_{max} 223 mμ (ϵ 6180).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.8, 87.0; H, 13.0, 13.1.

1,2-Dicarbomethoxy-4,5-diisopropyl-1,4-cyclohexadiene (XIII).—A solution of 600 mg (4.35 mmol) of diisopropylbutadiene VIII and 618 mg (4.35 mmol) of acetylenedicarboxylic acid dimethyl ester in 10 ml of benzene was refluxed for 5 hr. The solvent was evaporated, and the residue was recrystallized from petroleum ether (bp 40–60°). The yield of adduct XIII, mp 97–100° (Kofler blok), was 720 mg (60%): ir spectrum (KBr disk), absorptions at 1710 and 1650 cm^{-1}; nmr spectrum (10% in deuterioacetone), doublet at τ 9.05 and 8.93 (methyl protons), singlet at 7.07 (methylene protons), singlet at 6.27 (ester methyl protons).

Anal. Calcd for $C_{16}H_{24}O_4$ (280.35): C, 68.55; H, 8.63. Found: C, 68.3, 68.3; H, 8.5, 8.6.

Registry No.—IV, 16134-09-1; VII, 16134-10-4; VIII, 16134-06-8; XI, 16134-07-9; XII, 16170-26-6; XIII, 16134-08-0; 2,3-diphenyl-1,3-butadiene, 2548-47-2.

(23) C. F. H. Allen, C. G. Eliot, and A. Bell, *Can. J. Res.*, **17B**, 75 (1939); *Chem. Abstr.*, **33**, 6284 (1939).

Photocyclization Reactions of Phenylthioethenes

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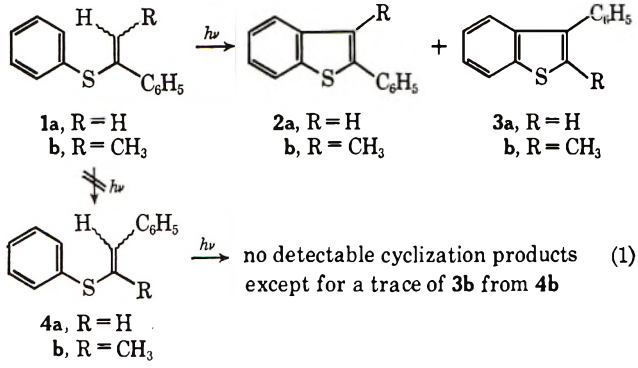
Upon irradiation, a number of phenylthioethenes undergo a low-yield cyclization reaction (up to 11.5% yield) in addition to the formation of high molecular weight products. Photolysis of 1-phenyl-1-phenylthioethene (**1a**) leads to cyclization to form "normal" 2-phenylbenzo[*b*]thiophene (**2a**) and "abnormal" 3-phenylbenzo[*b*]-thiophene (**3a**) in low yields. Similar results were obtained with 1-phenyl-1-phenylthiopropene-1 (**1b**) which gave 3-methyl-2-phenylbenzo[*b*]thiophene (**2b**) and 2-methyl-3-phenylbenzo[*b*]thiophene (**3b**). The yields of the "normal" cyclization products **2a** and **2b** were raised in the presence of iodine. Photolysis of **1a** and **1b** did not yield detectable amounts of the isomeric 1-phenyl-2-phenylthioethene (**4a**) or 1-phenyl-2-phenylthiopropene-1 (**4b**), respectively, nor did these isomers upon independent photolysis yield more than a trace of cyclization products. The benzo[*b*]thiophenes were not interconverted upon photolysis. Some other phenylthioethenes as well as phenyl sulfide formed "normal" benzo[*b*]thiophenes in low yields but no detectable amounts of "abnormal" cyclization products.

The currently favored interpretation of the photochemically induced valence bond isomerizations found in arylthiophenes involves an intermediate with an expanded valence shell for sulfur.[1] A study of some thioethenes was undertaken in order to gain information about the photochemical behavior of other unsaturated sulfur-containing systems. Phenylthioethenes proved to be particularly interesting and were investigated in some detail.

Results

Photolysis of 1-phenyl-1-phenylthioethene (**1a**) under N_2 in ether solution gave 2-phenylbenzo[*b*]thiophene (**2a**) and 3-phenylbenzo[*b*]thiophene (**3a**) (eq 1).



1a, R = H; **b**, R = CH_3 — **2a**, R = H; **b**, R = CH_3 — **3a**, R = H; **b**, R = CH_3

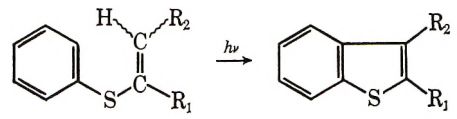
4a, R = H; **b**, R = CH_3

no detectable cyclization products except for a trace of **3b** from **4b** (1)

The yield of **2a** was raised from a trace (<1%) to 5% in the absence and the presence of iodine, respectively, while the yield of **3a** was about 4% either with or without iodine. No photochemically induced interconversion of **2a** and **3a** occurred. No 1-phenyl-2-phenylthioethene (**4a**) could be detected in the photolysis mixtures nor did this sulfide give any observable amounts of cyclization products **2a** or **3a** (eq 1) thereby eliminating the possibility that sulfide isomerization precedes ring closure.

In a similar manner photolysis of 1-phenyl-1-phenylthiopropene-1 (**1b**) gave 3-methyl-2-phenylbenzo[*b*]-thiophene (**2b**) and 2-methyl-3-phenylbenzo[*b*]thiophene (**3b**) in yields of 2 and 4%, respectively. In the presence of iodine the yield of **2b** was raised to 8% while that of **3b** was 3.5%. No detectable isomerization of **1b** to 1-phenyl-2-phenylthiopropene-1 (**4b**) took place nor did **4b** upon photolysis yield any identifiable product other than a trace of **3b**. Interconversion of **2b** and **3b** did not occur upon photolysis. The cyclization reaction proceeded in nearly the same yield at 300 as at 254 mμ (see Experimental Section). Attempts to raise the yield by using different oxidizing agents failed. Benzophenone did not have any effect on the cyclization reaction.

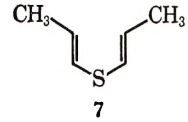
The photochemical reactions of some other phenylthioethenes (**5a–h**) were examined and the results of these experiments are shown in eq 2. In the cases



5 **6** (2)

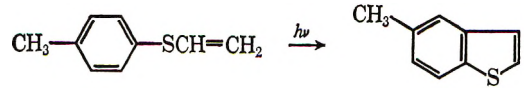
	Yield, % Without I_2	Yield, % With I_2
a, R_1 = R_2 = H	6.5	9.5
b, R_1 = CH_3; R_2 = H	...	9.0[2]
c, R_1 = H; R_2 = CH_3	...	2.5[2]
d, R_1 = CH_3; R_2 = CH_3	...	5.0[2]
e, R_1 = R_2 = —$(CH_2)_4$—	...	6.0[2]
f, R_1 = R_2 = C_6H_5	...	0.0[2-4]
g, R_1 = H; R_2 = C_6H_5S	...	0.0[2,3]
h, R_1 = R_2 = —(CH=CH)$_2$—	0[3,4]	2.5[4]

where cyclization occurred only the "normal" products (**6**) could be found (eq 2). In the case of 1-phenylthioethene (**5a**) it was shown that the yield of benzo[*b*]-thiophene was enhanced in the presence of iodine. 1,2-Di(phenylthio)ethene (**5g**) and 1-(1-propenylthio)-propene-1 (**7**) (eq 3) gave no detectable amounts of cyclization products.



7 no cyclization products (3)

The photochemical cyclization of *p*-tolylthioethene (**8**) proceeded in the presence of iodine to give 5-methylbenzo[*b*]thiophene (**9**) in 9% yield (eq 4). No other



8 **9** (4)

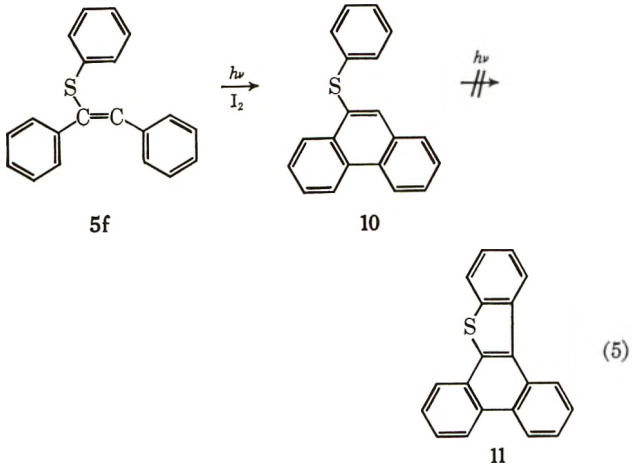
(1) For a summary of results, see H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).

(2) Yield determined only in the presence of iodine.
(3) This product could not be detected.
(4) Other product(s) were also identified.

cyclization products were detected. The rate of cyclization of **8** was much slower than that of phenylthioethene (**5a**) (see Experimental Section).

Phenyl sulfide (**5h**), upon photolysis in the presence of iodine, gave, in addition to the reported[5] phenyl disulfide (5% yield) and biphenyl (7.5% yield), bibenzothiophene (**6h**) in 2.5% yield. In the absence of iodine only biphenyl and phenyl disulfide were found, as previously reported.[5]

Photolysis of 1,2-diphenyl-1-phenylthioethene (**5f**) in the presence of iodine gave a 78% yield of 9-phenylthiophenanthrene (**10**) (eq 5) and no observable



5f **10** **11** (5)

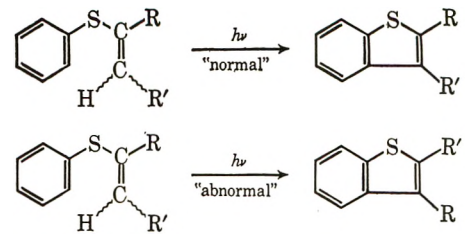
amounts of **6f** or **11**. The product **10** was identified by comparison with material prepared by an unambiguous synthesis. None of the cyclization product **11** was observed when **10** was photolyzed independently.

A number of attempts were made to characterize the other materials formed from photolyses of the phenylthioethenes. In the cases of **5b** and **5c** considerable amounts of phenyl disulfide were formed; this product was, however, found in no more than trace amounts in the photolyses of **5a** and **5d–h**. The crude photolysis mixtures consisted of a benzene- or ether-soluble oil as well as an undefined black or brown deposit. The soluble oil contained the benzo[*b*]thiophene plus undistillable material which resisted characterization.

No reactions were observed with any of the phenylthioethenes in solution in the dark. Addition of a trace of acid or iodine also failed to induce any dark reactions. The possibility that the cyclization products arise from ground-state free-radical reactions was examined with **1b**; reaction at 80° in cyclohexane with azobisisobutyronitrile (AIBN) as initiator led only to formation of high molecular weight products and no benzo[*b*]thiophenes. The possibility that free phenylthiyl radicals might play a role in the photolyses was examined with **1b**; photolysis in the presence of phenyl disulfide and iodine led to products **2b** and **3b** in decreased rather than increased yield.

Discussion

In the photochemically induced cyclization of phenylthioethenes substituted in the α position with hydrogen or methyl, only the "normal" products are observed (eq 6). Iodine seems to enhance the yields in these reactions. When the α position is substituted with phenyl an "abnormal" benzo[*b*]thiophene is formed (eq 7) in addition to the "normal" product (eq 6). The



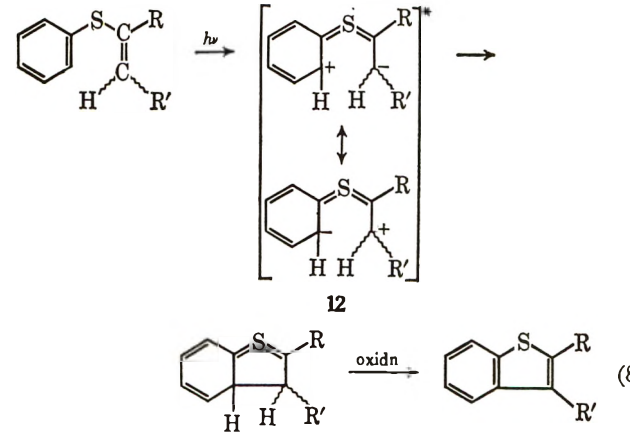
(6)

(7)

yields of the "abnormal" products appear to be insensitive to the presence of iodine. These "abnormal" benzo[*b*]thiophenes must be primary photoproducts derived from a photoreaction of the α-phenyl-substituted phenylthioethenes.

The photolysis of *p*-tolylthioethene (**8**) was carried out in order to determine if "normal" cyclization involves bond formation between the terminal carbon atom of the vinyl group and an *ortho* carbon in the phenyl ring. The formation of 5-methylbenzo[*b*]thiophene (**9**) as the exclusive product from this reaction supports this conclusion and argues against any unusual rearrangements in the phenyl ring. More involved labeling experiments with other systems are planned in order to check this possibility further.

A possible mechanistic rationalization for the formation of normal product is shown in eq 8.[6] The effectiveness of iodine in oxidizing the proposed dihydro intermediate has ample precedent in other systems.[7]



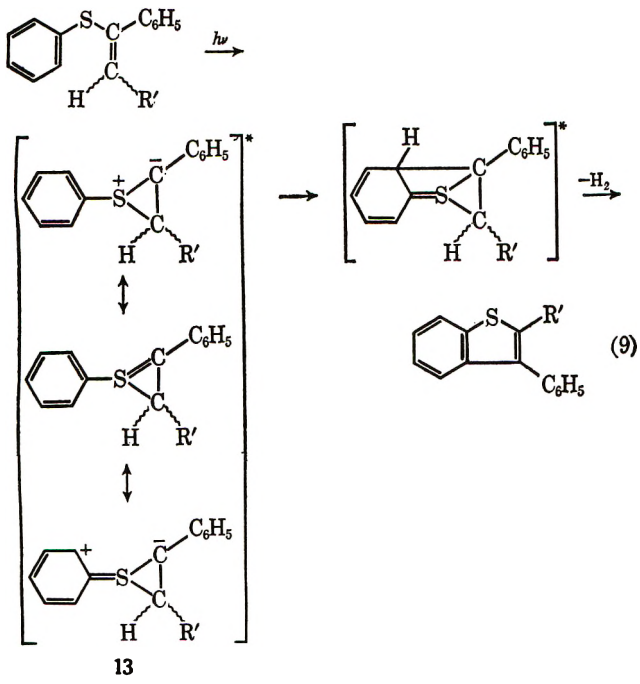
12 (8)

The presence of a phenyl group in the α position of the phenylthioethene appears to be essential to "abnormal" cyclization. This effect might arise from stabilization of structures such as **13** derived from interaction of the sulfur atom with the vinylic double bond (eq 9). Subsequent ring expansion followed by loss of hydrogen provides a rationalization for the formation of "abnormal" product. The failure to obtain "abnormal" cyclization products when the α position is substituted by hydrogen or methyl could be attributed to the

(5) W. Carruthers, *Nature*, **209**, 908 (1966); N. Kharasch and A. I. A. Khodair, *Chem. Commun.*, 98 (1967).

(6) One may, of course, imagine other valence bond structures for the proposed (excited?) intermediate **12**. Some precedent exists for sulfur valence shell expansion in photochemical reactions.[1]

(7) See, for example, F. B. Mallory, C. S. Wood, J. T. Gordon, L. C. Lindquist, and M. L. Savitz, *J. Amer. Chem. Soc.*, **84**, 4361 (1962).



13

(9)

inability of these substituents to stabilize effectively an adjacent partially charged center. The apparent ineffectiveness of iodine in the formation of the "abnormal" product suggests a spontaneous elimination of hydrogen in the formation of the thiophene ring.

Experimental Section

All melting points are corrected. Ultraviolet spectra were taken on a Zeiss PMQ II spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 instrument with tetramethylsilane (TMS) as internal reference. For mass spectra an Associated Electronic Industries MS 9 mass spectrophotometer was used.

Microanalyses were carried out in the analytical section of this department under the direction of Mr. W. Hazenberg.

The small-scale photolyses were performed with a Hanau S 81 high pressure mercury lamp. Larger scale reactions were done using a Hanau Q 700 high pressure mercury lamp. The equipment has been described previously.[8] A few reactions were carried out in a Rayonet photochemical reactor using the light sources described elsewhere in this section. All irradiations were performed under nitrogen either with or without a trace of iodine as noted. The irradiations were continued until the starting material had disappeared. The irradiated solutions were concentrated by means of a rotatory evaporator, checked by glpc, and then chromatographed over aluminium oxide (Merck active neutral, activity I). The oily residue thus obtained contained higher molecular weight products in addition to the cyclization products. Preliminary identification and yield calculations were done by glpc using a F & M Model 810 gas chromatograph equipped with hydrogen flame detectors. Preparative glpc was done either with an F & M Model 775 Prepmaster or with a F & M Model 700 gas chromatograph, both equipped with thermal conductivity detectors.

1-Phenyl-2-phenylthioethene (4a)[9] had uv maxima (96% C_2H_5OH) at 304 mμ (ϵ 18,000); **1-phenyl-1-phenylthiopropene-1** (1b)[10] had uv maxima (96% C_2H_5OH) at 250 mμ (ϵ 17,100); **phenylthioethene** (5a)[11] had uv maxima (96% C_2H_5OH) at 247 mμ (ϵ 8300) and 265 (8000); **1-phenylthiopropene-1** (5c)[12] had uv maxima (96% C_2H_5OH) at 248 mμ (ϵ 10,200) and 264 (10,800); **1-phenylthiocyclohexene** (5e)[13] had uv maxima (96% C_2H_5OH) at 247 mμ (ϵ 8400) and 260 (7000); **1,2-diphenyl-1-phenylthioethene** (5f)[10] had uv maxima (96% C_2H_5OH) at 263 mμ (ϵ 15,100) and 308 (12,300); **1,2-di(phenylthio)ethene** (5g)[14] had uv maxima (96% C_2H_5OH) at 280 mμ (ϵ 16,300); **1-(1-propenylthio)propene-1** (7)[15] had uv maxima (96% C_2H_5OH) at 240 mμ (ϵ 8400); and **5-methylbenzo[*b*]thiophene** (9)[16] had uv maxima (96% C_2H_5OH) at 230 mμ (ϵ 28,700), 258 (6300), 286 (1800), 291 (2400), 296 (2200), and 303 (3200).

These compounds were prepared as described in the literature.

1-Phenyl-2-phenylthiopropene-1 (4b)[17] was prepared in an analogous manner to 4a[9] from the addition of thiophenol to methyl phenyl acetylene: bp 138–140° (1.1 mm); n^{20}D 1.6457; uv, λ_{max} (96% C_2H_5OH) 260 mμ (ϵ 12,500), 285 (12,300); nmr (CCl_4), τ 8.0 (m, 3, CH_3, *cis–trans* isomers present), 3.4 (m, 1, =CH), and 2.8 [m, 10, $(C_6H_5)_2$].

1-Phenyl-1-phenylthioethene (1a) and **2-phenylthiopropene-1** (5b) were prepared in low yield as described for 1-phenyl-1-phenylthiopropene-1 (1b)[10] by using acetophenone and acetone, respectively, in place of propiophenone. Campaigne and coworkers[10] did not obtain 1a in a reaction carried out under similar conditions. **1-Phenyl-1-phenylthioethene** (1a)[18] had the following properties: bp 90–91.5° (0.12 mm); n^{21}D 1.6323; uv, shoulder (96% C_2H_5OH) 244 mμ (ϵ 11,000); nmr (CCl_4), τ 4.48 (s, 1, =CHH), 4.82 (s, 1, =CHH), 2.8 [m, 10, $(C_6H_5)_2$]. **2-Phenylthiopropene-1** (5b) had the following properties: bp 91° (14 mm), n^{20}D 1.5642 [lit.[19] bp 68–69° (8 mm), n^{20}D 1.5690]; uv λ_{max} (96% C_2H_5OH) 244 mμ (ϵ 5100) and 264 (4000); nmr (CCl_4), τ 8.05 (q, 3, J = 1.2 and 0.7 Hz, CH_3), 5.15 (m, 1, =CHH), 4.90 (m, 1, =CHH), 2.75 (m, 5, C_6H_5).

2-Phenylthiobutene-2 (5d) was prepared by isomerization of 3-phenylthiobutene-1[20] with potassium *t*-butoxide in dimethoxyethane:[15] bp 85–86° (1 mm); n^{21}D 1.5707; uv λ_{max} (96% C_2H_5OH) 247 mμ (ϵ 8900) and 261 (7000); nmr (CCl_4), τ 8.10 (m, 6, $(CH_3)_2$), 4.10 (m, 1, =CH), 2.80 (m, 5, C_6H_5).

***p*-Tolylthioethene** (8) was prepared by a multistep synthesis beginning from the reaction of *p*-tolylthiol with 1-chloro-2-hydroxyethane.[21] The 1-*p*-tolylthio-2-hydroxyethane obtained was converted into 1-*p*-tolylthio-2-chloroethane by treatment with thionyl chloride.[22] Reaction[11] with aqueous KOH gave 8: bp 95–97° (15 mm); n^{20}D 1.5770 [lit.[9] bp 78.0° (4.0 mm); n^{20}D 1.5727]; uv λ_{max} (C_6H_{12}) 250 mμ (ϵ 7300) and 267 (7000).

Photolysis of 1-phenyl-1-phenylthioethene (1a) (190 mg in 125 ml of ether) in the presence of a trace of iodine gave two products detectable by glpc (6-ft DEGS, 190°). These were isolated from the exit port of the F & M 700 (6-ft DEGS, 170°). The ir spectra of these compounds were identical in all respects with those of 3-phenylbenzo[*b*]thiophene (3a) and 2-phenylbenzo[*b*]thiophene (2a), respectively. Further confirmation of the identity of 2a was obtained from its isolation, in very low yield, as a precipitate from another reaction mixture; ir and uv spectra were identical with those of authentic material and a mixture melting point determination with the latter showed no depression. No isomeric 1-phenyl-2-phenylthioethene (4a) could be detected in gas chromatograms of samples taken during the course of photolysis. Product yields from irradiations carried out in the presence of iodine, calculated by glpc (4-ft DEGS, 190°), were about 5% 2a and 4% 3a. Without iodine the yield of 3a remained approximately the same while only a trace of 2a was formed.

2-Phenylbenzo[*b*]thiophene (2a)[23] had mp 170–172°; uv maxima (CH_2Cl_2) were at 232 mμ (ϵ 17,400), 256 (9800), 299

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(18,700). Irradiation of this material (125 mg in 125 ml of ether) either with or without iodine failed to give any 3-phenylbenzo[b]thiophene (3a). On one occasion irradiation without iodine led to the formation of a small amount of an extremely insoluble white solid which detonated upon an attempt to determine its melting point.[24] This material is likely peroxidic in nature.

3-Phenylbenzo[b]thiophene (3a) was prepared by the described method:[25] bp 117–118° (0.25 mm); n^{20}D 1.6823 [lit.[25] bp 100–120° (0.1 mm); $n^{20.5}$D 1.6792]; uv, λ_{max} (CH_2Cl_2) 235 mμ (ε 29,500), 264 (8300), 294 (6000), 303 (6200). Irradiation (320 mg in 115 ml of ether) with or without iodine failed to produce 2-phenylbenzo[b]thiophene (2a) or any other identifiable products other than recovered starting material.

Irradiation of 1-phenyl-2-phenylthioethene (4a) (isomer with J_{vinyl} = 15 Hz, mp 33.5–34°; 201 mg in 120 ml of ether) for 2 hr with or without iodine gave an oil in which no 2- or 3-phenylbenzo[b]thiophene (2a and 3a) could be detected by glpc (6-ft DEGS, 190°) or ir spectroscopy. Only the presence of starting material and its geometrical isomer (J_{vinyl} = 10 Hz) could be demonstrated.

Photolysis of 1-phenyl-1-phenylthiopropene-1 (1b) was always done with one pure isomer (mp 42.5–43°). Irradiation (500 mg in 150 ml ether) with an S-81 lamp for 20 min led to a mixture of geometrical isomers as shown by the nmr spectrum which gave an additional doublet for the methyl protons and new vinyl splittings. Very small amounts of two longer retention time products could also be seen in the gas chromatograms. Irradiation for 5 hr led to disappearance of the starting material and its geometric isomer and an increase in the amount of the two longer retention time products. These latter products, prepared on larger scale by photolysis with a Q-700 lamp, were isolated by preparative gas chromatography (F & M 775, 8-ft 25% DEGS, 195°). Infrared, uv, and nmr spectra and glpc retention times of these two photoproducts were identical with those of authentic 2-methyl-3-phenylbenzo[b]thiophene (3b) and 3-methyl-2-phenylbenzo[b]thiophene (2b). The molecular weights determined by mass spectrometry agreed with those calculated for the above mentioned products. The yields calculated by glpc (4-ft DEGS, 190°) were 2% 2b and 4% 3b. When the reactions were carried out in the presence of traces of iodine the yields were 8% 2b and 3.5% 3b.

Examination of crude irradiation mixtures by nmr spectroscopy showed no peaks assignable to the isomers of the starting sulfide, 1-phenyl-2-phenylthiopropene-1 (4b) or 2-phenyl-1-phenylthiopropene-1; this was also substantiated by gas chromatographic separations.

The same reaction was observed, although in lower yields, in methanol solution. Photolyses in ethanol with cupric chloride and iodine as oxidant or in benzene with selenium as oxidant failed to give any cyclization products. Reactions in ether solution with iodine as oxidant carried out in Rayonet reactor using 3000-Å lamps gave similar yields with those carried out with the S-81 lamps. Further reactions in the same reactor showed that equimolar amounts of benzophenone had no observable effect on the photolysis (although *cis–trans* equilibrium was very rapidly established in the presence of benzophenone upon brief exposure to room light). Starting material disappeared but no cyclization products were formed when benzene was used as solvent with iodine as oxidant. Irradiation with 3500-Å lamps in benzene solution with added benzophenone likewise caused disappearance of starting material but no benzo[b]thiophenes were formed.

3-Methyl-2-phenylbenzo[b]thiophene (2b) was prepared in 45% yield by cyclization of 1-phenyl-1-phenylthiopropan-2-one with polyphosphoric acid as described for 3-phenylbenzo[b]thiophene (3a):[25] mp 77–78°; uv, λ_{max} (CH_2Cl_2) 236 mμ (ε 20,800), 251 (18,600), 293 (15,900); nmr (CCl_4), τ 7.60 (s, 3, CH_3) and 2.75 (m, 9, aromatic H). Irradiation of 2b (125 mg in 125 ml of ether) with or without iodine failed to yield any 2-methyl-3-phenylbenzo[b]thiophene (3b) or any other identifiable products other than recovered starting material.

Anal. Calcd for $C_{15}H_{12}S$: C, 80.31; H, 5.40; S, 14.29. Found: C, 80.0; H, 5.5; S, 14.1.

2-Methyl-3-phenylbenzo[b]thiophene (3b)[26] was prepared in 70% yield by cyclization of α-(phenylthio)propiophenone with polyphosphoric acid: bp 112–114° (0.15 mm) [lit.[23] bp 145–150 (3 mm)]; n^{20}D 1.6630; mp 37.5–39°; uv, λ_{max} (CH_2Cl_2) 236 mμ (ε 31,700), 266 (9300), 293 (4800), 302 (4600); nmr (CCl_4), τ 7.57 (s, 3, CH_3) and 2.7 (m, 9, aromatic H). Irradiation of this material (300 mg in 150 ml of ether) with or without iodine failed to produce any 3-methyl-2-phenylbenzo[b]thiophene (2b).

Irradiation of 1-phenyl-2-phenylthiopropene-1 (4b) (225 mg in 125 ml of ether) in the presence of a trace of iodine gave an oil after chromatography over aluminium oxide. By glpc (4-ft DEGS, 190°) a trace of a compound (<1%) was observed which had a retention time the same as that of 2-methyl-3-phenylbenzo[b]thiophene (3b).

Irradiation of phenylthioethene (5a) (220 mg in 150 ml of ether) in the presence of iodine for 1 hr gave in 9.5% yield as determined by glpc (6-ft DEGS, 140°) benzo[b]thiophene (6a). The uv spectrum of material isolated by means of glpc (4-ft SE-30, 150°) was identical with that of authentic benzo[b]-thiophene. In the absence of iodine the yield was 6.5%.

Irradiation of 2-phenylthiopropene-1 (5b) (400 mg in 115 ml of ether) in the presence of iodine gave 2-methylbenzo[b]thiophene (6b) in 9% yield as determined by glpc (4-ft SE-30, 180°). This product was identified by its glpc retention time and by the characteristic peak in the nmr spectrum for the methyl protons: τ 7.50 (d, J = *ca.* 1 Hz). No 3-methylbenzo[b]-thiophene (6c) could be detected either by nmr spectroscopy or glpc. A large amount of phenyl disulfide was formed which was isolated by preparative glpc and identified by comparison with authentic material.

2-Methylbenzo[b]thiophene (6b) was prepared following the described procedure:[27] uv, λ_{max} (C_2H_5OH) 229 mμ (ε 29,100), 260 (7900), 287 (1900), 298 (2200); nmr (CCl_4), τ 7.50 (d, 3, J = *ca.* 1 Hz, CH_3) and 2.7 (m, 5, aromatic H).

3-Methylbenzo[b]thiophene (6c) was obtained as reported in the literature:[28] uv λ_{max} (C_2H_5OH) 230 mμ (ε 29,300), 262 (4500), 290 (2800), 299 (3300); nmr (CCl_4), τ 7.70 (d, 3, J = *ca.* 1.5 Hz, CH_3) and 2.7 (m, 5, aromatic H).

Irradiation of 1-phenylthiopropene-1 (5c) (*cis–trans* mixture, 400 mg in 115 ml of ether) in the presence of iodine for 1.5 hr gave 3-methylbenzo[b]thiophene (6c) in 2.5% yield as determined by glpc (4-ft SE-30, 180°). The product was identified by its glpc retention time and the characteristic peak in the nmr spectrum for the methyl protons: τ 7.70 (d, J = *ca.* 1.5 Hz). No 2-methylbenzo[b]thiophene (6b) could be detected by nmr spectroscopy or glpc. A large amount of phenyl disulfide was formed which was isolated by preparative glpc.

Photolysis of 2-phenylthiobutene-2 (5d) (300 mg in 115 ml of ether) in the presence of iodine for 2.25 hr led to the formation of 2,3-dimethylbenzo[b]thiophene (6d) in 5% yield as determined by glpc (4-ft SE-30, 165°). A small amount of this product was trapped from the exit port of the F & M 700 and its ir spectrum was shown to be identical with that of authentic 6d prepared as described in the literature.[28]

Photolysis of 1-phenylthiocyclohexene (5e) (1.0 g in 550 ml of ether) in a Q-700 lamp for 3 hr with a trace of iodine gave 1,2,3,4-tetrahydrodibenzo[b]thiophene (6e) in 6% yield as determined by glpc (4-ft SE-30, 260°). This product was isolated from the exit port of the F & M 700 and its ir spectrum was shown to be identical with that of authentic 6e prepared as described in the literature.[29]

Photolysis of *p*-tolylthioethene (8) (365 mg in 125 ml of ether) for 50 hr in the presence of iodine gave, after work-up, 202 mg of an oil. The ir spectrum of this oil showed mainly peaks corresponding to 5-methylbenzo[b]thiophene (9) plus a few peaks in the aromatic region. The 5-methylbenzo[b]thiophene was isolated by glpc separation (4-ft SE-30, 170°) and its ir and nmr spectra were shown to be completely identical with those of authentic material. The yield calculated by glpc was 9%. The balance of the oil was undistillable and we were unable to characterize any product from it. Upon standing in the dark in ether solution containing hydrogen iodide no cyclization occurred eliminating the possibility of a "dark" acid-catalyzed reaction.

Photolysis of 1,2-diphenyl-1-phenylthioethene (5f) (200 mg in 115 ml of ether) for 3.75 hr in the presence of iodine gave,

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after work-up, 180 mg of crude solid, mp 110–130°. This material, after recrystallization from *n*-hexane, gave 156 mg (78% yield) of white crystals, mp 141–143°, shown by glpc (4-ft SE-30, 250°) and ir, nmr, and uv spectra to be 9-phenylthiophenanthrene (**10**). No other reaction products could be detected.

9-Phenylthiophenanthrene (**10**) was prepared by reaction of the Grignard reagent of 9-bromophenanthrene[29] in benzene–ether with phenyl disulfide.[30] After repeated sublimations, chromatography over aluminium oxide, and recrystallization from methanol, a 40% yield of **10** was obtained, mp 134–136°. The material appeared to contain a trace of phenyl disulfide but ir, uv, and nmr spectra agreed with those of photolysis product **10**. Irradiation of **10** for 6.5 hr in ether solution in the presence of iodine led only to slow decomposition.

Anal. Calcd for $C_{20}H_{14}S$: C, 83.87; H, 4.93; S, 11.20. Found: C, 84.2; H, 4.8; S, 10.8.

Irradiation of phenyl sulfide (**5h**) (1.5 g in 550 ml of ether) in the Q-700 lamp for 3 hr in the presence of iodine led to formation of biphenyl (7.5% yield), dibenzothiophene (**6h**) (2.5% yield), and phenyl disulfide (5% yield) as determined by glpc (4-ft SE-30, 185°). These products were collected from the exit port of the gas chromatograph and either their uv or ir spectra shown to be identical with those of the authentic materials. When phenyl sulfide (500 mg in 115 ml ether) was irradiated for 5.3 hr in the absence of I_2 only biphenyl and phenyl disulfide could be identified.

Photolysis of 1,2-diphenylthioethene (**5g**) **and 1-(1-propenylthio)propene-1** (**7**) on a small scale in the presence of iodine failed to yield any cyclization products.

Dark reactions were not observed with the phenylthioethenes in ether solution. Addition of iodine likewise failed to promote a dark reaction. The reaction of **1b** at 80° in the dark in cyclohexane solution with AIBN initiator was examined; the material was consumed under these conditions but no benzo[*b*]thiophenes were formed. A photochemical reaction of **1b** carried out with an equimolar amount of phenyl disulfide gave a somewhat lower yield of **2b** and **3b** than a comparison reaction run without phenyl disulfide.

Registry No.—**1a**, 16336-45-1; **1b**, 16336-46-2; **2b**, 10371-50-3; **5a**, 1822-73-7; **5b**, 7594-43-6; **5c** (*cis*), 16336-50-8; **5c** (*trans*), 15436-04-1; **5d**, 16336-52-0; **5e**, 4922-47-8; **5f**, 6052-46-6; **5h**, 139-66-2; **8**, 16336-54-2; **10**, 16336-55-3.

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Chemistry of Enolates. V. Solvent Effects on the Activity of Carbanions[1]

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The kinetics and orientation in the alkylation of ketone enolates are extremely sensitive to solvent media. Alkylation rates and O/C product ratios are markedly increased by polyether solvents capable of chelating the accompanying metallic cation and by certain polar additives which exhibit first-order participation in the reaction kinetics. Increased electrical conductance of the enolate solutions parallels these chemical effects. In a specific solvent system, O/C product ratios are dependent on the steric requirements of both enolate and alkylating agent.

Much recent research has uncovered several factors affecting the reactivity and orientation of ambident[2] anions in nucleophilic reactions.[2-11] The factor producing the most significant effects is the reaction medium. Anions derived from phenols,[3-5] pyrroles,[8] ketones,[9] fluorene,[7] and malonic ester[6] exhibit similar behavior to changes in media. Two distinct effects are recognized: anion solvation by hydrogen bonding in protic solvents[3] and solvation of the accompanying cation by the bulk media,[7] the reaction product,[10] or an additive.[6]

Although ketone enolates are among the simpler ambident ions and are widely found in synthetic reactions, very little concerning their properties in solution or their orientation in the alkylation reaction has been reported. In this study ten dialkyl and alkyl aryl ketones are converted into the corresponding alkali metal enolates in a variety of solvent systems. Information on the nature of the enolates in solution is obtained from measurements of electrical conductivity, infrared and nmr spectra, boiling point elevation, orientation, and kinetics of alkylation.

Results and Discussion

Table I contains a summary of kinetic data for the alkylation of sodiodiphenylacetophenone in diglyme and mixed solvent systems. The alkylation of this ketone in these solvents occurs exclusively on oxygen to give enol ethers which, unlike ketonic products, do not compete in the solvation of the cation. Thus, excellent first-order dependence on enolate can be observed through the second and third half-lives of the reaction. A comparison of the alkylation of this ketone with that of butyrophenone in monoglyme is shown in Figure 1. Autocatalysis in the latter reaction causes the downward curvature of the line as the concentration of ketonic product increases.[10]

Most of the alkylations were carried out by a large excess of halide under pseudo-first-order conditions, although two runs made under second-order conditions gave linear plots (Figure 2) and rate constants in good agreement with those calculated from pseudo-first-order constants. These results are consistent with

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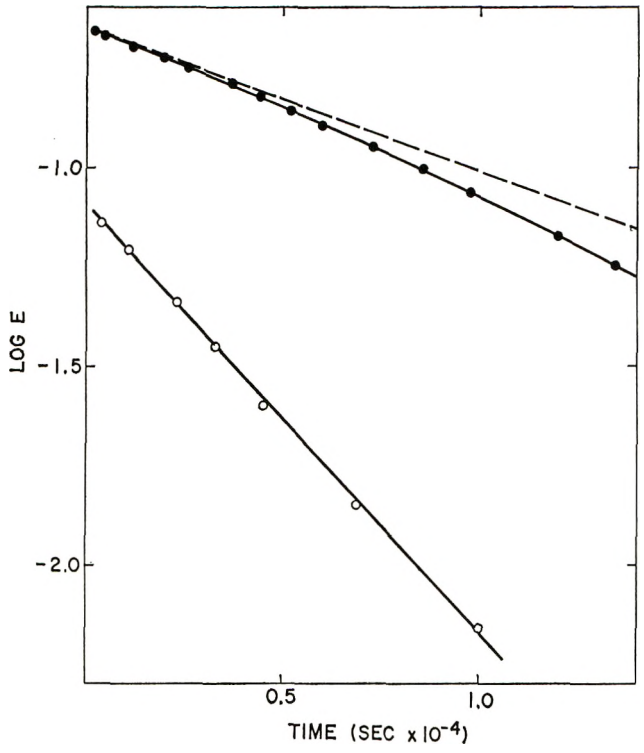


Figure 1.—Comparison of oxygen alkylation of an enolate with autocatalytic carbon alkylation: ○, ethylation of 0.073 *M* sodiodiphenylacetophenone in diglyme by 1.61 *M* ethyl bromide; ●, alkylation of 0.260 *M* sodiobutyrophenone in monoglyme by 1.39 *M* isobutyl bromide.

TABLE I

ALKYLATION OF SODIODIPHENYLACETOPHENONE IN DIGLYME AT 30°

Enolate, *M*	Halide (*M*)	Additive[a] (*M*)	$k_2 \times 10^4$, M^{-1} sec^{-1}
0.073	C_2H_5Br (1.72)		1.74
0.069	C_2H_5Br (0.19)		1.81
0.068	C_2H_5Br (0.28)	DMSO (0.14)	4.5
0.067	C_2H_5Br (0.26)	DMSO (0.27)	7.1
0.066	C_2H_5Br (0.35)	DMSO (0.43)	12.7
0.065	C_2H_5Br (0.27)	DMSO (0.65)	15.3
0.063	*n*-C_3H_7Br (1.41)		1.24
0.074	*n*-C_3H_7Br (0.21)		1.22
0.064	*n*-C_3H_7Br (0.66)	DMA (0.33)	3.4
0.061	*n*-C_3H_7Br (0.88)	DEA (0.16)	1.4
0.062	*n*-C_3H_7Br (0.66)	DEA (0.24)	2.0
0.064	*n*-C_3H_7Br (0.65)	DEA (0.33)	2.6
0.070	*n*-C_3H_7I (0.20)		9.4

[a] DMSO = dimethyl sulfoxide; DMA = N,N-dimethylacetamide; DEA = N,N-diethylacetamide.

those obtained in diethyl ether where the kinetic order for the halide at concentrations below 1 *M* was unity.[10]

Specific rates for alkylations of sodiobutyrophenone in several solvent systems are listed in Table II. The alkylation of butyrophenone is much faster than that of diphenylacetophenone; in diglyme at 30°, specific rates for ethylation by ethyl bromide are 91 × 10^{-4} and 1.7 × 10^{-4} M^{-1} sec^{-1}, respectively. Although the alkylations by low-molecular-weight bromides and iodides were too rapid at 30° for precise measurement, a comparison of solvents was made by alkylations with chlorides and branched-chain bromides. The expected order of reactivity for the halides was observed. Solvents are listed in order of increasing effectiveness. Comparisons with four halides show

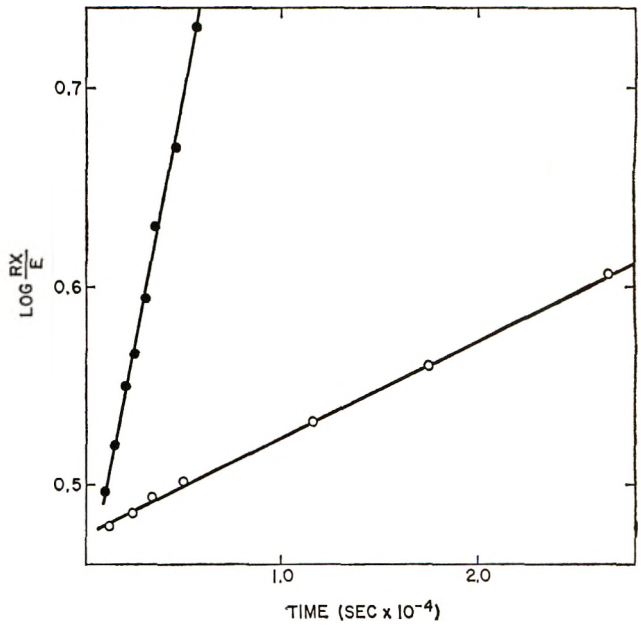
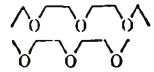
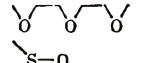


Figure 2.—Propylation of 0.074 *M* sodiodiphenylacetophenone in diglyme at 30°: ○, with 0.214 *M* *n*-propyl bromide; ●, with 0.197 *M* *n*-propyl iodide.

TABLE II

MEDIUM EFFECTS IN THE ALKYLATION OF SODIOBUTYROPHENONE

Solvent	$k_2 \times 10^4$, M^{-1} sec^{-1} [a]				
	C_2H_5Br	*n*-C_4H_9Br	*i*-C_4H_9Br	*i*-$C_5H_{11}Br$	*n*-C_3H_7Cl
	0.01		0.00043		
				0.05[b]	
			1.1[c]	2.9[d]	0.02[e]
		6.3		2.8	
	91	38	4.9	8.1	0.07
					76.1[f]

[a] Obtained under pseudo-first-order conditions from 0.14–0.18 *M* enolate and excess halide. [b] 0.34 in the presence of 0.43 *M* hexamethylphosphoramide. [c] 2.6 in the presence of 0.82 *M* N,N-dimethylacetamide. [d] No change in the presence of 0.54 *M* dimethylcyanamide. [e] 0.15 in the presence of 0.61 *M* dimethyl sulfoxide. [f] Unpublished results of Dr. J. A. Miller of this laboratory.

that diglyme is three to five times as effective as monoglyme and 10^4 times as effective as ethyl ether. Dimethyl sulfoxide exhibits a rate enhancement of 10^3 over diglyme. The observed order among the ethers suggests chelation of the cation. Diglyme can form two five-membered chelate rings, the optimum size for stability.[12] Two diglyme molecules could form six-coordinate sodium ion which has been observed in complexes with salicylaldehyde.[13] The terminal ethyl groups in diethylene glycol diethyl ether hinder chelation. Probably the best evidence is found in a comparison of 1,2-dimethoxyethane and 1,3-dimethoxypropane; separation of the ether functions by an additional carbon atom produces a 60-fold decrease in the rate of isoamylation.

This explanation of the role of the solvent ignores differences in dielectric properties of the media. Among

(12) J. L. Down, J. Lewis, B. Moore, and G. Wilkinson, *J. Chem. Soc.*, 3767 (1959).

(13) N. V. Sidgwick and F. M. Brewer, *ibid.*, 2379 (1925).

TABLE III

MOLAR CONDUCTANCES OF ENOLATES

Sodium enolate	M	Solvent system (M)[a]	Λ_m, cm² mol⁻¹ ohm⁻¹
Acetophenone	0.10	Diethyl ether	0.000[b]
Diphenylacetophenone	0.016	1,2-Dimethoxyethane	0.12
Butyrophenone	0.18	1,3-Dimethoxypropane	0.002
	0.10	1,2-Dimethoxyethane	0.035
	0.10	N,N-Dimethylacetamide (0.98)	0.082
	0.10	N-Methylpyrrolidone (0.95)	0.085
	0.10	N,N-Dimethylcyanamide (0.98)	0.244
	0.10	Dimethyl sulfoxide (1.28)	0.250
	0.10	Hexamethylphosphoramide (0.94)	0.255

[a] Molar concentration of additive in dimethoxyethane. [b] Reference 14, $R > 2.5 \times 10^6$ ohms.

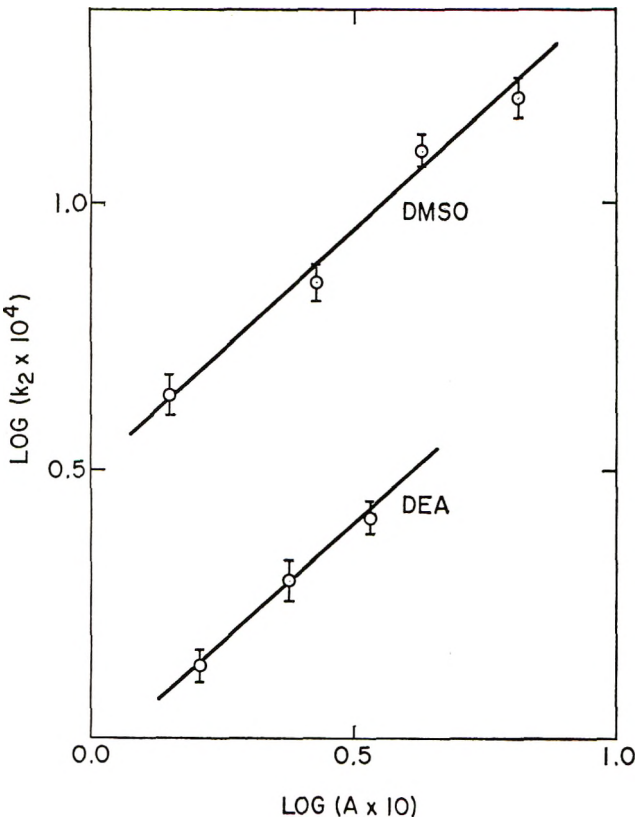


Figure 3.—Kinetic order in additive: ethylation of sodiodiphenylacetophenone in diglyme–dimethyl sulfoxide and propylation of this enolate in diglyme–diethylacetamide.

the ethers listed, the variation in dielectric constant is small; *e.g.*, the value for diglyme is only 0.07 larger than that for diethylene glycol diethyl ether. In the alkylation of sodio-*n*-butylmalonate, monoglyme as an additive was six times more effective than tetrahydrofuran even though the two ethers have nearly identical dielectric constants.[6,12] The small differences cannot account for the large variation in the ability to promote alkylation.

Pronounced rate enhancement was observed when alkylations of diphenylacetophenone (Table I) and butyrophenone (Table II, footnotes *b–e*) were conducted in the presence of dimethyl sulfoxide, hexamethylphosphoramide, and N,N-dialkylacetamides. These additives characterized by the presence of a highly polar bond to an oxygen atom had proved effective catalysts in alkylations of benzene solutions of sodio-*n*-butylmalonate.[6] Their effectiveness in relatively small concentrations suggests a specific solvation of the cation. Consistent with this view is the finding that the rate of alkylation of sodiodiphenylacetophenone exhibits first-order dependence on the additives, N,N-diethylacetamide and dimethyl sulfoxide. The participation order, n, is defined by the relation $k_2 = k_2'[A]^n$ where k_2 is the second-order specific rate (Table I) and k_2' is the additive-independent specific rate. Plots of log k_2 *vs.* log A for ethylations in the presence of dimethyl sulfoxide and propylations in the presence of diethylacetamide were linear (Figure 3) with approximately unit slopes.

Conductance Studies.—Sodium enolates of ketones are nonconductors in diethyl ether although sodium triphenylmethide has molar conductances of 0.05–0.72 in this solvent.[14] Data summarized in Table III show that the conductance increases with the solvating ability of the polyether and the polar additives. In Figure 4 is plotted the logarithm of molar conductance *vs.* the logarithm of enolate concentration for a solution of sodiobutyrophenone in monoglyme. The slope of the line is −0.5, a value indicative of the dissociation of a species A^+B^- into ions. In view of the ebulliometric study of sodiobutyrophenone, which shows that the enolate is a trimer, a possible structure for B^- is a triple ion, $Na^+[Na_2(enolate)_3]^-$.

Conductances for the solutions containing the five polar additives are included in Figure 4. This comparison shows the two structurally similar carboxamides, N-methylpyrrolidone and N,N-dimethylacetamide, to have an approximately equal ability to increase the conductivity although they are not so effective as hexamethylphosphoramide, dimethyl sulfoxide, and dimethylcyanamide. With the exception of the last compound, the order of the effectiveness of these additives parallels the order in catalyzing the alkylation of the enolates. Triethylenediamine and N,N,N,N-tetramethylethylenediamine did not increase the conductance. Catalytic action by these amines was not investigated because of their posssible alkylation. However, Zaugg[6] has shown that pyridine is less effective than monoglyme in catalyzing the alkylation of sodio-*n*-butylmalonate, and Garst[11] reported that *n*-propylamine is less effective than either monoglyme or diglyme in lowering the π–π^* transition of sodium benzophenone ketyl.

Boiling point elevations for 0.5 *m* solutions of sodiobutyrophenone in 1,2-dimethoxyethane correspond to average aggregation numbers of 2.5–2.7, values 16%

(14) D. G. Hill, J. Burkus, S. M. Luck, and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 2787 (1959).

TABLE IV

ORIENTATION IN THE ALKYLATION OF ENOLATES

$C_6H_5C(O^-M^+)=CRR'$

R	R′	M⁺	Solvent	O/C alkylation ratio[a] MeI	Allyl Br	EtX[b]	n-PrX[b]	i-AmBr	EtTos
H	C_6H_5	Na	DME		0.0	0.0		0.0	
CH_3	CH_3	Na	Et_2O	0.0			0.0		0.63[c]
		Na	DME			0.19	0.25	0.36	
		Na	Diglyme	0.0	0.05	0.16	0.27		1.2[d]
C_2H_5	CH_3	Na	Diglyme		0.2	0.61			2.4
C_2H_5	C_6H_5	Na	Diglyme			0.76			3.0
C_6H_5	C_6H_5	K	t-BuOH	0.04		1.4	2.5[e]		
		Na	t-BuOH			1.8[g]			
		Na	Diglyme	0.09[f]		18	>100		
C_6H_5	Mesityl	K	t-BuOH			>100	>100		

[a] Exclusive of small quantities of dehydrohalogenation product. [b] Alkyl bromides were used except in t-butyl alcohol where the alkylating agent was the iodide. [c] Ethyl sulfate gave 0.34. [d] Also for ethyl sulfate and MeTos. [e] Ref 12. [f] O/C = 1.0 in 50:50 diglyme–DMSO. [g] In one series of experiments, the O/C ratio was dependent on the concentration of enolate; M of ketone, M of t-OBu, % alkylation, and O/C ratio for five solutions are as follows: 0.24, 0.25, 70, 1.8; 0.21, 0.24, 71. 1.8; 0.059, 0.110, 54, 1.3; 0.030, 0.104, 56, 1.2; 0.011, 0.037, 21, 0.01.

below those measured in diethyl ether.[10] These results, together with the increased electrical conductivities suggest that the effective cation-solvating media break up enolate–cation aggregates into smaller ions.

O/C Orientation.—The usual synthetic processes for the alkylation of acetophenone, deoxybenzoin, and their homologs lead to high yields of C-alkyl products. However, the procedures are not designed to detect enol ethers which are easily lost by hydrolysis. Several instances of O alkylation of ketones have been reported.[15–17] To determine structural and solvent effects on orientation, analyses by ir and vpc techniques of t_∞ samples from several of the kinetic runs were made, and other alkylations were conducted solely for this purpose. The results are listed in Table IV.

The O/C alkylation ratio is quite sensitive to changes in the structure of the enolate, the structure of the alkylating agent and the solvent. Isobutyrophenone and deoxybenzoin resemble the simpler n-alkyl phenyl ketones in that alkylation by halides in diethyl ether leads exclusively to C-alkyl products. In polyether solvents isobutyrophenone gives as much as 27% enol ether depending on the structure of the halide, while only C alkylation is observed for deoxybenzoin even with isopropyl iodide (see Experimental Section). As the size of the substituent groups at the α position in the enolate increases, the proportion of O alkylation becomes significantly larger until, in the propylation of diphenylacetophenone, the enol ether is the sole product.

Carbon alkylation results in an sp^3-hydridized carbon atom with the three substituents at 109° whereas oxygen alkylation results in an sp^2-hybridized carbon with only two groups forming a much larger angle. Thus, the effects of the geometry of the products on the transition state favor O alkylation as the substituents on the enolate and halide increase in size. The halides are listed from left to right in Table IV in order of increasing steric requirement, and the ketones from top to bottom in increasing hindrance to C alkylation. Steric factors in both reagents are important; O/C ratios increase from left to right and from top to bottom. The high ratios observed with ethyl sulfate and methyl and ethyl tosylates are in accord with the known ability of these reagents to alkylate the atom of higher electronegativity in an ambident ion.[18] This preference of a highly electrophilic reagent has been attributed to a gain in electrostatic stability in the transition state.[2,19]

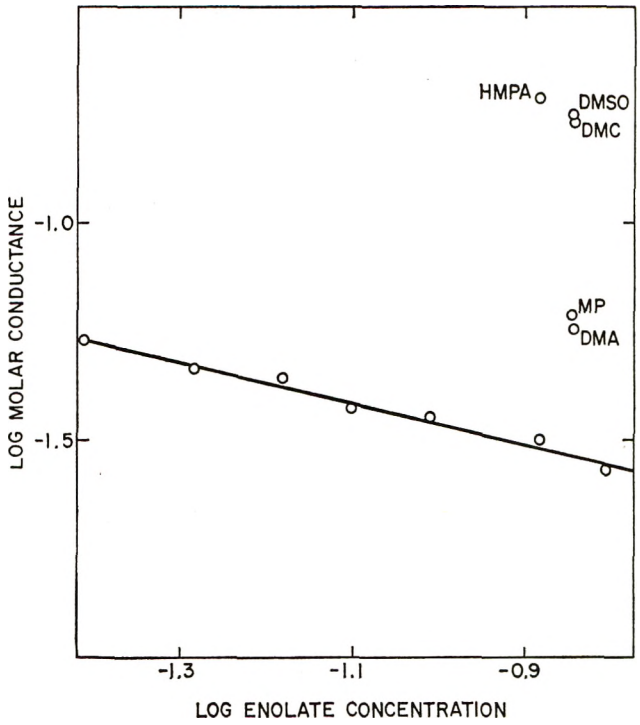


Figure 4.—Conductance of sodiobutyrophenone in monoglyme. Effect of concentration and additives (*cf.* Table III).

The large decrease in O/C ratio for the ethylation of diphenylacetophenone as the solvent is changed from diglyme to t-butyl alcohol was reported in an earlier communication[9] and now has been confirmed for methylations and propylations of this ketone. Although Rinderknecht[15] isolated the C-propyl product, α,α-diphenylvalerophenone, in about 6% yield when the alkylation was conducted in t-butyl alcohol, com-

(15) H. Rinderknecht, *J. Amer. Chem. Soc.*, **73**, 5770 (1951).
(16) N. Sperber, R. Fricano, and D. Papa, *ibid.*, **72**, 3068 (1950).
(17) G. Wash, B. Shive, and H. L. Lochte, *ibid.*, **63**, 2975 (1941).
(18) K. Auwers, *Chem. Ber.*, **45**, 994 (1912), *Ann. Chem.*, **393**, 338 (1912); H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 61 (1952).
(19) M. Bersohn, *J. Amer. Chem. Soc.*, **83**, 2136 (1961).

plete O propylation to 1-propoxy-1,2,2-triphenylethylene resulted in diglyme both in the presence and absence of N,N-dialkylacetamides. Kornblum has presented convincing evidence that similar orientation in phenoxide ions is the result of hydrogen bonding of the anion in protic solvents.[3]

More effective hydrogen bonding resulting in increased hindrance and lower nucleophilicity at the oxygen atom would be expected at lower enolate concentrations. In one series of experiments in *t*-butyl alcohol the O/C ratio decreased markedly as the concentration of enolate was decreased from 0.24 to 0.011 *M* (Table IV, footnote *g*). In contrast, dilution in aprotic solvents ordinarily favors alkylation at the more electronegative atom.[8,20]

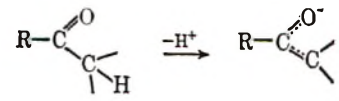
In aprotic solvents, the O/C ratio depends primarily on the ability of the solvent to solvate the cation. In ethyl ether where the enolate consists of trimeric species, nucleophilicity at oxygen is low and carbon alkylation occurs probably by a six-centered transition state.[10,21] A solvate of sodiodeoxybenzoin isolated from monoglyme has been shown by nmr and equivalent weight determinations to contain one molecule of solvent per ion pair;[22] yet even in this solvent the aggregation number is 2.7, and appreciable C alkylation occurs. In the presence of molecules which can better solvate the cation and in this way free the anion, alkylation at the more nucleophilic oxygen is preferred. Thus, the medium effect on the activity of the anion operates indirectly *via* the cation.

The solubilities of sodiodiphenylacetophenone in ether, monoglyme, and diglyme are 0.004, 0.016, and >0.092 *M*, respectively. These solubilities parallel the ability of the solvent to enhance electrical conductivity and alkylation rate. A similar correlation between solubility and N alkylation of pyrrylpotassium has been observed.[8]

It is believed that the observed aprotic medium effects originate through variations in the enolate–cation interaction. Thus, the better chelating polyethers, the polar amides, the very polar dimethyl sulfoxide, and hexamethylphosphoramide all interact with the sodium ion, thereby decreasing the degree of its interaction with the enolate. Alkylation reactions are faster because the dissociated enolate, unencumbered by the cation, can better function as a nucleophile. Oxygen alkylation increases at the expense of carbon alkylation because in the dissociated enolate the charge density is greatest at the oxygen atom. Finally, the solvated cation and dissociated enolate are electrical conductors.

Infrared and nuclear magnetic resonance spectra of enolate solutions can be interpreted to show that the excess negative charge is localized on the oxygen atom of the anion as expected on the basis of electronegativity. The large shift in the carbonyl absorption toward lower frequencies and an nmr shift indicative of diamagnetic anisotropic deshielding for the remaining hydrogens of an enolized methyl ketone are explainable on this basis.

The formation of an enolate can be followed by the disappearance of the carbonyl peak at 1725–1667 cm^{-1} and the appearance of a peak at 1610–1560 cm^{-1} corresponding to the change shown.



It is interesting to note that the enolate resembles a carboxylate anion. The ionization of a carboxylic acid similarly results in the disappearance of the carbonyl frequency and the emergence of a band between 1610 and 1560 cm^{-1} attributed to the antisymmetrical vibrations of the $-COO^-$ structure.[23] By analogy, this characteristic band of enolate solutions may be attributed to asymmetrical stretching of the structure containing the delocalized negative charge. Although the force constant for a bond is a function of both bond order and polarizability, numerous linear correlations have been made in terms of bond order alone.[24] By an extension of these correlations, the bond order for pinacolone decreases from 0.90 ($\nu_{C=O}$ 1710 cm^{-1}) to 0.73 ($\nu_{C=O}$ 1575 cm^{-1}) as a result of enolate formation. This result implies a much reduced π-bond density between carbon and oxygen. The frequency shift is in the same direction but greater in magnitude than those found when other typical electron releasing groups are conjugated with the carbonyl.[25] Another spectral feature similar to that observed for benzoic acid is the disappearance of the out-of-plane bending vibrations of ring hydrogens at 687 and 755 cm^{-1} when acetophenone is converted into its enolate.

The nmr spectra of pinacolone and its sodium enolate exhibit significant differences. The *t*-butyl hydrogens at 1.13 ppm are shifted upfield to 1.07 ppm as expected by increased electron density at oxygen. The 2.11-ppm peak corresponding to the methyl hydrogens is not present in the enolate but is replaced by a peak at 3.10 ppm representing the two remaining hydrogens. Estimates of relative magnitudes of the peaks are in accord with this assignment. The large downfield shift can be explained if it is assumed that the carbon atom to which these protons are attached cannot rotate freely. Although negative charge on oxygen should shield the hydrogen atoms, the effect is overcome by the diamagnetic anisotropic deshielding made possible by the rigid structure.

Sodium enolates of butyrophenone and diphenylacetophenone are cleaved by oxygen to give sodium benzoate and carbonyl compounds. Diphenylacetophenone gives a quantitative yield of sodium benzoate and benzophenone. Heretofore, only the former product of such cleavages has been isolated,[26] for most enolates give enolizable aldehydes and ketones which are further degraded. For example, sodiobutyrophenone gives propionaldehyde which undergoes a proton transfer with the original enolate to produce butyrophenone (23%) and propionaldehyde enolate.

(20) P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).

(21) A. Brändström, *Ark. Kemi*, **6**, 155 (1954); **7**, 81 (1954); **13**, 51 (1958).

(22) Unpublished results of Dr. W. L. Kelly of this laboratory.

(23) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

(24) A. Streitwieser, Jr., "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961, p 234.

(25) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J. 1963, p 495.

(26) W. von E. Doering and R. M. Haines, *J. Amer. Chem. Soc.*, **76**, 482 (1954).

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer.

Solvents.—1,3-Dimethoxypropane was prepared in 81% yield from 221 g of 51% sodium hydride dispersion in mineral oil, 152 g of Eastman trimethylene glycol, and 613 g of methyl iodide. The hydride was stirred with 500 ml of tetrahydrofuran during the dropwise addition of a solution of the glycol in 200 ml of the same solvent. The condenser was then cooled to Dry Ice temperatures for the addition of the methyl iodide. Finally the mixture was refluxed overnight, sodium iodide filtered, and washed with five 100-ml portions of tetrahydrofuran, and the product fractionally distilled from a small piece of sodium. The 1,3-dimethoxypropane, bp 103.2° (730 mm), was separated from a small amount of lower boiling impurity by refractionation through a spinning-band column.

Eastman diethylene glycol diethyl ether was first chromatographed on a 54 × 1.5 cm column of alumina to remove peroxides and effect preliminary drying. Fractional distillation from lithium aluminum hydride gave ether, bp 65–66.0° (6.3 mm).

Diethyl ether, monoglyme [bp 83.7° (745 mm)] and diglyme [bp 55.0° (10 mm)] were fractionally distilled from lithium aluminum hydride. Preliminary drying of the glyme solvents (Ansul Chemical Co.) was accomplished by stirring and heating overnight with calcium hydride.

The following solvents were distilled from calcium hydride prior to their use: hexamethylphosphoramide (Aldrich), bp 104.9° (9.5 mm); N,N,N,N-tetramethylethylenediamine (Rohm and Haas), bp 119° (735 mm); N-methyl-2-pyrrolidone (Antara), bp 81.5° (11 mm); dimethyl sulfoxide (Crown Zellerbach), bp 71.5° (10 mm); and N,N-dimethylcyanamide (American Cyanamid), bp 118° (217 mm). The following solvents were fractionated and stored over anhydrous magnesium sulfate: N,N-dimethylacetamide (Eastman), bp 165° (725 mm); and N,N-diethylacetamide (Eastman), bp 66° (10 mm).

Ketones.—Eastman butyrophenone was stirred for several days with activated charcoal and anhydrous magnesium sulfate. Fractional distillation gave yellow material, bp 55° (1.5 mm). The yellow color and a trace of higher boiling material (glpc analysis) were completely removed by chromatography on a column of alumina. α-Methylbutyrophenone, bp 98° (18 mm), was made from propiophenone, sodium hydride, and ethyl bromide in diglyme.

α,α-Diphenylacetophenone was prepared by adding in small portions a solution of 50 g of desyl chloride[27] in 150 ml of dry benzene to a suspension of 32 g of aluminum chloride in 100 ml of benzene. The mixture was refluxed for 1 hr and poured onto ice. A benzene extract of the product was evaporated to give 60 g of crude solid. Two crystallizations from ethanol gave white needles, mp 135–137° (lit.[28] mp 136°).

α,α-Dimethylbutyrophenone and 1-ethoxy-1-phenyl-2-methylpropene were prepared by stirring for 2 days 28 g of ethyl *p*-toluenesulfonate and 200 ml of 0.35 *M* sodioisobutyrophenone. The enolate was made over a period of 36 hr at 85° by stirring a twofold excess of sodium hydride with a diglyme solution of the ketone. An infrared spectrum of the enolate solution showed no carbonyl absorption. Fractional distillation of the alkylation mixture through a spinning-band column gave one fraction, 1.54 g, of enol ether, bp 57° (2 mm), with characteristic vinyl ether absorption at 1126 and 1042 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.88; H, 9.15.

The last fraction, 3.56 g, was dimethylbutyrophenone, bp 79–80° (2 mm), with strong absorption at 1661, 1163, and 954 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.16.

α-Ethyldeoxybenzoin was prepared in 80% yield by refluxing for 24 hr 750 ml of 0.084 *M* sodiodeoxybenzoin in monoglyme and 10 ml of ethyl iodide. The enolate was obtained by stirring for 5 hr 4.0 g of sodium hydride and 16.5 g of deoxybenzoin in 900 ml of dry monoglyme. After alkylation, solvent was removed through a short column, and the precipitated sodium iodide was extracted with ether. Removal of ether and recrystallization of the solid from ethanol gave 11.2 g of white crystals, mp 53.5–55.0° (lit.[29] mp 58°). α-Mesityldeoxybenzoin, mp 113–115°, was prepared as described previously.[30]

Alkylation of Enolate Solutions.—The apparatus for the preparation, storage, and alkylation of enolates was essentially that used in an earlier study.[31] Sodium enolates in polyether solvents were made from the ketones and sodium hydride as described for solutions in diethyl ether.[10] Enolate formation from α,α-diphenylacetophenone was complete within a few minutes as evidenced by vigorous evolution of hydrogen, immediate formation of a yellow color, and the disappearance of carbonyl absorption in the infrared. With butyrophenone, hydrogen evolution was slow, and stirring was continued for 7 days. Concentrations determined by quenching aliquots in water and titrating with standard acid were in excellent agreement with those calculated from the amounts of ketone and solvent used. Because phenolphthalein gave premature end points in aqueous diglyme and diethylene glycol diethyl ether, bromophenol blue was used in experiments with these solvents. The kinetic reaction vessel was thoroughly flamed in a stream of nitrogen before each run. Unless otherwise indicated, kinetic measurements were made at 30.00 ± 0.05°. Samples at t_∞ in ether or monoglyme were taken directly without hydrolysis for product studies by glpc.

Product Studies.—A typical procedure for ethylation in *t*-butyl alcohol consisted of dissolving 0.0125 g-atom of sodium or potassium in 50 ml of dry alcohol, adding an equivalent amount of ketone followed by an excess of alkyl halide, and refluxing overnight. Solvent was removed under vacuum after the addition of a few milliliters of water. The residue was triturated with water, washed free of halide ion, dried in a desiccator, weighed, and dissolved in carbon tetrachloride for infrared analysis. 1,2,2-Triphenyl-1-butanone, 1,2,2-triphenyl-1-ethoxyethene, and 1,2,2-triphenyl-1-propoxyethene, the C-ethyl, O-ethyl, and O-propyl alkylation products of α,α-diphenylacetophenone, were prepared as described[15] and used as references for quantitative infrared analyses. Beer's law plots for α,α-diphenylacetophenone and its O- and C-ethyl derivatives were constructed at 1224, 1208, and 1092 cm^{-1}. The results of the ethylations are listed in Table IV. A product study of the propylation of this ketone in diglyme was carried out on the t_∞ sample from a kinetic run. Excess *n*-propyl bromide was removed under vacuum at 50°. To the residue was added 300 ml of water to precipitate the reaction product which was then filtered, washed with water, and dried in a desiccator. The infrared spectrum was identical with that of pure 1-propoxy-1,2,2-triphenylethene except for an extremely small carbonyl-stretching peak. In a similar manner, product studies were carried out for the propylation with a twofold excess of *n*-propyl bromide, with *n*-propyl iodide, with added N,N-dimethylacetamide, and with added N,N-diethylacetamide. In all cases, only O alkylation resulted. Methylation by methyl iodide of the potassium enolate formed from 5.0 g of this ketone and 1.1 g of potassium in 75 ml of dry *t*-butyl alcohol gave a product whose spectrum was consistent with C methylation except for a very small peak at 1089 cm^{-1}. This peak disappeared when the product was refluxed with ethanolic hydrogen chloride.

Isopropylation of deoxybenzoin was carried out by refluxing overnight a solution of 0.023 g-atom of potassium, 0.015 mol of ketone, and 20 ml of isopropyl iodide in 100 ml of dry *t*-butyl alcohol. The solvent was removed under vacuum to give only the C-alkyl ketone (95%). The infrared spectrum gave a single carbonyl peak and no absorbance characteristic of enol ether. The spectrum was unchanged when a sample was refluxed for 2 hr with dilute hydrochloric acid. One recrystallization from ethanol gave α-isopropyldeoxybenzoin, mp 71–73° (lit.[32] mp 71–72°).

Glpc analyses were made at 80–160° with a spiral glass column packed with methylsilicone (GE SF-96) on 100–140 mesh Gaschrom Z. Under these conditions the enol ethers did not undergo decomposition or rearrangement. Enol ether peaks were identified by hydrolysis of a second sample with 1 drop of concentrated hydrochloric acid prior to chromatographic analysis. The enol ether peak vanished in the second chromatogram, and the small peak representing original ketone increased proportionately.

(27) A. M. Ward, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 159.

(28) R. Anschutz and P. Forster, *Ann. Chem.*, **368**, 92 (1909).

(29) V. Meyer and L. Oelkers, *Chem. Ber.*, **21**, 1295 (1888).

(30) R. C. Fuson, L. J. Armstrong, D. H. Chadwick, J. W. Kneisley, S. P. Rowland, W. J. Shenk, Jr., and Q. F. Soper, *J. Amer. Chem. Soc.*, **67**, 386 (1945).

(31) H. D. Zook and W. L. Rellahan, *ibid.*, **79**, 881 (1957).

(32) M. Tiffeneau and A. Orekhoff, *Bull. Soc. Chim. Fr.*, [4] **33**, 211 (1923).

The O/C product ratios were calculated directly from peak areas. Thermal response values relative to acetophenone were determined for a number of the products, but their use was not warranted.

Conductivity Measurements.—Resistances were measured in a 25-ml conductivity cell surmounted on the kinetic apparatus in place of the automatic sampling buret. Solvents and solutions were forced into the cell by increasing the nitrogen pressure in the reaction vessel. The cell was drained under a nitrogen atmosphere and flushed thoroughly with dry solvent before and after measurements were made. Resistances were measured with a Wheatstone bridge, 5000-cps audiofrequency oscillator, and earphones to detect the null point.

Cleavage of Sodiodiphenylacetophenone by Oxygen.—Immediate formation of solid, evolution of heat, and fading of yellow color occurred when oxygen gas was bubbled through a solution of 11.1 mmol of enolate in 150 ml of diglyme. After 12 hr of oxygen treatment, the semisolid mixture was dissolved in 100 ml of water to give a clear solution which required only 0.4 mmol of standard acid for titration to phenolphthalein. The solution was steam distilled to give 1.84 g (92%) of benzophenone, mp 43–46°. The infrared spectrum was superimposable on that of an authentic sample of benzophenone. The steam distilland was made alkaline with potassium carbonate solution and extracted with three 100-ml portions of ether. Evaporation of these extracts yielded no more than a trace of oily substance. The alkaline layer was acidified with concentrated hydrochloric acid and extracted with three 100-ml portions of ether. Evaporation of these extracts left 1.32 g (99%) of white solid, mp 120–122.5°. This substance did not depress the melting point of pure benzoic acid.

Registry No.—Sodiodiphenylacetophenone, 16282-12-5; sodiobutyrophenone, 16310-84-2; α-methylbutyrophenone, 938-87-4; α,α-diphenylacetophenone, 1733-63-7; α,α-dimethylbutyrophenone, 829-10-7; 1-ethoxy-1-phenyl-2-methylpropene, 16282-15-8; α-ethyldeoxybenzoin, 16282-16-9; α-mesityldeoxybenzoin, 16282-17-0.

Condensations at Methyl Groups of Phenyl *o*- and *p*-Tolyl Sulfones with Electrophilic Compounds by Sodium Amide. Truce–Smiles Rearrangement[1]

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Ionizations of methyl hydrogens of phenyl *o*- and *p*-tolyl sulfones were effected by sodium amide in liquid ammonia to form sodio salts, which were condensed with benzyl chloride, 1,4-dibromobutane, benzophenone, and methyl benzoate to give corresponding derivatives. Ionization of the phenyl *o*-tolyl sulfone occurred more slowly than that of the *para* isomer. The addition reactions of the sodio salts with benzophenone were kinetically controlled. The condensations of the sodio *o*-tolyl sulfone with the electrophilic compounds represent trapping of the intermediate carbanion in the Truce–Smiles rearrangement of the sulfone to form a sulfinic acid, which was observed in low yield through the sodio salt in liquid ammonia and in good yield in refluxing tetrahydrofuran. The benzyl derivative of the *o*-tolyl sulfone underwent this type of rearrangement with *n*-butyllithium. Di-*p*-tolyl sulfone was benzylated at one of its methyl groups by means of sodium amide. The method appears to be quite general.

Although base-catalyzed condensations at the α carbon of dimethyl sulfone and other sulfones with electrophilic compounds are well known,[2] related reactions at the methyl groups of *o*- and *p*-tolyl sulfones have rarely been reported. The present investigation was concerned with such a study of phenyl *o*- and *p*-tolyl sulfones; the former sulfone promised to be of particular interest because it can undergo the base induced Truce–Smiles type of rearrangement.

Results with Phenyl *o*-Tolyl Sulfone.—This compound (**1**) was converted by sodium amide in liquid ammonia into sodio salt **1′**, which was condensed with benzyl chloride, 1,4-dibromobutane (0.5 mol equiv), benzophenone, and methyl benzoate to form **2**, **3**, **4**, and **5**, respectively (Scheme I).

The yields of the benzyl derivative **2**, the bis derivative **3**, and the addition product **4** were dependent on the conditions employed (see Discussion); the best yields obtained were 61, 58, and 76%, respectively. The yield of the benzoyl derivative **5** was dependent on the proportions of the reactants since, similar to other Claisen-type acylations and aroylations,[3] the product **5** was converted in the reaction mixture into its sodio salt; this last step was effected by either sodio sulfone **1′** or sodium amide. When 2 mol equiv of sodio sulfone **1′**/1 mol equiv of methyl benzoate was used (last step effected by **1′**), the yield of **5** based on the ester was 50%;[4] when 1 extra equiv of sodium amide was used to effect the last step, the yield of **5** based on sulfone **1** was 34%.

The structures of the condensation products were supported by analyses and absorption spectra. The structure of adduct **4** was confirmed by dehydration to form unsaturated sulfone **6** in 86% yield (eq 1).

$$4 \xrightarrow[\text{benzene (refluxing)}]{p\text{-}CH_3C_6H_4SO_3H} \underset{\mathbf{6}}{\overset{SO_2C_6H_5}{\underset{CH{=}C(C_6H_5)_2}{\bigcirc}}} \quad (1)$$

The infrared spectra of the products were similar to those of the starting sulfone **1** with certain significant differences (Table I).[5] The spectrum of carbinol sulfone **4** showed a strong hydroxyl peak, which was absent in that of the dehydration product **6**. The spectrum of the keto sulfone **5** exhibited a strong carbonyl peak.

(1) Supported by U. S. Public Health Service Research Grant No. CA 04455 from the National Cancer Institute and by the Army Research Office (Durham).

(2) See especially L. Field and E. T. Boyd, *J. Org. Chem.*, **26**, 1787 (1961), and D. F. Tavares and P. F. Vogt, *Can. J. Chem.*, **45**, 1519 (1967), and references cited therein.

(3) For related aroylations of ketones with esters by sodium amide, see *Org. Reactions*, **8**, Chapter 3 (1954).

(4) Theoretically one-half of sulfone **1** would be regenerated; actually the yield of **5** based on starting sulfone **1** used minus that recovered was 38%.

(5) See R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966.

SCHEME I

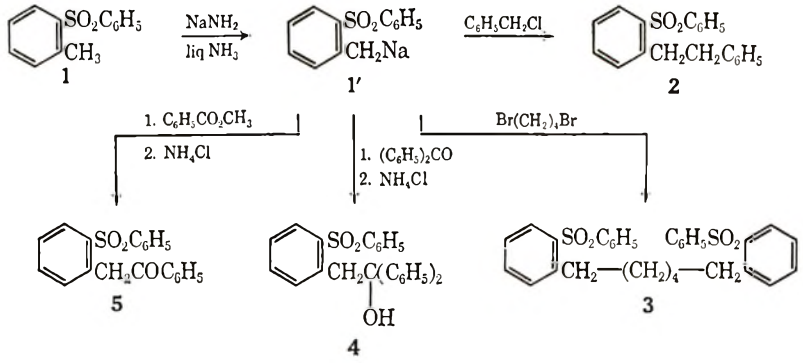


TABLE I

ASSIGNED INFRARED PEAKS OF PHENYL o-TOLYL SULFONE AND CONDENSATION PRODUCTS

(cm^{-1})

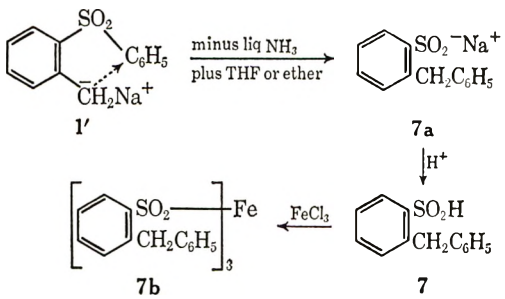
Sulfone	SO_2 stretching Asymm	SO_2 stretching Symm	*ortho* disubstitution	Monoaromatic substitution[a]	Other
1	1305, 1280	1145	763	752, 704	1380[b]
2	1290, 1285	1155	764	755, 698	*c*
3	1310, 1285	1150	760	*d*, 692	*c*
4	1300, 1285	1140	767	754, 706	3450[e]
5	1310, 1295, 1285	1140	762	750, 713	1675[f]
6	1290, 1280	1140	762	754, 695	

[a] The spectra of all these compounds except **3** had two other strong peaks in this region at 730–724 and at 687–682 cm^{-1}, possibly from C–S vibration. The spectrum of **3** had only the one peak at 727 cm^{-1}. [b] Symmetrical methyl bending. [c] No peaks in the 1380 region. [d] Absent or perhaps underneath the broad *ortho* peak at 760 cm^{-1}. [e] Hydroxyl. [f] Carbonyl.

The nmr spectrum[6] of the benzyl derivative **2** showed a sixteen-peak multiplet centered at 2.40 ppm (4.0 H) for the methylene protons and a complex aromatic multiplet from 6.7 to 7.9 ppm (14.0 H).

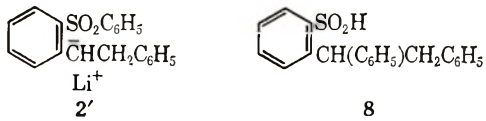
Interestingly, sodio sulfone **1′**, which was condensed in good yields with electrophilic compounds in liquid ammonia (see Scheme I), underwent the Truce–Smiles rearrangement on replacing the ammonia with tetrahydrofuran (THF) and refluxing to form 2-benzylbenzenesulfinic acid (**7**) in good yield; even in liquid ammonia, **7** was obtained in about 1% yield in connection with the benzylation of sodio sulfone **1′** (see Experimental Section). Sulfinic acid **7** was isolated as its sodio salt **7a** or, preferably, as its ferric derivative **7b** (Scheme II).

SCHEME II



Therefore the condensations of sodio sulfone **1′** with the electrophilic compounds (Scheme I) represent trapping of the intermediate carbanion in the Truce–Smiles rearrangement. Although *n*-butyllithium effects the rearrangement of sulfone **1** in refluxing ether–hexane to form sulfinic acid **7** in good yield,[7] this reagent appears not very satisfactory for trapping the intermediate carbanion. Thus the intermediate lithio sulfone formed with *n*-butyllithium has been trapped as its carbonation product by Truce and Norman[8] in only 12% yield, and as its benzophenone adduct **4** by us in only 13% yield, which is much less than that realized by us with sodio sulfone **1′** prepared with sodium amide (see Experimental Section).

Moreover, certain of the condensation products prepared by means of sodium amide in liquid ammonia (see Scheme I) were found to undergo the Truce–Smiles rearrangement. For example, the benzyl derivative **2** underwent rearrangement with *n*-butyllithium, presumably through lithio sulfone **2′**, to form sulfinic acid **8** in good yield; **8** was isolated as its ferric derivative and characterized as its *p*-toluidine salt.



At least certain of the other derivatives of sodio sulfone **1′** could probably also be rearranged under appropriate conditions.

Results with Phenyl *p*-Tolyl Sulfone and Di-*p*-tolyl Sulfone.—The former compound (**9**) was converted by sodium amide in liquid ammonia into sodio salt **9′**, which was condensed with four types of electrophilic compounds (Scheme III).

The yields of derivatives **10**, **11**, and **12** were dependent on the conditions employed (see Discussion); the best yields obtained were 92, 82, 51%, respectively. The yield of the benzoyl derivative **13** was 70% when the ratio of sodio sulfone **9′** to ester was 2:1,[9] and 53% when 1 extra equiv of sodium amide was used.[3]

Similarly, di-*p*-tolyl sulfone (**14**) was converted by a molecular equivalent of sodium amide in liquid ammonia into the corresponding monosodio salt, which was

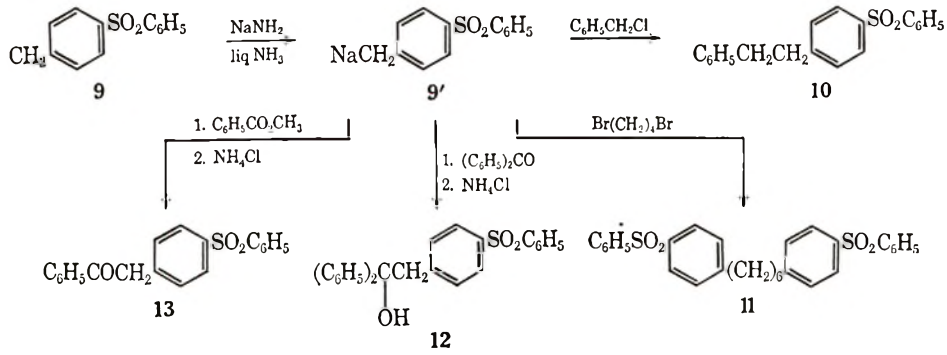
(6) All chemical shifts are reported as parts per million (δ) downfield from tetramethylsilane. Samples were determined in deuteriochloroform unless otherwise noted.

(7) (a) W. E. Truce and W. J. Ray, Jr., *J. Amer. Chem. Soc.*, **81**, 481 (1959); (b) for other interesting papers on the mechanism of this rearrangement of carbanions, see W. E. Truce, C. R. Robbins, and E. M. Kreider, *ibid.*, **88**, 4027 (1966), and references therein.

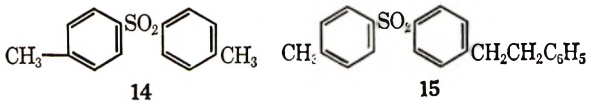
(8) O. L. Norman, Ph.D. Dissertation, Purdue University, 1953.

(9) The yield of **13** was 51% when based on starting sulfone **9**; see ref 4.

SCHEME III

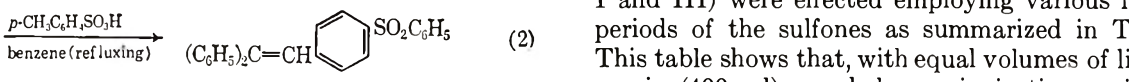


alkylated with benzyl chloride to form benzyl derivative **15** in 67% yield.



However, treatment of sulfone **14** with 2 mol equiv of sodium amide in liquid ammonia followed by 2 mol equiv of benzyl chloride failed to yield satisfactorily the corresponding dibenzyl derivative; instead there was obtained a mixture of the monobenzyl derivative **15**, starting sulfone **14**, and stilbene which arose through self-condensation of the halide, a type of reaction known to be effected by sodium amide.[10] The dibenzyl derivative possibly might be prepared by further benzylation of **15** through its monosodio salt.

The structures of the condensation products (Scheme III and **15**) were supported by analyses and absorption spectra. The structure of adduct **12** was confirmed by dehydration to form unsaturated sulfone **16** in 80% yield (eq 2).



Infrared data (Table II) show that the spectra of the products were similar to those of the starting sulfones with the expected differences for carbinol sulfone **12** and keto sulfone **13** which exhibited strong hydroxyl and carbonyl peaks, respectively. Surprisingly, the spectrum of the benzyl derivative **10** was practically identical with that of the starting sulfone **9**, both showing a peak at 1390 cm^{-1} which, in the case of **9**, may be assigned to the methyl group.[5] Such a peak was absent in the spectrum of the isomeric *o*-benzyl derivative **2** (see Table I).

The nmr spectrum[6] of the benzyl derivative **10** showed a singlet at 2.89 ppm (4.03 H) for the methylene protons, and a complex aromatic multiplet from 7.2 to 8.0 ppm (14.0 H). The nmr spectrum[6] of the monobenzyl derivative **15** exhibited a singlet at 2.4 ppm (3.14 H) for the methyl protons, another singlet at 2.9 ppm (3.96 H) for the methylene protons, and a multiplet from 7.2 to 7.9 ppm (13.0 H) for the aromatic protons.

TABLE II

ASSIGNED INFRARED PEAKS OF PHENYL *p*-TOLYL SULFONE, AND CONDENSATION PRODUCTS

(cm^{-1})

Sulfone	SO_2 stretching: Asymm	SO_2 stretching: Symm	*para* disubstitution	Monoaromatic substitution[a]	Other
9	1300, 1280	1155	819	756, 702	1390[b]
10	1310, 1290	1150	826	756, 702	1390[c]
11	1290	1145	809	758, *d*	
12	1290	1150	830	753, 702	3500
13	1325, 1315, 1290	1145	*d*	753, 716	1680
14	1315, 1295, 1285	1150	819	*e*	
15	1310, 1290, 1280	1145	819	751, 710	
16	1320, 1305	1155	827	*f*, 703	

[a] The spectra of all these compounds, except **14** and **15**, showed two other strong peaks in this region at 730–722 and at 693–683 cm^{-1}, possibly from C–S stretching. [b] Symmetrical methyl bending. [c] The origin of this peak is not clear. [d] Peak was absent. [e] This spectrum showed two peaks at 709 and 677 cm^{-1} which have been assigned to C–S stretching; see J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1332 (1951). [f] Other peaks in this region made assignment uncertain.

Discussion

The alkylations of sodio sulfones **1′** and **9′** (Schemes I and III) were effected employing various ionization periods of the sulfones as summarized in Table III. This table shows that, with equal volumes of liquid ammonia (400 ml), much longer ionization periods were required for satisfactory yields of alkylation products **2** and **3** from *o*-tolyl sulfone **1** than of **10** and **11** from the *p*-tolyl sulfone **9**. Moreover, by using 800 ml instead of 400 ml of liquid ammonia with *p*-tolyl sulfone **9**, the ionization time to give approximately the same yield of **10** was even less. The sodio salts of both **1** and **9** were decolorized almost immediately by benzyl chloride and, since this alkylation type of reaction is irreversible, the yields of the benzyl derivative **2** and **10** may be considered a rough measure of the rel-

TABLE III

YIELDS OF ALKYLATION PRODUCTS OF SULFONES 1 AND 9 EMPLOYING VARIOUS IONIZATION PERIODS

Tolyl sulfone	Ionization period, min	Solvent volume, ml	Halide	Product	Yield, %
1 (*ortho*)	20	400	$C_6H_5CH_2Cl$	2	45
1	300	400	$C_6H_5CH_2Cl$	2	61
9 (*para*)	5	800	$C_6H_5CH_2Cl$	10	82
9	15	800[a]	$C_6H_5CH_2Cl$	10	89
9	30	400	$C_6H_5CH_2Cl$	10	92
1 (*ortho*)	15	400	$Br(CH_2)_4Br$	3	26
1	60	400	$Br(CH_2)_4Br$	3	58
9 (*para*	15	800	$Br(CH_2)_4Br$	11	61
9	30	400	$Br(CH_2)_4Br$	11	82

[a] 0.03 mol of phenyl *p*-tolyl sulfone used.

(10) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

ative ease of ionization of the starting sulfones **1** and **9**. Actually, the relative ease of ionization of the *o*-tolyl sulfone **1** must have been even less than indicated by the relative yields of the alkylation products, since this sulfone was more soluble in liquid ammonia than *p*-tolyl sulfone **9**. The relatively slow rate of ionization of the *o*-tolyl sulfone **1** suggests that a steric factor is involved. A study of a possible metallic cation effect employing various alkali amides is contemplated.

Incidentally, in one of the experiments on the benzylation of the *o*-tolyl sulfone **1** in which the yield of the benzyl derivative **2** was relatively low, a considerable amount of stilbene was detected by thin layer chromatography; this self-condensation product of the benzyl chloride was presumably produced by sodium amide that had not yet effected the ionization of **1**.[10]

The carbonyl addition reactions of sodio sulfones **1′** and **9′** (Schemes I and III) were effected employing various condensation periods as summarized in Table IV. Because of possible reversion during work-up, the reaction mixtures were neutralized inversely with ammonium chloride. Table IV shows that the yields

TABLE IV

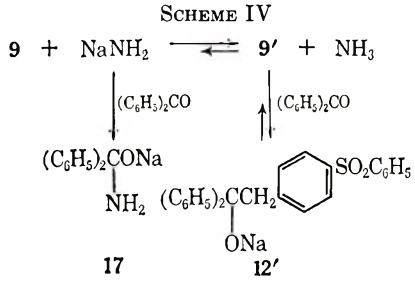
YIELDS OF ADDUCTS FROM SODIO SULFONE 1′ AND 9′ WITH BENZOPHENONE ON INVERSE NEUTRALIZATION AFTER VARIOUS CONDENSATION PERIODS

Sodio sulfone	Ionization period, min	Condensation period, min	Product	Yield, %
1′ (*ortho*)	120	1	4	76
1′	120	5	4	69
1′	120	30	4	*a*
9′ (*para*)	30	1	12	51
9′	30	5	12	6
9′	30	30	12	*b*

[a] No product detected; shown to be starting material by tlc; 58% starting sulfone **1** recovered. [b] No product detected; 56% starting sulfone **9** recovered.

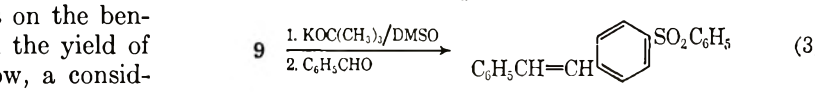
of adducts **4** and **12** were satisfactory only when the reaction mixtures were neutralized within a relatively short time. The time was less critical with the *o*-sodio sulfone **1′** than with the *p*-sodio sulfone **9′**; with the latter, less than 5 min appeared to be required for a satisfactory yield. These results are rationalized on the basis of a kinetic *vs.* thermodynamic control as illustrated in Scheme IV for the *para* case. The

SCHEME IV



kinetic control involves the initial addition reaction of sodio sulfone **9′** with benzophenone to form sodio adduct **12′**, and the thermodynamic control involves an addition reaction of sodium amide (present in equilibrium) with the ketone to form sodio adduct **17**. Such competing controls have recently been reported in the related addition reaction of disodiophenylacetamide with benzophenone, in which formation of the sodium amide adduct of the ketone (**17**) was established.[11]

It should be mentioned that *p*-tolyl sulfone **9** previously has been condensed with certain aromatic aldehydes by means of potassium *t*-butoxide in dimethyl sulfoxide (DMSO) to form the corresponding unsaturated sulfones; the best yield (40%) was obtained with benzaldehyde (eq 3).[12]



(3)

All of the products listed in Schemes I and III (and **15**) were new. The sodium amide method employed in these syntheses could probably be extended, not only to other electrophilic compounds, but also to certain substituted *o*- and *p*-tolyl sulfones to afford various derivatives having other functional groups. Moreover, the condensations involving the *o*-tolyl sulfones should furnish derivatives which may be useful for mechanistic studies of the Truce–Smiles rearrangement and for syntheses of resulting sulfinic acids.

Experimental Section[13]

Conversion of Phenyl *o*-Tolyl Sulfone (1) into Sodio Salt 1′.—To a stirred suspension of 0.02 mol of sodium amide in 400 ml of liquid ammonia[14] was added 4.64 g (0.02 mol) of phenyl *o*-tolyl sulfone (**1**)[7] to produce immediately a deep purple solution of sodio salt **1′**. No undissolved sulfone was observed. After stirring for an appropriate time (designated ionization period), the sodio salt **1′** (maximum amount 0.02 mol) was condensed with electrophilic compounds (or rearranged) as described below.

Alkylations of Sodio Salt 1′.—In Table I are summarized the yields of products obtained employing various ionization periods. The experiments which afforded the best yields are described below.

A. With Benzyl Chloride.—To a stirred solution of sodio salt **1′** (after an ionization period of 5 hr) was added 2.79 g (0.022 mol) of benzyl chloride in 50 ml of dry ether. The purple color of **1′** was immediately discharged (to light tan). The liquid ammonia was allowed to evaporate and more (500 ml) ether was added. The resulting ethereal suspension was stirred with 50 ml of water to dissolve the inorganic salts. The two layers were separated. The ethereal solution was dried and the solvent removed. The residue was recrystallized from absolute ethanol to give 3.97 g (61%) of the benzyl derivative **2**, mp 84–87 and 86–87° after several additional recrystallizations.

Anal. Calcd for $C_{20}H_{18}SO_2$: C, 74.50; H, 5.63; S, 9.94. Found: C, 74.59; H, 5.52; S, 9.97.

The original aqueous layer of the reaction product (see above) was neutralized with 50% hydrochloric acid. The resulting solution was treated with excess aqueous ferric chloride[15] to precipitate 0.05 g (*ca.* 1%) of the red ferric derivative of 2-benzylbenzenesulfinic acid (**7b**). The infrared spectrum of this

(11) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966).

(12) G. A. Russell, E. G. Janzen, H. D. Becker, and F. J. Smentowski, *J. Amer. Chem. Soc.*, **84**, 2652 (1962).

(13) Melting points were taken in open capillary tubes on a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method. The nmr spectra were obtained on a Varian A-60 spectrometer. All chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane standard. Commercial, anhydrous liquid ammonia was used; it was further dried in the preparation of sodium amide by addition of small pieces of sodium until a blue color persisted. *n*-Butyllithium (*ca.* 1.5 *M* in hexane) was obtained from Foote Mineral Co. Organic fractions were dried over anhydrous magnesium sulfate, and then concentrated or removed under reduced pressure using a Roto-vac (Labline).

(14) For preparation of sodium amide, see ref 10, p 122.

(15) J. Thomas, *J. Chem. Soc.*, **95**, 342 (1909).

slightly impure sample of **7b** was nearly superimposable on that of an authenic sample obtained from the Truce–Smiles rearrangement under more appropriate conditions (see below).

B. With 1,4-Dibromobutane.—To a stirred solution of sodio salt **1′** (after an ionization period of 1 hr) was added dropwise 2.37 g (0.010 mol) of 1,4-dibromobutane in 50 ml of dry ether. The purple color of **1′** slowly changed to brownish green. The ammonia was replaced by ether and the resulting suspension stirred with water. The solid was collected and recrystallized from benzene–ethanol to give 2.99 g (58%) of the bis derivative **3**, mp 154–157 and 156–158° after further recrystallizations.

Anal. Calcd for $C_{30}H_{30}S_2O_4$: C, 69.47; H, 5.83; S, 12.36. Found: C, 69.89; H, 5.87; S, 12.36.

Addition Reaction of Sodio Salt 1′ with Benzophenone.—In Table II are summarized the yields of product obtained employing various condensation periods; the 2-hr ionization period allowed is considered sufficient to form approximately 0.02 mol of sodio salt **1′**. The experiment which gave the best yield is described below.

To a stirred solution of sodio salt **1′** was added, during 1 min, 4.01 g (0.022 mol) of benzophenone in 50 ml of dry ether. The purple color of **1′** changed to red during the 1 min, after which the reaction mixture was poured into a solution of 2.36 g (0.044 mol) of ammonium chloride in liquid ammonia. The ammonia was replaced by ether. The resulting suspension was stirred with water and the mixture filtered. The solid (4.67 g), mp 166–168°, was combined with more (1.65 g) of solid, mp 162–165°, isolated from the filtrate to give 6.32 g (76%) of benzophenone adduct **4**, which melted at 166–167° after several recrystallizations from benzene–hexane.

Anal. Calcd for $C_{26}H_{22}SO_3$: C, 75.33; H, 5.35; S, 7.73. Found: C, 75.42; H, 5.39; S, 7.68.

Dehydration of 2 g (0.00483 mol) of adduct **4** was accomplished by refluxing with a catalytic amount (<0.1 g) of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene for 14 hr; the azeotrope of water and benzene was removed using a Dean–Stark water trap. The resulting solution was diluted with ether, washed with sodium bicarbonate solution, and dried. The solvent was removed to give 1.66 g (86%) of unsaturated sulfone **6**, mp 170–173 and 171–172.5° after recrystallization from benzene–hexane.

Anal. Calcd for $C_{26}H_{20}SO_2$: C, 78.76; H, 5.08. Found: C, 79.12; H, 5.19.

Benzoylation of Sodio Salt 1′.—To a stirred solution of sodio salt **1′** (ionization period of 4 hr to form presumably 0.02 mol of **1′**) was added 1.36 g (0.01 mol) of methyl benzoate in 50 ml of dry ether. The purple color of **1′** changed to reddish brown and finally to yellowish green. After neutralization with excess ammonium chloride (1.77 g, 0.033 mol), the ammonia was replaced by ether, and the resulting ethereal suspension was stirred with 50 ml of water. The layers were separated. The ethereal layer was dried and concentrated. The resulting precipitate (1.94 g), mp 117–124°, was collected by filtration and recrystallized from absolute ethanol to give 1.69 g (50%) of keto sulfone **5**, mp 128–130°.

Anal. Calcd for $C_{20}H_{16}SO_3$: C, 71.41; H, 4.80; S, 9.53. Found: C, 71.12; H, 4.78; S, 9.55.

Further concentration of the filtrate afforded 1.59 g (34%) of the crude starting sulfone **1**, mp 65–75°.

When 0.044 mol of sodium amide in 400 ml of liquid ammonia was treated with 0.02 mol of sulfone **1**, followed, after 5 hr, by 0.03 mol of methyl benzoate in 50 ml of dry ether, there was obtained, on working up the reaction mixture as described above, the keto sulfone **5**, mp 128–130°, in 34% yield (based on **1**).

Rearrangement of Sodio Salt 1′.—To a stirred suspension of 0.022 mol of sodium amide in 400 ml of liquid ammonia was added 0.02 mol of phenyl *o*-tolyl sulfone (**1**) and the ammonia replaced by freshly distilled tetrahydrofuran (THF). The resulting dark red solution of sodio salt **1′** was refluxed for 7 hr; the red color gradually faded and a tan solid precipitated. The solid was collected by filtration to give 2.73 g (54%) of crude sodio salt **7a** of 2-benzylbenzenesulfinic acid (**7**). The filtrate was diluted with ether, and water added. The layers were separated. The aqueous layer was neutralized with 50% hydrochloric acid and treated with aqueous ferric chloride to precipitate 0.82 g (16%) of the known[7a] red ferric derivative **7b**.

The combined yield of **7a** and **7b** was 70%. The sodio salt **7a** was identified by its infrared spectrum: 1435, 1025 (SO_2),[16] 952 (SO_2),[16] 879, 757, 726, and 695 cm^{-1}, and by conversion of a sample into the red ferric derivative **7b**. The latter derivative was identified by infrared spectrum [1590, 1485, 1465, 1445, 960–920 (very broad SO_2), 755, 728, and 679 cm^{-1}], and by conversion of a 1-g sample into the free sulfinic acid[7] and the mercuric chloride derivative[7,17] as described previously. The sulfinic acid **7**, isolated in 40% yield, melted at 68–76 and 74.5–76° after recrystallization from ether–petroleum ether (bp 30–65°) (lit.[7] mp 70–72°): infrared, 2830 OH,[15] 2470 (OH),[16] 1480, 1465, 1445, 1435, 1120, 1080, 1070 (SO_2),[16] 1035 (SO_2),[16] 833, 763, 747, 724, and 697 cm^{-1}. The mercuric chloride derivative melted at 142–144° (lit.[7] mp 147–148°).

When the sodio sulfone **1′** was prepared in liquid ammonia as described above, and the ammonia replaced by ether followed by 10 hr of refluxing, the red color of **1′** was still present and, on working up the reaction mixture, there was obtained sulfinic acid **7** as its ferric derivative **7b** in 12% yield; 38% of the sulfone **1** was recovered.

Results with Sulfone 1 and *n*-Butyllithium.—The rearrangement of sulfone **1** with this reagent was effected in ether–hexane as described by Truce and Ray[7] (refluxed 6 hr). There was obtained 2-benzylbenzenesulfinic acid (**7**), isolated as its ferric derivative **7b** in 54% yield. The infrared spectrum of a sample of this product was identical with that of **7b** obtained from the rearrangement of sulfone **1** with sodium amide as described above.

The intermediate lithio salt of sulfone **1** was trapped by treating 0.01 mol of sulfone **1** in 300 ml of dry ether at −80° with 0.011 mol of *n*-butyllithium in hexane (7.34 ml) and, after 6 hr, adding 0.011 mol of benzophenone in ether. After 30 min, the ethereal solution was washed with water, dried, and concentrated (reduced pressure) to give 0.55 g (13%) of slightly impure benzophenone adduct **4**, mp 155–160°. Admixture with a sample of authentic **4** did not depress the melting point; the infrared spectra of the two samples were superimposable.

Rearrangement of Benzyl Derivative 2.—Into a solution of 0.82 g (0.0025 mol) of **2** in 100 ml of dry ether was syringed 2 ml (0.0028 mol) of approximately 1.5 *M* *n*-butyllithium to form a deep red solution. After refluxing for 4 hr under nitrogen, the reaction mixture was stirred with 50 ml of iced water until all the solid dissolved. The two layers were separated. The cooled aqueous layer was acidified with 50% hydrochloric acid to form an oil, which was taken up in ether. The ethereal solution was extracted with sodium bicarbonate. This bicarbonate solution was neutralized with 50% hydrochloric acid and treated with aqueous ferric chloride to precipitate a red solid which was collected by filtration to give 0.49 g (60%) of the ferric derivative of sulfinic acid **8**: infrared, 1620, 1510, 1460, 970–940 (broad), 759, and 700 cm^{-1}.

An aqueous suspension of this ferric derivative was treated with excess concentrated ammonium hydroxide to leave a brown suspension of ferric hydroxide, which was removed by filtration. The cooled aqueous filtrate was acidified with concentrated hydrochloric acid to form an oil, which failed to crystallize. This oil was dissolved in absolute ethanol, and the solution treated with excess *p*-toluidine. The resulting solution was warmed slightly and then added dropwise to 75 ml of chilled stirred, dry ether. The solid which precipitated was collected by filtration to give the *p*-toluidine salt of sulfinic acid **8**: mp 160–163 and 162–163° after two recrystallizations from ethanol–ether; infrared, 3400, 2830, 2580, 1510, 1435, 1020 (SO_2),[16] 915 (SO_2),[16] 808, 760, 754, and 695 cm^{-1}.

Anal. Calcd for $C_{27}H_{27}NSO_2$: C, 75.49; H, 6.34; N, 3.26; S, 7.46. Found: C, 75.33; H, 6.27; N, 3.28; S, 7.29.

Conversion of Phenyl *p*-Tolyl Sulfone (9) into Sodio Salt 9′.—To a stirred suspension of 0.022 mol of sodium amide in 400–800 ml of liquid ammonia was added 0.02 mol of phenyl *p*-tolyl sulfone **9**,[18] mp 125–127° (lit.[19] mp 125°), to produce a deep red solution of sodio salt **9′**. All of the sulfone appeared to dissolve within 15 and 30 min when the volume of liquid ammonia was 800 and 400 ml, respectively. After stirring for an appropriate time (designated ionization period), the sodio salt **9′** was condensed with electrophilic compounds as described below.

(16) S. Detoni and D. Hadzi, *J. Chem. Soc.*, 3163 (1955).

(17) See F. C. Whitman, F. H. Hamilton, and N. Thurman, *J. Amer. Chem. Soc.*, **45**, 1066 (1923).

(18) Prepared in 77% yield from thiophene-free benzene (dried over sodium) and *p*-toluenesulfonyl chloride by means of aluminum chloride as described for similar sulfones; see ref 7.

(19) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 4174 (1957).

Alkylations of Sodio Salt 9′.—In Table III are summarized yields of products obtained employing various ionization periods; the experiments which gave the best yields are described below.

A. With Benzyl Chloride.—To a stirred solution of sodio salt 9′ in 400 ml of liquid ammonia (ionization period, 30 min) was added 2.79 g (0.022 mol) of benzyl chloride in 50 ml of dry ether. The color of 9′ was changed immediately to a brighter red which faded slowly. The reaction mixture was worked up as described above for benzylation of sodio salt 1′ to give a white solid, mp 124–128°, upon removal of the ether. One recrystallization from absolute ethanol afforded 5.89 g (92%) of benzyl derivative **10**, mp 130–132.5 and 133.5–135° after several more recrystallizations from absolute ethanol.

Anal. Calcd for $C_{20}H_{18}SO_2$: C, 74.51; H, 5.63; S, 9.94. Found: C, 74.52; H, 5.73; S, 9.95.

B. With 1,4-Dibromobutane.—To a stirred solution of sodio salt 9′ in 400 ml of liquid ammonia (ionization period, 30 min) was added 0.01 mol of 1,4-dibromobutane in dry ether. The color changed to dark brown. The reaction mixture was worked up as described above for the corresponding reaction of the sodio salt 1′ to give, after trituration with water and benzene, 4.24 g (82%) of the bis derivative **11**, mp 224–228 and 229.5–231° after four recrystallizations from large volumes of benzene.

Anal. Calcd for $C_{30}H_{30}S_2O_4$: C, 69.47; H, 5.83; S, 12.36. Found: C, 69.62; H, 5.83; S, 12.04.

Addition Reaction of Sodio Salt 9′ with Benzophenone.—In Table IV are summarized the yields of products obtained employing various condensation periods; the experiment which gave the best yield is described below.

To a stirred solution of sodio salt 9′ in 800 ml of liquid ammonia (ionization period, 30 min) was added, during 1 min, 4.01 g (0.022 mol) of benzophenone in 50 ml of dry ether. The dark color became lighter red. After 1 min the reaction mixture was inversely neutralized and worked up as described above for the addition reaction of sodio salt 1′ to give, after recrystallization from THF–ethanol, 4.01 g (51%) of benzophenone adduct **12**, mp 203–205 and 208–210° after further recrystallizations.

Anal. Calcd for $C_{26}H_{22}SO_3$: C, 75.33; H, 5.35; S, 7.73. Found: C, 75.04; H, 5.36; S, 8.40.

Dehydration of 2 g of adduct **12** was effected as described for dehydration of adduct **4** to give (in two crops) 1.53 g (80%) of unsaturated sulfone **16**, mp 181–184 and 182.5–184° after several recrystallizations from benzene–hexane.

Anal. Calcd for $C_{26}H_{20}SO_2$: C, 78.76; H, 5.08. Found: C, 78.88; H, 5.14.

Benzoylation of Sodio Salt 9′.—To a stirred solution of 0.02 mol of sodio salt 9′ in 400 ml of liquid ammonia (ionization period, 30 min) was added dropwise 1.36 g (0.01 mol) of methyl benzoate in dry ether. The red color gradually changed to yellow. After 1 hr the reaction mixture was worked up as described for the benzoylation of sodio salt 1′ to give, on recrystallization of the product from acetonitrile, 2.37 g (70% based on the ester) of keto sulfone **13**, mp 213–216 and 215–217° after several recrystallizations from large volumes of acetonitrile.

Anal. Calcd for $C_{20}H_{16}SO_3$: C, 71.41; H, 4.80; S, 9.53. Found: C, 71.01; H, 4.82; S, 9.30.

There was recovered from the original filtrate 1.44 g (30%) of the starting sulfone **9**, mp 123–125°.

When 0.044 mol of sodium amide in 400 ml of liquid ammonia was treated with 0.02 mol of sulfone **9** in a manner described before for sulfone **1**, 3.59 g (53%) of crude ketone sulfone **13**, mp 205–215°, was obtained. Further purification was not attempted since the yield was low.

Monobenzylation of Di-p-tolyl Sulfone (14).—To a stirred suspension of 0.022 mol of sodium amide in 400 ml of liquid ammonia was added 4.94 g (0.02 mol) of commercial sulfone **14** to form a deep red solution. After 30 min, 2.79 g (0.022 mol) of benzyl chloride in 50 ml of dry ether was added. The reaction mixture was worked up as usual to give, after one recrystallization from absolute ethanol, 5.91 g (81%) of monobenzyl derivative **15**, mp 120–130°; a second recrystallization gave 4.54 g (67%) of **15**, mp 126–130 and 135–136° after several recrystallizations from absolute ethanol.

Anal. Calcd for $C_{21}H_{20}SO_2$: C, 74.97; H, 5.99; S, 9.53. Found: C, 74.74; H, 6.00; S, 9.63.

Attempted Dibenzylation of Di-p-tolyl Sulfone (15).—To a stirred suspension of 0.066 mol of sodium amide in 800 ml of liquid ammonia was added 0.03 mol of di-*p*-tolyl sulfone (**15**) which gradually dissolved. After 30 min, 0.066 mol of benzyl chloride was added. The purple color characteristic of stilbene formation was observed.[10] The reaction mixture was worked up to give a mixture of solids which was indicated by thin layer chromatography to consist of monobenzyl derivative **16**, stilbene, starting sulfone **15**, and a trace of an unidentified compound.

Registry No.—**1**, 7018-84-0; **1′**, 16425-98-2; **2**, 16425-99-3; **3**, 16426-00-9; **4**, 16426-01-0; **5**, 16426-02-1; **6**, 16426-03-2; **7**, 16426-04-3; **8** *p*-toluidine salt, 16426-05-4; **8** ferric derivative, 16426-14-5; **9**, 640-57-3; **9′**, 16426-07-6; **10**, 16426-08-7; **11**, 16426-09-8; **12**, 16426-10-1; **13**, 16426-11-2; **15**, 16426-12-3; **16**, 16426-13-4; sodium amide, 7782-92-5.

The Reduction of Alkyl Aryl Sulfoxides by Iodide Ions in Acid Solution[1]

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The pseudo-first-order rate constants for the reduction of some aryl alkyl sulfoxides in 4 M perchloric acid 0.2 M in iodide ion were determined and are methyl phenyl (22×10^{-5} sec^{-1}), ethyl phenyl (14×10^{-5}), isopropyl phenyl (0.46×10^{-5}), t-butyl phenyl (0.012×10^{-5}), methyl p-anisyl (27×10^{-6}), methyl p-tolyl (31×10^{-6}), methyl m-tolyl (26×10^{-6}), methyl m-anisyl (15×10^{-5}), methyl p-chlorophenyl (13×10^{-5}), methyl m-chlorophenyl (9.4×10^{-5}), methyl m-nitrophenyl (3.2×10^{-5}), and methyl p-nitrophenyl (5.1×10^{-5}). The kinetics were first order in sulfoxide and first order in iodide ion. An analysis of the substituent effects using the procedure of Taft indicated that the p-nitro group was stabilizing the transition state more than the ground state. This argues against the rate-determining decomposition of an intermediate such as $IS(R_2)OH$ or $IS(R_2)OH_2^+$. Assuming that the reaction was second order in acid as indicated by data in the literature a mechanism was proposed involving rate-determining attack of iodide ion on the sulfur of the monoprotonated sulfoxide while a hydronium ion acted as an acid catalyst allowing concerted departure of a water molecule from sulfur as the iodide ion approached.

Sulfoxides can be reduced by numerous reducing agents among which is iodide ion in acid solution[3] (eq 1). To learn more about the mechanism of this

$$R_2SO + 2H^+ + 2I^- \longrightarrow R_2S + H_2O + I_2 \qquad (1)$$

reaction and the influence of structure on reactivity in particular, and substitution at tetravalent tricoordinate sulfur in general, we carried out the work described below. During the course of our work, several articles appeared on this reaction[4-6] as well as some on the reverse reaction, the oxidation of sulfides by iodine,[7] which proved helpful in interpreting our data.

Results

The sulfoxides studied are listed in Tables I and II. Nine of these are *meta*- and *para*-substituted methyl phenyl sulfoxides chosen to study the effect of structure on reactivity while keeping steric effects at the reaction center constant; the remaining three were chosen to study steric effects.

The kinetics were run in aqueous perchloric acid solution under nitrogen with iodide ion in excess so that pseudo-first-order conditions with respect to the disappearance of sulfoxide pertained. The kinetics were followed by titrating the iodine liberated with sodium thiosulfate. The initial sulfoxide concentrations were about 0.005 M, the initial iodide concentration was 0.2 M, and the perchloric acid was 4 M. Generally, the reactions were followed for one half-life, although good first-order plots could be obtained for two half-lives. Beyond this point, the experimental points of first-order plots began to show a lot of scatter. This probably was caused by oxidation of iodide ion by oxygen not completely excluded from the reaction vessels. No organic products other than the sulfide were detected when methyl phenyl sulfoxide was reduced at greater than kinetic concentrations.

TABLE I

RATE CONSTANTS FOR THE REDUCTION OF $XC_6H_4SOCH_3$ (0.005 M) BY IODIDE ION (0.20 M) IN PERCHLORIC ACID (4.00 M) AT 35°

X	$k \times 10^5$, sec^{-1} [a]	X	$k \times 10^5$, sec^{-1}
p-CH_3O[b]	27.3 ± 0.5	p-Cl[g]	12.9 ± 0.5
p-CH_3[c]	31.1 ± 1.2	m-Cl[h]	9.41 ± 0.50
m-CH_3[d]	25.5 ± 0.1	m-NO_2[i]	3.20 ± 0.20
H[e]	22.1 ± 0.6	p-NO_2[j]	5.12 ± 0.17
m-CH_3O[f]	14.6 ± 0.3		

[a] Based on three runs each, average deviation given. [b] Registry no.: 3517-99-5; [c] 934-72-5; [d] 13150-71-5; [e] 1193-82-4; [f] 13150-72-6; [g] 934-73-6; [h] 13150-73-7; [i] 3272-42-2; [j] 940-12-5.

TABLE II

RATE CONSTANTS FOR THE REDUCTION OF C_6H_5SOR (0.005 M) BY IODIDE ION (0.20 M) IN PERCHLORIC ACID (4.0 M) AT 35°, FOR THE REACTION OF ALKYLTHIOSULFATES WITH SULFITE ION, AND FOR THE REACTION OF ALKYL BROMIDES WITH BROMIDE ION

	C_6H_5SOR		$RSSO_3^-$ [a]	RCH_2Br[b]
R	$k \times 10^5$, sec^{-1}	$100k_R/k_{CH_3}$	$100k_R/k_{CH_3}$	$100k_R/k_{HCl}$
CH_3	22.1 ± 0.6	100 (100)[c]	100	100
CH_3CH_2[d]	13.7 ± 0.2	62 (81)	50	65
$(CH_3)_2CH$[e]	0.455 ± 0.024	2.1 (1.8)	0.7	3.3
$(CH_3)_3C$[f]	0.012[g]	0.05 (0.07)	0.0006	0.0015

[a] Reference 10. [b] Reference 11. [c] Values in parentheses are from ref 5. [d] Registry no.: 4170-80-3; [e] 4170-69-8; [f] 4170-71-2. [g] Estimated from an initial and final point after correcting, by means of a blank, for iodine formation due to oxygen.

Several runs were carried out using methyl phenyl sulfoxide in which the hydrogen and iodide ions were kept in excess while the initial sulfoxide concentration was varied. The results presented in Table III indicate that the reaction is first order in sulfoxide in agreement with the results obtained by others.[4,5]

Table III lists the first-order rate constants which increased with increasing acid concentration indicating that the reaction is acid catalyzed. A plot of log k *vs.* H_0 gave a straight line of slope 1.82. Montanari, *et al.*, obtained a slope of 1.22 for the reduction of dimethyl sulfoxide.[5b] These values were obtained using the H_0 values of Paul and Long.[8] Using the values of Yates and Wai,[9] the slopes are 2.1 and 1.3, respectively. The effect of the sodium iodide on the H_0 values is not known.

(1) This research was supported in part by the U. S. Public Health Service under Grant No. GM-10244.

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(9) K. Yates and H. Wai, *J. Amer. Chem. Soc.*, **86**, 5408 (1964).

TABLE III

DEPENDENCE OF RATE CONSTANTS FOR THE REDUCTION OF METHYL PHENYL SULFOXIDE BY IODIDE ION (0.20 *M*) ON PERCHLORIC ACID CONCENTRATION AND ON SULFOXIDE CONCENTRATION AT 35°

Sulfoxide, *M*	$HClO_4$, *M*	$k \times 10^5$, sec^{-1}
0.010	4.0	21.7
0.005	4.0	22.1
0.001	4.0	19.0
0.005	3.0	2.64 ± 0.28[a]
0.005	3.5	7.50 ± 0.10[a]
0.005	4.5	58.8 ± 1.1[a]

[a] These runs in triplicate.

The effect of iodide ion concentration was also studied. Since the reaction appears to be reversible when the iodide ion concentration approaches the sulfoxide concentration,[4c,5] we varied the initial iodide ion concentration from 0.025 to 0.3 *M* while keeping the initial methyl phenyl sulfoxide concentration at 0.005 *M*. The first-order rate constant was then calculated assuming that the reaction was first order in sulfoxide and zero order in iodide ion. Then the second-order rate constants were determined assuming that the reaction was first order in both sulfoxide and iodide ion. The results are listed in Table IV. Although both the first- and second-order rate constants increase with increasing iodide ion concentration, the first-order constants increase 20-fold while the second-order constants increase only by a factor of two over the 0.025–0.3 *M* range of iodide ion concentration. We conclude that the reaction is first order in iodide ion with the slight increase in second-order rate constants being a salt effect.

TABLE IV

DEPENDENCE OF RATE CONSTANTS FOR THE REDUCTION OF METHYL PHENYL SULFOXIDE (0.005 *M*) ON IODIDE ION CONCENTRATION IN PERCHLORIC ACID (4.0 *M*) AT 35°

I^-, *M*	$k^a \times 10^5$, sec^{-1}	$k^a \times 10^4$ l. mol^{-1} sec^{-1}
0.025	1.78 ± 0.00	5.79 ± 0.02
0.050	4.21 ± 0.00	7.62 ± 0.05
0.100	8.68 ± 0.25	9.18 ± 0.00
0.200	22.1 ± 0.6	10.73 ± 0.10
0.300	37.1 ± 0.4	12.49 ± 0.14

[a] All runs in duplicate except for 0.2 *M* in triplicate.

Discussion

Several mechanisms seem consistent with the kinetic evidence which requires involvement of one sulfoxide molecule, one iodide ion, and an unknown number of protons or hydronium ions in the transition state. These mechanisms all presuppose a preequilibrium protonation of the sulfoxide (eq 2). Thereafter, they differ in certain details of one or more intermediate steps, but, with the exception of one, finally converge in agreeing to the formation of R_2SI^+ which reacts rapidly with iodide ion in one or more steps to give the products (eq 3). The iodine reacts further to give triodide ion.

$$R_2SO + H_3O^+ \rightleftharpoons R_2SOH^+ + H_2O \quad (2)$$

$$R_2SI^+ + I^- \longrightarrow R_2S + I_2 \quad (3)$$

One possible mechanism, quite reminiscent of an SN2 displacement on carbon, involves the formation of a sulfur to iodine bond with the synchronous breakage of the sulfur to oxygen bond. This is depicted by eq 4 where the transition state, with charges omitted, has partially formed and broken bonds are indicated by dotted lines.

$$I^- + R_2SOH^+ \longrightarrow I\cdots S(R_2)\cdots OH \longrightarrow ISR_2^+ + OH^- \quad (4)$$

The mechanism may be modified by the inclusion of a hydronium ion with consequent displacement of a water molecule rather than a hydroxide ion (eq 5).

$$I^- + R_2SOH^+ + H_3O^+ \longrightarrow I\cdots S(R_2)\cdots OH\cdots H\cdots OH_2 \longrightarrow ISR_2^+ + 2H_2O \quad (5)$$

Diprotonation of the sulfoxide prior to iodide ion attack seems unlikely since a dication involving adjacent positive charges on sulfur and oxygen would be formed.

Alternatively, mechanisms involving tetravalent tetracoordinate sulfur intermediates, analogous to SF_4 in structure, may be formulated. The first is given by eq 6 and 7. Either the formation or decomposition of the intermediate could be rate determining. Again the mechanism may be modified by the inclusion of additional acid (eq 8–10) to avoid expulsion of a hydroxide ion.

$$I^- + R_2SOH^+ \longrightarrow IS(R)_2OH \quad (6)$$

$$IS(R_2)OH \longrightarrow ISR_2^+ + OH^- \quad (7)$$

$$I^- + R_2SOH^+ \longrightarrow IS(R)_2OH \quad (8)$$

$$IS(R)_2OH + H_3O^+ \longrightarrow IS(R)_2OH_2^+ + H_2O \quad (9)$$

$$IS(R)_2OH_2^+ \longrightarrow ISR_2^+ + H_2O \quad (10)$$

Another possible mechanism involving a monoprotonated sulfoxide is rate-determining attack by iodide ion on the sulfinyl oxygen rather than on sulfur (eq 11 and 12).[4c,6]

$$R_2SOH^+ + I^- \longrightarrow R_2S + HOI \quad (11)$$

$$HOI + HO_3^+ + I^- \longrightarrow I_2 + 2H_2O \quad (12)$$

Some evidence against this possibility has been given.[5,6] We carried out the reduction of the methyl, ethyl, isopropyl, and *t*-butyl phenyl sulfoxides hoping to shed some more light on this point. Our thought was to plot our rate constants *vs.* those of Fava and Iliceto[10] for the reaction of alkylthiosulfates with radioactive sulfite ion (eq 13). Our results, those of

$$RSSO_3^- + S^*O_3^{2-} \longrightarrow RSS^*O_3^- + SO_3^{2-} \quad (13)$$

Fava and Iliceto, and those of de la Mare[11] for the exchange of radiobromide in a series of alkyl bromides are listed in Table II. The radiobromide exchange follows an SN2 pathway. Fava and Iliceto argued that their data supported a similar pathway for nucleophilic substitution on divalent sulfur; *i.e.*, the sulfite ion attacked the divalent sulfur of the thiosulfate from a direction backside to the departing sulfite ion. In order to make this comparison, a methylene group in de la Mare's work was taken to equal the divalent sulfur atom in Fava and Iliceto's work. A similar assumption must be made in order to compare the influence of steric factors on the sulfoxide reduction with the other two sets of data (Table II). The general trend in data suggests that steric effects parallel one another in these three reaction series. One might say that this is

(10) A. Fava and A. Iliceto, *J. Amer. Chem. Soc.*, **80**, 3478 (1958).
(11) P. B. D. de la Mare, *J. Chem. Soc.*, 3180 (1955).

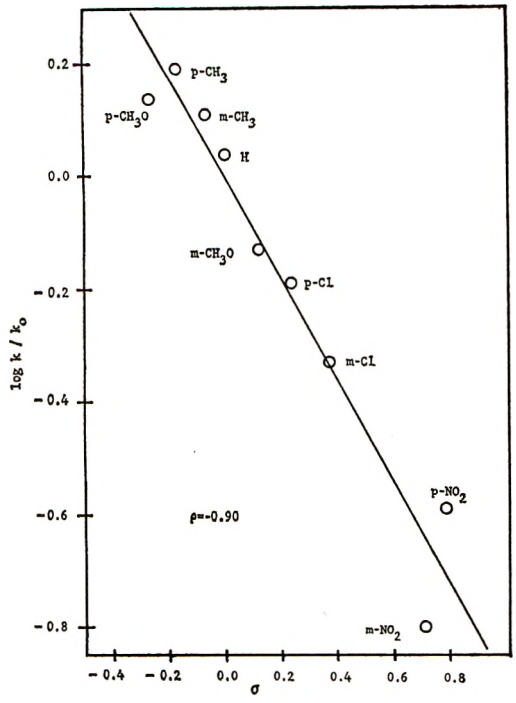

Figure 1.—Hammett plot of pseudo-first-order rate constants.

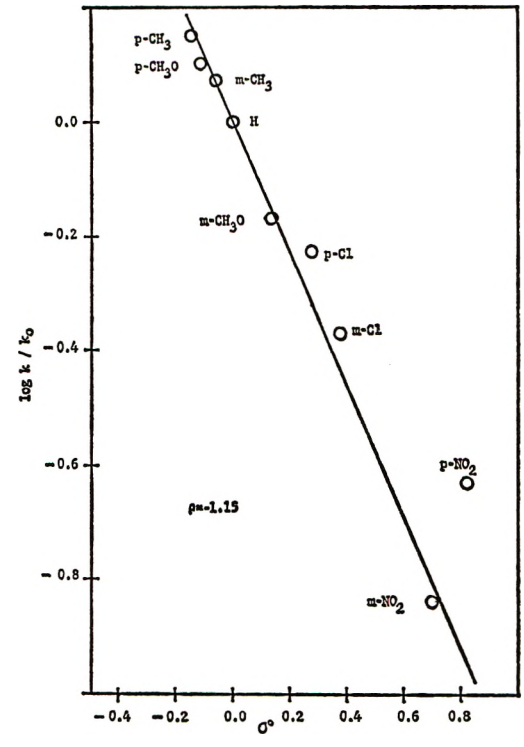

Figure 2.—Taft–Hammett plot of pseudo-first-order rate constants.

evidence for the backside attack of iodide ion on the sulfoxide sulfur presumably with inversion of configuration.[12] Unfortunately, the analogy is not so straightforward for sulfoxides. The effect of the alkyl groups on the basicity of the sulfoxides has been neglected. If one knew the pK_a's of these sulfoxides, a more valid comparison of steric factors might be possible. Nevertheless, the effects of differences in basicity should exert a minor influence on the rate constants compared with the steric effects. This reason taken together with the work in the literature makes us exclude the mechanism illustrated by eq 11 and 12 from further consideration in this article.

The remaining mechanistic possibilities differ in two essential points: (1) the presence or absence of a tetracoordinate intermediate, and (2) the number of protons or hydronium ions involved in the transition state. Krueger[6] found the reduction of dimethyl sulfoxide in dimethyl sulfoxide–water mixtures to be first order in iodide ion and second order in acid. Deviation from third-order kinetics occurred when the sulfoxide ion concentration dropped to 62.5%. Montanari and coworkers found the reduction of methyl phenyl sulfoxide and dimethyl sulfoxide in 77.4% acetic acid to be second order in hydriodic acid.[5a] If we consider the hydriodic acid concentration to be equal to the acid concentration (H^+) and to the iodide concentration, then the rate equation is first order in acid and first order in iodide ion. If the acetic acid is functioning as a general acid catalyst, then we can reconcile the difference in acid dependence found by Krueger and by Montanari and coworkers. The mechanisms involving either eq 5 or eq 8–10 are consistent with Krueger's data and our interpretation of Montanari's results.

The effects of substituent changes on the phenyl group on the observed rate constants, k, were also measured. A Hammett plot of log (k/k_0) *vs.* σ had a ρ of -0.90, a correlation coefficient of 0.971, and a standard derivation of 0.08 (Figure 1).

In addition, a search for specific resonance effects was made using the procedure of Taft.[13] The first-order rate constants, k, listed in Table I were used. The four *meta*-substituted and the unsubstituted phenyl methyl sulfoxide were used to define the slope of a Hammett plot according to Taft's procedure (Figure 2). The resulting equation was log $(k/k_0) = -1.15$ with a correlation coefficient of 0.998 and a standard deviation of 0.04. Next, the log (k/k_0) values were placed on the plot using the *para* σ^0 values. These σ values are based on several reaction series in which direct resonance interaction between the reaction center and the substituted benzene ring were excluded. A deviation of a *para* value from the straight line is a measure of the greater resonance stabilization of the ground state, R_2SO, relative to the transition state, or *vice versa*, in the reaction. It should be pointed out that we can neglect resonance effects on any intermediates.

The deviations from the line, $\bar{\sigma} - \sigma^0$, where $\bar{\sigma} = -\log (k/k_0)/1.15$, are small except for the case of *p*-nitrophenyl methyl sulfoxide where it is equal to -0.27 σ units.[14] The value of k is larger than one would expect. This is due to resonance stabilization of the transition state relative to the ground state; the nitro group is accepting electrons to a greater extent in the transition state than in the ground state.

(12) Inversion of configuration at a tricoordinate sulfur atom undergoing a nucleophilic displacement reaction has been established for several reactions: exchange of alkoxy groups in sulfinate esters [H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925)]; sulfinate esters to sulfoxides [P. Bickart, M. Axelrod, J. Jacobus, and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 697 (1967)]; alkoxysulfonium salts to sulfoxides [C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965)]; and sulfoxides to sulfilimines [J. Day and D. J. Cram, *ibid.*, **87**, 4398 (1965)].

(13) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960). For a similar approach, see H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

(14) The other specific resonance effects are *p*-CH_3O, 0.04; *p*-CH_3, 0.02; and *p*-Cl, -0.07.

If an intermediate is formed in the reaction, its rate-determining decomposition by expulsion of a hydroxide ion (eq 7) or a water molecule (eq 10) is not to be expected. Neither of these processes is consistent with the specific resonance effect observed for the *p*-nitro group. Election withdrawal should not favor bond breakage with loss of either a hydroxide ion or a water molecule.

If the reaction (eq 1) is second order in acid as the literature evidence strongly suggests, we can narrow down the mechanistic possibilities to two. The first involves eq 5 as the rate-determining step; the second involves eq 8–10 with either 9 or 10 being rate determining. However, the analysis of our substituent effects argues against eq 10 as the rate-determining step. Equation 9 is also an unlikely rate-determining step. Transfer of a proton from one oxygen atom to another is usually very fast;[15] thus eq 8 is also unacceptable as it involves only one proton.

We are left with one possibility (eq 5), which satisfies the criteria of being first order in sulfoxide and first order in iodide, of involving two protons, and of not being inconsistent with the substituent effect analysis. The over-all process (eq 1) would then involve a series of steps given by eq 2, 5, and 3 in that order.[16]

Experimental Section

Sulfoxides.—All of the sulfoxides used in this work were known compounds. The melting points and boiling points of the aryl methyl sulfoxides used in this study were reported earlier.[17] The melting point (or boiling point where pressures are given) of the other sulfoxides are phenyl ethyl sulfoxide, 91–92° (0.5 mm) [lit.[18] 101–102 (1 mm)]; phenyl isopropyl sulfoxide, 85–86° (0.25 mm) [lit.[18] 127° (7 mm)]; phenyl *t*-butyl sulfoxide, 56.5–57.5° (lit.[18] 58–59°).

Procedure for Kinetic Runs.—Baker and Adamson reagent grade 70% perchloric acid and Mallinkrodt analytical reagent grade sodium iodide dried at 125° were used to prepare the acid and iodide ion stock solutions, respectively. Oxygen-free, distilled water was prepared by refluxing the water while passing a stream of prepurified nitrogen through it. All solutions were prepared under nitrogen. Transferral of stock solutions to the reaction flasks was done by syringe. All flasks were sealed by rubber serum caps.

Three stock solutions were prepared: one of perchloric acid, one of sulfoxide dissolved in the perchloric acid, and one of sodium iodide.

The reaction vessels were 125-ml erlenmeyer flasks. Sodium iodide solution (10 ml) was added to each of the flasks followed by 14 ml of perchloric acid solution. After reaching constant temperature (35.00 ± 0.02°), 1 ml of sulfoxide solution was added. At the end of the appropriate time, each flask was cooled and crushed ice was added to quench the reaction. The iodine liberated was titrated with standard sodium thiosulfate solution. The acid concentration of the runs was determined by titration with standardized sodium hydroxide.

The amount of iodine formed by dissolved oxygen was corrected for by running a blank and assuming that the iodine formation was proportional to time.

The pseudo-first-order rate constants were obtained from the slope of log [R_2SO] *vs.* time plots. An IBM 360 digital computer was used.[20] Generally seven points were included in these plots excluding the initial concentration. All of the data were also plotted graphically in order to see if any deviation from linearity was present. Second-order rate constants were determined graphically.

(15) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

(16) NOTE ADDED IN PROOF.—See D. Landini, F. Montanari, G. Modena, and G. Scorrano, *Chem. Commun.*, 86 (1968), for the results of a study on the acid dependence of the reduction of sulfoxides by halide ions which complements the investigation described above.

(17) K. K. Andersen, W. H. Edmonds, J. B. Biasotti, and R. A. Strecker, *J. Org. Chem.*, **31**, 2859 (1966).

(18) A. Cerniani, G. Modena, and P. Todesco, *Gazz. Chim. Ital.*, **90**, 3 (1960).

(19) I. V. Baliah and R. Varadachari, *J. Indian Chem. Soc.*, **37**, 321 (1960).

(20) The authors wish to thank Professor J. J. Uebel for supplying the least-squares plot computer program.

A Nuclear Magnetic Resonance Investigation of the Conformational Preferences of Isomeric Thioxanthenol Sulfoxides and Related Compounds

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The trimethylsilyl and acetyl derivatives of isomeric thioxanthenol sulfoxides and 2-chlorothioxanthenol sulfoxides have been prepared. Configurations have been assigned to these compounds on the basis of their ultraviolet spectra. The parent alcohols, these derivatives, and related compounds have been assigned preferred conformations on the basis of their nmr spectra. The sulfinyl group has been found to prefer the pseudo-equatorial conformation. *trans*-Thioxanthenol sulfoxide appears to exist in the same conformation in solution as in the solid state. 9-Trimethylsiloxythioxanthene prefers that conformation in which the substituent occupies the pseudo-equatorial position.

The thioxanthene ring system serves as an excellent model for stereochemical studies of diaryl sulfur compounds because of the conformational restrictions inherent in this heterocyclic ring system. The initial report of our studies in this area presented the results of the single crystal X-ray analysis of *trans*-thioxanthen-9-ol 10-oxide (1β).[2] As part of a general study of the stereochemistry of this system we have investigated the conformational preferences in solution of a number of *cis*- and *trans*-9-substituted thioxanthene sulfoxides. The purpose of this report is to present the results of an nmr study of the conformational preferences of some of these compounds. Furthermore, the surprising differences[2,3] in the ultraviolet spectra of 1β and 1α (the corresponding *cis* isomer) suggested[3] that ultraviolet spectroscopy could serve as a simple criterion for assigning configuration to other pairs of thioxanthene sulfoxides which possess a dipolar functional group in the 9 position. This report broadens the application of ultraviolet spectroscopy in assigning configurations to heterocyclic sulfoxides.

(1) To whom inquiries should be directed. Support of this research by U. S. Public Health Service Research Grant No. CA-10139 from the National Cancer Institute is gratefully acknowledged.

(2) A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *J. Org. Chem.*, **32**, 2465 (1967).

(3) A. L. Ternay, Jr., and D. W. Chasar, *ibid.*, **32**, 3814 (1967).

TABLE I

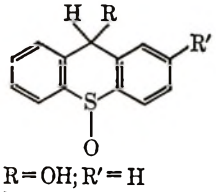
Compound	Ultraviolet spectrum[a-c]	Infrared spectrum[d,e]
cis-Thioxanthen-9-ol 10-oxide (1α)[f]	272 (866); 232 (8300); *204* (41,900)	1010, 1098
trans-Thioxanthen-9-ol 10-oxide (1β)[f]	285 (558); 273 (1620); *250* (4420); 233 (8060); *214* (42,000)	1002, 1023, 1077
cis-2-Chlorothioxanthen-9-ol 10-oxide (2α)	253 (6350); *234* (1290); *205* (44,300)	1028, 1066, 1100
trans-2-Chlorothioxanthen-9-ol 10-oxide (2β)	283 (1100); *255* (6690); 235 (11,000); *215* (39,000)	1010, 1031, 1071, 1100
cis-9-Trimethylsiloxythioxanthene 10-oxide (5α)	272 (830); 268 (1150); 263 (1760); 234 (8280); 228 (9900); *204* (41,300)	1039
trans-9-Trimethylsiloxythioxanthene 10-oxide (5β)	271 (1700); 263 (2700); *250* (4040); *215* (45,800)	1034, 1049, 1079
cis-2-Chloro-9-trimethylsiloxythioxanthene 10-oxide (6α)	279 (515); 268 (1880); 261 (3500); 252 (6400); 237 (12,900); *234* (13,100); 209 (41,200); *205* (43,300)	1035
trans-2-Chloro-9-trimethylsiloxythioxanthene 10-oxide (6β)	282 (900); 271 (3100); 263 (5000); 253 (6050); 235 (10,700); *216* (42,000)	1035, 1050, 1075, 1095
cis-9-Acetoxythioxanthene 10-oxide (7α)	283 (230); 272 (980); 268 (1310); 262 (2010); 233 (9200); 227 (11,100); *203* (41,200)	1032, 1093
trans-9-Acetoxythioxanthene 10-oxide (7β)	276 (1110); 269 (1820); 262 (2550); 250 (3900); 231 (9250); *215* (45,800)	1012, 1043, 1095
cis-2-Chloro-9-acetoxythioxanthene 10-oxide (8α)	286 (270); 261 (370); 251 (6900); *233* (13,600); 209 (40,200); *204* (44,000)	1036, 1078
trans-2-Chloro-9-acetoxythioxanthene 10-oxide (8β)	284 (780); 276 (1690); 269 (2800); 262 (4200), 254 (5620); 234 (12,100); *216* (44,800)	1020, 1043, 1079, 1085

[a] Spectra in 95% ethanol. [b] Wavelengths are in mμ, followed by the molecular extinction coefficient (ε) in parentheses; maxima are in italics, and other values refer to shoulders or inflections. [c] Several poorly defined points have been omitted; complete curves are available upon request. [d] Spectra were obtained as Nujol mulls. [e] Only those bands of moderately strong intensity, occurring in the 1000–1100-cm^{-1} region, are listed. Values are in cm^{-1}. [f] See ref 2.

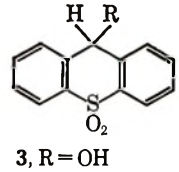
Results and Discussion

Configurational Assignments.—It was found[2] that *cis*- and *trans*-thioxanthenol sulfoxides (1α and 1β) possess strikingly different short-wavelength transitions in the ultraviolet region of the spectrum. Thus, 1α possesses an intense (ε *ca.* 40,000) transition at 204 mμ, whereas 1β possesses its intense (ε *ca.* 40,000) transition, 10 mμ to longer wavelengths, at 214 mμ. A similar pattern was observed for the isomeric 2-chlorothioxanthen-9-ol 10-oxides (2α and 2β).[4]

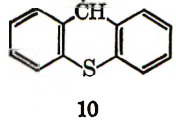
The corresponding acetyl and trimethylsilyl derivatives of 1α, 1β, 2α, and 2β have now been prepared, starting from the appropriate alcohols. While the acetylation reaction is accompanied by configurational interconversion, the trimethylsilylation proceeds with little or no stereomutation. The derivatives which have been prepared possess the same pattern in their ultraviolet spectra that has been observed in the parent alcohols. Thus, one of each of the isomeric pairs of derivatives (those labeled α) exhibits an intense (ε *ca.* 40,000) short-wavelength transition at *ca.* 10 mμ below the intense short-wavelength transitions observed for the other member of each of the isomeric pairs of derivatives (those labeled β). The appropriate data are collected in Table I.



1, R = OH; R′ = H
2, R = OH; R′ = Cl
5, R = OSi(CH$_3$)$_3$; R′ = H
6, R = OSi(CH$_3$)$_3$; R′ = Cl
7, R = OCOCH$_3$; R′ = H
8, R = OCOCH$_3$; R′ = Cl



3, R = OH
4, R = OSi(CH$_3$)$_3$
9, R = OCOCH$_3$



10

The infrared spectra of these derivatives support the assignment of configuration based upon their method of synthesis (for the trimethylsilyl derivatives) and upon their ultraviolet spectra (for trimethylsilyl and acetyl derivatives). It had been established previously[2] that 1α and 2α display a simpler infrared absorption pattern in the S–O stretching region than do the corresponding *trans* isomers (1β and 2β). The data collected in Table I reveal that all of the isomers labeled β possess two strong absorptions in the region from 1050 to 1000 cm^{-1} while all of the α isomers exhibit only a single strong absorption in this region.

Thus, as in the case of the isomeric sulfoxide alcohols (1α,β and 2α,β), both infrared and ultraviolet spectra can be employed for configurational assignments. The subsequent discussion indicates that nmr spectra can also be used as an aid in configurational assignments.

Conformational Analysis.—Several properties of the nmr spectra of the compounds under discussion have been employed in order to assign conformational preference.[5,6]

It is instructive to begin with an analysis of the conformational distribution within thioxanthenol sulfone (3). This compound displays a moderately intense absorption at 3508 cm^{-1} (1.3×10^{-5} *M*, CCl_4), considered to arise from an intramolecular hydrogen bond between the hydroxyl group and the sulfonyl group. The nmr spectrum of 3 offers support for the existence of this hydrogen bond. Thus, even in deuteriochloroform it is possible to observe coupling between the methine proton (C-9) and the hydroxyl proton (Table II). Since rapid exchange would be expected to

(4) Throughout this paper the designations α and β will be assigned to the *cis* and *trans* configurations, respectively.

(5) It seems unreasonable to assign to these compounds a static conformation. Rather, these results probably represent the preferred conformation in a conformationally mobile system. A similar conclusion has been reached for the thianthrene system.[6]

(6) (a) K. F. Purcell and J. R. Berschied, Jr., *J. Amer. Chem. Soc.*, **89**, 1579 (1967); (b) J. Chickos and K. Mislow, *ibid.*, **89**, 4815 (1967).

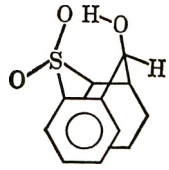
TABLE II
NMR SPECTRA[a,b]

Compd	δ_{C-H}	$\delta_{aromatic}$	$\delta_{Si(CH_3)_3}$	δ_{OCOCH_3}
1α[c,d]	330	442–480		
1β[c,d]	359	442–465		
		474–486		
5α	326	440–484	21	
5β	359	440–460	6	
		470–490		
6α	325	437–485	22	
6β	360	438–460	7	
		469–484		
7α	397	440–465		150
		470–492		
7β	413	437–468		116
		470–490		
8α	396	437–467		152
		467–488		
8β	412	440–471		118
		471–492		
3[c]	361[e]	440–490		
4	377	445–491	22	
9	430	440–457		140
		473–490		
10	317	426–467	16	

[a] Spectra were obtained from deuteriochloroform solutions. Chemical shifts are reported in hertz downfield from internal TMS; values are reported to the nearest hertz. [b] Copies of the spectra are available upon request. [c] The spectrum could only be obtained by the computer averaging of transients. [d] The position of the OH resonance could not be determined under these conditions. [e] This frequency represents the center of a doublet with J = 8.0 Hz. The OH proton appears as a doublet (J = 8.0 Hz) centered at 197 Hz.

average out this coupling, it is to be concluded that rapid exchange is not occurring and a hydrogen-bonded proton would be consistent with this interpretation.[7] The magnitude of the coupling, moreover, can be readily understood in light of the transoid arrangement of the H–O–C–H bond that would be required for the formation of an intramolecular hydrogen bond.[8]

Thus, both the infrared spectra and the nmr spectra indicate that thioxanthenol sulfone exists in the conformation of structure **3**.



3

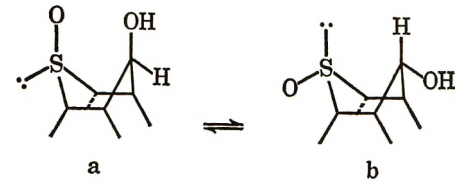
It is suggested that the line position of the methine proton of thioxanthenol sulfone (361 Hz) should be representative of a methine proton in this series that is in the pseudo-equatorial position and *relatively* removed from the magnetic anisotropy of the S–O bond.

The trimethylsilyl derivative of **3** (**4**) might be expected to prefer a conformation in which the 9 substituent exists in the pseudo-equatorial array. Moreover, Carruthers'[9] suggestion that 9-*t*-butyl-9,10-dihydroanthracene exists with the *t*-butyl group in the pseudo-equatorial position supports the availability of this position for the trimethylsiloxy moiety.

If this conformation is favored, one might anticipate a downfield shift of the methine resonance because of the sulfone anisotropy.[10] Indeed, the line position (377 Hz) of this proton occurs 16 Hz downfield from the corresponding alcohol. Johnson–Bovey calculations suggest that a pseudo-axial proton should be more shielded than a pseudo-equatorial proton by virtue of the ring anisotropy.[11] Thus, the 16-Hz downfield shift represents the composite result of the sulfonyl and the aryl anisotropies.

The resonance frequency (359 Hz) of the methine proton of *trans*-thioxanthenol sulfoxide (1β) is almost identical with that which is observed for the corresponding sulfone and suggests, therefore, that the preferred conformation of 1β is that in which the methine proton occupies the pseudo-equatorial geometry. Thus, it appears that the conformation observed for 1β in the solid state[2] is also the preferred conformation in solution.[12]

cis-Thioxanthen-9-ol 10-oxide (1α) can be thought of as existing in two possible conformations. The methine proton would be expected to absorb at *ca.* 360 Hz if conformer a predominates. In reality the resonance frequency is upfield of this value, occurring at 330 Hz. This increased shielding is interpreted as signifying a preponderance of conformer b.



a **b**

The coupling that was observed in the spectrum of **3** appears to be absent in the spectrum of 1α (Table II). These results, however, should not be construed as indicating that the hydrogen bond present in **3** is stronger than that which might have been thought to exist in pseudo-diaxial 1α (*i.e.*, that the sulfonyl is a more powerful hydrogen-bond acceptor than is the sulfoxide group). Whereas it is tempting to draw such a conclusion, the different geometric requirements of the sulfonyl and the sulfinyl moieties may, at least in part, control the preferred conformation of the hydroxyl group.

A similar argument, based upon the line position of the methine proton, also can be applied to the trimethylsilyl derivatives of the corresponding alcohols. To wit, the *cis* isomers (5α and 6α) exhibit this absorption at *ca.* 325 Hz while the corresponding *trans* isomers (5β and 6β) exhibit this absorption at *ca.* 360 Hz (Table II). These frequencies are consistent with the α isomers possessing an axial methine proton and the β isomers possessing an equatorial methine proton.

It is not possible to apply this procedure directly to the corresponding acetates of these alcohols since the methine resonance position has been shifted downfield (see Table II), presumably because of the inductive effect and the anisotropy associated with the acetyl group.

(7) We have examined the nmr spectra of benzhydrol, xanthydrol, and thioxanthenol, in addition to the derivatives of thioxanthenol presented in this paper. Thioxanthenol sulfone (**3**) is the only compound of those examined which displays this coupling in deuteriochloroform.

(8) J. J. Uebel and H. W. Goodwin, *J. Org. Chem.*, **31**, 2040 (1966), and references cited therein.

(9) W. Carruthers and G. E. Hall, *J. Chem. Soc., Sect. B*, 861 (1966).

(10) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966), and references cited therein.

(11) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(12) Strictly speaking, these conclusions are only applicable to chloroform solutions.

However, even in this instance the methine resonance for the two stereoisomers (7α,β and 8α,β) is separated by 16 Hz; the *trans* isomers exhibit a resonance farther downfield than the corresponding *cis* isomers (413 *vs.* 397 Hz). On the bases of these chemical-shift data, it is concluded that the conformational distribution within the various acetates is similar to that which has been observed for the corresponding alcohols and their trimethylsiloxy derivatives.

In the compounds under discussion the C-9–H bonds can assume two extreme arrays relative to the planes of the aromatic rings. In light of the demonstrated dependence of long-range coupling upon geometry,[13] it might be anticipated that the band width of a pseudo-axial proton would be broadened relative to that of a pseudo-equatorial proton.

The trimethylsilyl derivatives of the various alcohols were chosen as subjects for *spin-decoupling experiments*. The results of these double irradiation experiments are included in Table III. These data reveal that there

TABLE III

SPIN DECOUPLING OF TRIMETHYLSILYL DERIVATIVES[a]

Compd	δ_{irr}[b]	w_0[c]	w_{irr}[d]
10	444	5.6	2.5
4	466	6.1	2.3
6α	460	6.0	2.5
6β	457	4.0	2.5

[a] Decoupling experiments were performed on deuteriochloroform solutions using a Varian Model HA-100 in conjunction with an H. P. Model 200CD wide-range oscillator (sweep time, 250 secs; sweep width, 250 Hz). [b] The frequency of irradiation, calculated for 60 MHz. [c] Band width at half-height (mm) before irradiation. [d] Band width at half-height (mm) during irradiation.

are, indeed, differences in the half-band widths of the C-9 protons in these isomers, the *cis* isomer (α) possessing a broader absorption than the corresponding *trans* isomer. This suggests that the C-9 proton of an α isomer is coupled to the aromatic protons to a larger extent than is the C-9 proton of the corresponding β isomer. Confirmation of this hypothesis was obtained by irradiating the region of aromatic absorption; decoupling resulted in a considerable sharpening of the resonance line for the α isomer but minor sharpening for the β isomer.

These decoupling experiments support the conformational assignment already suggested for **4**, 6α, and 6β.

The spin-decoupling technique was also applied to 9-trimethylsiloxythioxanthene (**10**). The decrease in the half-band width of the methine resonance (Table III) is taken as evidence that the methine proton exists to a considerable degree in the pseudo-axial position. This observation suggests that the preferred conformation of **4** may *not* reflect the results of interaction between a sulfonyl oxygen atom and the trimethylsiloxy group but, rather, simply the preferred conformation of the trimethylsiloxy group in this particular ring system. Thus, it may not be correct to assume, *a priori*, that a substituted 9,10-dihydroanthracene, or a heterocyclic analog,[14] bearing a nonpolar substituent on a *meso* position will exist with that substituent in the pseudo-axial conformation.[15]

Purcell[6a] has recently demonstrated that those protons *peri* to the sulfoxide group in thianthrene disulfoxides are deshielded relative to the remainder of the aryl protons. Moreover, although the conformation of the sulfoxide oxygen atom affects the chemical shift of these protons, they are always deshielded relative to the other aryl protons. Examination of the data in Table II reveals that the regions due to aromatic absorptions for the α and β stereoisomers are different, the α possessing a broad multiplet while the β exhibit two distinct regions of absorption. This is quite clear for the isomers of **1**, **5**, and **6**. The inductive effect and/or the anisotropic effect of the acetyl moiety may account for the less clear separation observed in **7** and **8**. However, within a given pair of isomers the low-field limit is essentially the same. Moreover, for all of the compounds that have been examined, this value is fairly constant (*ca.* 485–490 cps). This suggests that, for all of the compounds that have been examined, the hydrogens *peri* to the sulfoxide group are in the same environment and the disappearance of two distinct regions in the nmr is due to a change in the shielding of the hydrogens *peri* to C-9 as the substituent at C-9 changes conformation.

It appears, in summary, that in all of the sulfoxides which have been discussed, *the sulfinyl oxygen occupies the pseudo-equatorial position.*[16]

What the *most* significant factor is in dictating this conformational preference has yet to be determined. However, several considerations may be involved including (a) a preferred conformation for electronic interaction between the sulfinyl group and the aryl π system, (b) hydrogen bonding (or some other attractive interaction) between the aryl *peri* hydrogens and the sulfinyl oxygen atom, or (c) a purely steric (bulk) effect, similar to that which probably dictates the conformation of **10**. A study of the temperature dependence of these and related spectra will be the subject of a future communication.

The nmr spectra of secondary alcohols have been studied in dimethyl sulfoxide (DMSO) because of the coupling that is exhibited between the hydroxylic proton and the corresponding methine proton.[8,17] The magnitude of the coupling constant that is observed for substituted cyclohexanols has been used as a conformational probe.[8] The spectra of *cis*- and *trans*-thioxanthen-9-ol 10-oxides (and the corresponding 2-chloro derivatives) in d_6-DMSO have been determined. The data presented in Table IV clearly reveal that J is dependent upon configuration. Indeed, the magnitude of the difference between the J's observed for the two stereoisomers is much larger than the values observed[8] in the cyclohexanols. It is tempting to construe the large differences in J_{HCOH} to arise because of a favored cisoid rotamer for the β isomer (*trans* configuration, $J \approx 3$ Hz) and a favored transoid rotamer for the α isomer (*cis* configuration, $J \approx 6$ Hz). Such a picture would be consistent with the structure of the β isomer in

(13) See, for example, P. T. Lansbury, J. F. Bieron, and A. J. Lacher, *J. Amer. Chem. Soc.*, **88**, 1482 (1966), and references cited therein.

(14) The geometries of the folded analogs, while not identical with that of 9,10-dihydroanthracene, are, nonetheless, quite similar. For pertinent reports, see ref 2 and citations therein.

(15) A. H. Beckett and B. A. Mulley, *Chem. Ind.* (London), 146 (1955), and subsequent papers in this series.

(16) Thioxanthene sulfoxide also appears to prefer that conformation in which the sulfinyl oxygen atom is pseudo-equatorial (unpublished results, with L. Ens).

(17) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

TABLE IV

NMR SPECTRA IN d_6-DMSO[a]

Compd	δ_{C-H}[b]	δ_{OH}[b,c]	J_{CHOH}
1α	328	418	6.5
1β	360	378	3.1
2α	329	426	6.3
2β	360	387	3.4

[a] Values are reported in hertz downfield from internal TMS. [b] The center of the doublet. [c] The resonance position of the hydroxyl proton was found to be independent of concentration over the range examined. Identification of the hydroxyl absorption was achieved by observing the disappearance of the signal upon addition of D_2O.

the solid state, the H–C–O–H having been shown[2] to be 34°.

Experimental Section[18]

The preparation of the following compounds has already been described:[2,3] *cis*- and *trans*-thioxanthen-9-ol 10-oxide (1α,β); *cis*- and *trans*-2-chlorothioxanthen-9-ol 10-oxide (2α,β); and thioxanthen-9-ol 10,10-dioxide (**3**).

9-Trimethylsiloxythioxanthene 10,10-Dioxide (4).—Thioxanthen-9-ol 10,10-dioxide (**3**) (0.50 g, 0.0020 mol) was dissolved, with shaking, in a mixture of pyridine (10 ml), hexamethyldisilazane (2 ml), and trimethylchlorosilane (1 ml).[19] After 5 min, water (40 ml) was added and the upper layer was evaporated with nitrogen. Water (*ca.* 300 ml) was then added and the resultant solid was removed by filtration. A chloroform solution of this solid was dried (magnesium sulfate) and the solvent was removed (stream of nitrogen) to afford 0.53 g (0.0017 mol) (85% yield) of **4**, mp 122–124°. This solid was homogeneous on tlc[20] and the infrared spectrum exhibited intense absorptions at 1305, 1250, 1200, 1163, 1135, 1108, 1052, 884, 845, and 750 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_3SSi$: C, 60.34; H, 5.70; S, 10.07; Si, 8.82. Found: C, 60.15; H, 5.68; H, 10.07; Si, 8.55.

***cis*-9-Trimethylsiloxythioxanthene 10-Oxide (5α).**—The general method described for **4** was used for **5α**. Thus, 1.0 g (0.0044 mol) of **1α** was treated with a mixture of 20 ml of pyridine, 4 ml of hexamethyldisilazane, and 2 ml of trimethylchlorosilane to afford 0.86 g (0.0029 mol) (66% yield) of a white solid, mp 118–119.5°. Purification by vacuum sublimation afforded a material which was homogeneous on tlc, mp 119–120.6°.

Anal. Calcd for $C_{16}H_{18}O_2SSi$: C, 63.54; H, 6.00; S, 10.60; Si, 9.28. Found: C, 63.32; H, 5.87; S, 10.58; Si, 9.06.

***trans*-9-Trimethylsiloxythioxanthene 10-oxide (5β)** was prepared in the same manner, starting with **1β**. The product, mp 99–101°, was obtained in an 80% yield and was homogeneous on tlc.

Anal. Found: C, 63.29; H, 5.92; S, 10.35; Si, 8.94.

***cis*-2-Chloro-9-trimethylsiloxythioxanthene 10-Oxide (6α).**—The general method described above was used to convert 0.89 g (0.0034 mol) of **2α** into crude **6α** (1.12 g, 0.0033 mol, 99%), mp 169–170.5°. Recrystallization from ethyl acetate afforded 0.72 g of **6α**, mp 170.5–171.5°. This material was homogeneous on tlc.

Anal. Calcd for $C_{16}H_{17}O_2ClSSi$: C, 57.04; H, 5.09; Cl, 10.52; S, 9.52; Si, 8.34. Found: C, 56.90; H, 5.12; Cl, 10.23; S, 9.66; Si, 8.12.

***trans*-2-Chloro-9-trimethylsiloxythioxanthene 10-oxide (6β)** was prepared in the same manner. The crude product, mp 148–150°, was obtained in a 92% yield. Recrystallization from ethyl acetate afforded a material, mp 151–152° (74% yield), which was homogeneous on tlc.

Anal. Found: C, 57.18; H, 5.07; Cl, 10.46; S, 9.49; Si, 8.15.

9-Acetoxythioxanthene 10,10-Dioxide (9).—Thioxanthenol sulfone (**3**) was acetylated according to the procedure described by Fehnel.[21] Thus, 0.24 g (0.00098 mol) of **3** afforded 0.28 g (0.00097 mol) (98%) of **9**, mp 156–157.5° (lit.[21] mp 155.5–56°). The infrared spectrum (Nujol) possessed absorptions at 1755, 1300, 1160, and 1200 cm^{-1}.

***trans*-9-Acetoxythioxanthene 10-Oxide (7β).**—A mixture (*ca.* 1:1) of **1α** and **1β** (3.00 g, 0.013 mol) was dissolved in acetic anhydride (15 ml) containing 2 drops of 96% sulfuric acid. The resultant solution was shaken for 5 min. After an additional 5 min, the solution was diluted with water (30 ml) and then allowed to stand for 1 hr. The resulting solid was removed by filtration, washed with water, and dried under vacuum (sodium hydroxide) to afford 3.37 g (0.012 mol, 95% yield) of crude product, mp 127–141°. The nmr indicated that this product consisted of *ca.* 80% *trans* isomer and 20% *cis* isomer.[22]

Several recrystallizations from ethyl acetate afforded 1.8 g (0.0066 mol, 51% yield) of **7β**, mp 149–150°.

Anal. Calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44; S, 11.74. Found: C, 65.92; H, 4.45; S, 11.79.

***cis*-9-Acetoxythioxanthene 10-Oxide (7α).**—The ethyl acetate mother liquors from the recrystallizations described above were combined and concentrated to *ca.* one-third the initial volume (steam bath). Upon cooling, two different types of crystals were deposited. The yellow crystalline material (the other material was colorless) was found to be **7β** contaminated with thioxanthone. The colorless crystals were found (ir, nmr) to be **7α** contaminated with **7β**. These colorless crystals were removed mechanically. This operation was repeated on several batches of mother liquors to afford *ca.* 0.5 g of crude **7α**. Recrystallization (ethyl acetate) afforded 0.38 g (0.0014 mol, 13%) of **7α**, mp 149.5–151°. Although **7α** and **7β** have similar melting points, their spectral behavior (Tables I and II) clearly indicates that these are stereoisomers.

Anal. Found: C, 66.05; H, 4.49; S, 11.81.

***cis*- and *trans*-2-Chloro-9-acetoxythioxanthene 10-Oxide (8α,β).**—A mixture of **3α** and **3β** (2.00 g, 0.0076 mol) was dissolved in acetic anhydride (8 ml) with 1 drop of 96% sulfuric acid and then worked up as described for **7β** to afford 2.13 g (0.0070 mol, 92%) of a light yellow solid, mp 133–142°. (The nmr indicated that this mixture contained both stereoisomers.)

Slow crystallization of this solid from ethyl acetate afforded two types of crystals. Mechanical separation afforded 0.12 g of a yellow solid (mp 169–180°) and 1.51 g of a white, crystalline solid, mp 139–148°.

Recrystallization of the yellow solid from ethyl acetate afforded 0.07 g (0.0002 mol, 3.0% yield) of a feathery, white solid, **8α**, mp 183–184°.

Anal. Calcd for $C_{15}H_{11}O_3ClS$: C, 58.73; H, 3.61; S, 10.45; Cl, 11.56. Found: C, 58.55; H, 3.81; S, 10.60; Cl, 11.67.

The white, crystalline solid, mp 139–148°, was recrystallized from ethyl acetate to afford 1.13 g (0.0037 mol, 49%) of **8β**, mp 147–148.5°.

Anal. Found: C, 58.56; H, 3.64; S, 10.63; Cl, 11.78.

9-Trimethylsiloxythioxanthene (10).—Thioxanthen-9-ol[2] (5.0 g, 0.023 mol) was refluxed 15 hr in 50 ml of hexamethyldisilazane in the presence of 0.5 g of sea sand (Fisher ignited). Upon cooling, thioxanthenol precipitated out. The supernatant was concentrated to one-third the initial volume to afford more solid. The remaining solution was concentrated to dryness (stream of nitrogen) to afford 4.1 g of an off-white solid, mp 69–100°. Vacuum sublimation of this material yielded 1.5 g of a white solid, mp 67–80°. Four recrystallizations (95% ethanol) afforded 0.89 g (0.0031 mol, 13%) of **10**, a white, crystalline solid, mp 82–84. The infrared spectrum of **10** exhibited intense absorptions at 1254, 1200, 1105, 1060, 885, 845, and 745 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}OSSi$: C, 67.09; H, 6.33; S, 11.19; Si, 9.80. Found: C, 67.30; H, 6.09; S, 11.38; Si, 9.55.

(18) Melting points were obtained in a Mel-Temp apparatus and are corrected. Infrared spectra were recorded on either a Beckman Model IR-8 or a Perkin-Elmer Model 521. Ultraviolet spectra (320-200 mμ) were recorded on a Cary Model 15. Nmr spectra were recorded on a Varian Model A-60 or a Varian Model HA-60A equipped with a Varian Model C-1024 time-averaging computer except where indicated. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatographies were performed employing glass plates coated with silica containing a fluorescent indicator. Development was achieved with ethyl acetate, chloroform or chloroform–ethyl acetate mixtures (9:1 v/v). Ultraviolet light and/or iodine vapor were used for visualization.

(19) The procedure is that of C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(20) Several preparations afforded small amounts of **3**. Vacuum sublimation readily purified these samples.

(21) E. A. Fehnel, *ibid.*, **71**, 1063 (1949).

(22) Preparation of all of the isomeric acetates described herein, starting with *isomerically pure* sulfoxide alcohol, inevitably led to mixtures consisting of approximately 80% *trans* isomer and 20% *cis* isomer. Indeed, we have observed that the isomeric acetates do equilibrate under the reaction conditions (acetic anhydride and traces of concentrated sulfuric acid). The mechanism of the equilibration is under investigation.

Registry No.—1α, 13096-56-5; 1β, 13096-57-6; 2α, 10396-60-1; 2β, 13096-61-2; **3**, 16354-75-9; **4**, 16354-76-0; 5α, 16354-77-1; 5β, 16354-78-2; 6α, 16354-79-3; 6β, 16354-80-6; 7α, 16354-81-7; 7β, 16354-82-8; 8α, 16354-83-9; 8β, 16354-84-0; **9**, 3353-98-8; **10**, 16354-86-2.

Reactions of Mercuric Salts with Bis(diethylthiocarbamoyl) Disulfide and Benzenesulfenyl Chloride

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When mercuric carboxylates were treated with bis(diethylthiocarbamoyl) disulfide (1), acid anhydrides were obtained in good yields along with mercuric diethyldithiocarbamate and an unidentified oxygenated product. Further, it was found that treatment of mercuric carboxylates with 2 equiv of benzenesulfenyl chloride (5) gave acid anhydrides, diphenyl disulfide, and mercuric chloride in high yields. A transient intermediate of this reaction, sulfenyl carboxylate, was trapped by treating a mercuric carboxylate with 5 in the presence of an olefin. Reactions of mercuric thiolates with these organic sulfur compounds were also studied.

As part of a continuing study on the behavior of organic sulfur compounds in redox reaction systems, reactions of lead thiolates with disulfides were examined in our laboratory[1] (eq 1). It was concluded that the

$$Pb(SR)_2 + R'SSR' \longrightarrow Pb(SR')_2 + RSSR \quad (1)$$

R, R′ = C_6H_5, $C_6H_5\overset{\|}{C}(O)$, $C_6H_5\overset{\|}{C}(S)$, $Et_2N\overset{\|}{C}(S)$

oxidizing power of the disulfides increases in the following order: diphenyl disulfide < dibenzoyl disulfide < bis(thiobenzoyl) disulfide < bis(diethylthiocarbamoyl) disulfide. The present paper deals with the reactions of some mercuric salts, such as mercuric carboxylates and mercuric thiolates, with some sulfides or benzenesulfenyl chloride.

In the first place, the reaction of a metal salt having the metal–oxygen bond, such as lead, silver, zinc, and mercuric acetates, was tried with the assumption that an oxidative coupling product, organic diacyl peroxide, and a metal salt of a thiol would result by the following redox reaction (eq 2). Among various metal acetates

$$M(O\overset{\|}{C}CH_3)_2 + R'SSR' \not\longrightarrow M(SR')_2 + CH_3\overset{\|}{C}OO\overset{\|}{C}CH_3 \quad (2)$$

examined, mercuric and silver[2] acetates were found to react with bis(diethylthiocarbamoyl) disulfide (1) at room temperature, while cadmium, lead, and zinc acetates did not react in boiling chloroform. In addition, it was established that diphenyl disulfide and dibenzoyl disulfide did not react with mercuric acetate in boiling chloroform, and the starting materials were recovered quantitatively. This result suggests that the reactivities of the disulfides in this reaction depend on the oxidizing power of the disulfides.

Next, the reactions of various mercuric carboxylates with disulfide 1 were studied in detail. Contrary to our expectations, diacyl peroxides could not be obtained when mercuric carboxylates were treated with 1 at room temperature. Instead, acid anhydrides and mercuric diethyldithiocarbamate (2) were obtained in good yields together with a substantial amount of a yellow precipitate. Similarly, the anhydride of carbobenzyloxyglycine was also obtained from the corresponding mercuric salt in 72% yield as shown in Table I. However, when mercuric propionate or benzoate was allowed to react with 1 in the presence of water under the same conditions, 66 or 95% of the corresponding acid and 86 or 96% of 2 were obtained. Gas evolution was not observed in the reaction (eq 3).

TABLE I
REACTIONS OF MERCURIC CARBOXYLATES WITH BIS(DIETHYLTHIOCARBAMOYL) DISULFIDE

Mercuric carboxylate	Solvent	Yield, % Anhydride	Yield, % $(Et_2N\overset{\|}{C}S)_2Hg$
Acetate	Benzene	68	75
Propionate	CH_2Cl_2	84	50
Butyrate	CH_2Cl_2	86	54
Benzoate	CH_2Cl_2	67	53
Succinate	CH_2Cl_2	88	76
Phthalate	Benzene	57	76
Cbo-Gly	Dioxane	72	68

$$(RC\overset{\|}{O})_2Hg + (Et_2N\overset{\|}{C}S)_2 \longrightarrow (RC\overset{\|}{O})_2O + (Et_2N\overset{\|}{C}S)_2Hg \quad (3)$$

1 2

The structure of 2 was confirmed by elemental analysis and the infrared spectrum. In the case of mercuric acetate, propionate, and butyrate, the yellow precipitate decomposed in the reaction mixture at room temperature in about 20 min into a black solid. This may be mercuric sulfide. With mercuric succinate and phthalate, the yellow precipitate (3) was rather stable and could be isolated. Compound 3 might be an oxygenated product. The infrared spectrum of 3 showed a strong band at 1700 cm^{-1}. Recrystallization of 3 from acetonitrile gave pale yellow crystals (4) whose infrared spectrum differed from that of 3. The infrared spectrum of 4 was almost identical with that of 2, but showed no band at 1700 cm^{-1}. Elemental analysis and the infrared spectrum of 4 indicated a molecular formula of $C_{10}H_{20}N_2O_6S_4Hg$ or $C_{10}H_{20}N_2O_4S_5Hg$, which corresponds formally to a combination of 2 and O_6 or of 2, SO_2, and O_2, but its structure

(1) T. Mukaiyama and T. Endo, *Bull. Chem. Soc. Jap.*, **40**, 2388 (1967).

(2) In this case, only silver diethyldithiocarbamate could be isolated in 94% yield.

remains unknown. As demonstrated above, the mechanism for this reaction has not yet been established.

Further, an anhydride was prepared by a one-step procedure[3] from a free carboxylic acid, diarylmercury, and **1**. When 2 equiv of benzoic acid and di-*p*-anisylmercury were allowed to react with **1** in boiling benzene for 30 min, benzoic anhydride (72%) and **2** (50%) were obtained along with a substantial amount of a black solid (eq 4).

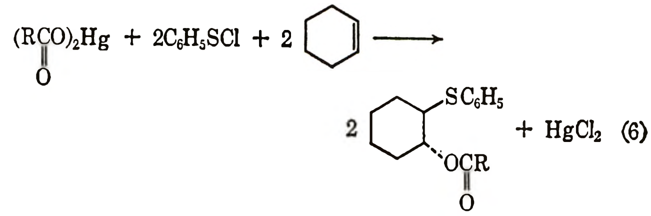
$$2C_6H_5CO_2H + (p\text{-}CH_3OC_6H_4)_2Hg + (Et_2NC(=S)S)_2 \longrightarrow (C_6H_5C(=O))_2O + 2C_6H_5OCH_3 + (Et_2NC(=S)S)_2Hg \quad (4)$$

It was also expected that the use of sulfenyl chloride in place of disulfide **1** in the above reaction (eq 3) would lead to the formation of acid anhydrides along with the disulfide and mercuric chloride. Indeed, mercuric carboxylates reacted readily with 2 equiv of benzenesulfenyl chloride (**5**) at room temperature to give acid anhydrides, diphenyl disulfide, and mercuric chloride in high yields.[4] However, when methyl benzenesulfenate or N,N-diethylbenzenesulfenamide was used as the sulfenyl compound in this reaction, no reaction occurred, and the starting materials were recovered almost quantitatively. No gas evolution was observed in the reaction with benzenesulfenyl chloride (eq 5). The anhydrides were obtained by a

$$(RC(=O)O)_2Hg + 2C_6H_5SCl\ (\mathbf{5}) \longrightarrow (RC(=O))_2O + C_6H_5SSC_6H_5 + HgCl_2 \quad (5)$$

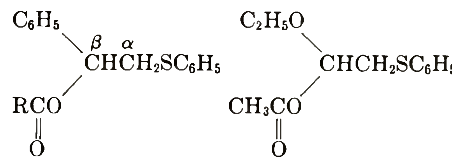
simple procedure. After separating mercuric chloride and acid anhydrides, diphenyl disulfide was isolated by chromatography over alumina using ether as an eluent. During this procedure an oxygenated product containing an organic sulfur compound might be adsorbed in alumina as an ether-soluble mercury complex. It should be noted that the yields of diphenyl disulfide were always less than 75% as shown in Table II. It is interesting to note that sulfenyl chloride **5** and disulfide **1** behaved similarly toward mercuric carboxylates to give acid anhydrides in high yields.

Furthermore, in connection with investigations of the mechanism of the reaction (eq 5), some attempts to trap a transient intermediate were made. When a mercuric carboxylate was allowed to react with 2 equiv of **5** in the presence of 2 equiv of cyclohexene at room temperature in methylene chloride, the addition product, 2-acyloxycyclohexyl phenyl sulfide (**6**), and mercuric chloride were obtained in good yields (eq 6). The



6a, R = CH_3
b, R = C_6H_5

acid anhydride and diphenyl disulfide could not be isolated. The formation of **6** would be explained by assuming that phenylthio and acyloxy moieties or benzenesulfenyl carboxylates[5] initially formed from mercuric carboxylates and **5** might add faster to cyclohexene than sulfenyl chloride[6,7] (**5**). Similar adducts (**7** and **8**) were obtained when styrene or



7a, R = CH_3
b, R = C_6H_5 **8**

ethyl vinyl ether was used as an "acceptor" in the above reaction (eq 6). Physical properties and analytical data of these adducts are listed in Table III. On the other hand, no addition product was formed with acrylonitrile and chalcone under the same conditions. The observed olefinic reactivity would be explained by the familiar argument.

The coupling constant (J_{12} = 8 cps) observed for **6** supports the *trans* structure of adduct **6**. The structural assignments of **7** and **8** are based on hydrolysis and spectral and analytical data. Alkaline hydrolysis of **7b** gave the corresponding alcohol[8] (**9**) and benzoic acid in 70 and 82% yields, respectively. The methy-

$$\mathbf{7b} \xrightarrow{OH^-} C_6H_5CH(OH)CH_2SC_6H_5\ (\mathbf{9}) + C_6H_5CO_2H \quad (7)$$

lene protons of **7** resonated as two quartets with a geminal coupling constant of 14 cps and vicinal *J* of 6 and 8 cps. This pattern is explained by nonequivalency of the methylene protons. The quartet at

TABLE II

REACTIONS OF MERCURIC CARBOXYLATES WITH BENZENESULFENYL CHLORIDE

Mercuric carboxylate	Solvent	Yield, % Anhydride	$C_6H_5SSC_6H_5$	$HgCl_2$
Acetate	Ether	69	75	80
Propionate	Ether	61	71	82
Butyrate	Ether	85	74	83
Benzoate	CH_2Cl_2	80[a]	66	92
Succinate	CH_2Cl_2	91	75	92
Phthalate	CH_2Cl_2	81	72	90

[a] Since benzoic anhydride could not be separated from diphenyl disulfide by fractional distillation, the yield was determined from the weight of the corresponding anilide derived from the anhydride.

(3) T. Mukaiyama, I. Kuwajima, and Z. Suzuki, *J. Org. Chem.*, **28**, 2024 (1963).

(4) Further reactions of **5** were tried by the use of the other metal carboxylates. In the case of silver acetate or benzoate, 69 or 71% of the corresponding anhydride, 72 or 68% of diphenyl disulfide, and 95 or 92% of silver chloride were obtained, respectively. With cupric benzoate, a black precipitate was formed, which, on filtration, rapidly decomposed to a pale blue solid presumably by moisture.

(5) (a) A. J. Havlik and N. Kharasch, *J. Amer. Chem. Soc.*, **78**, 1207 (1956); (b) R. E. Putnam and W. H. Sharkey, *ibid.*, **79**, 6526 (1957).

(6) G. Wittig and F. Vidal, *Chem. Ber.*, **81**, 368 (1948).

(7) (a) N. Kharasch and C. M. Buess, *J. Amer. Chem. Soc.*, **71**, 2724 (1949); (b) D. J. Cram, *ibid.*, **71**, 3884 (1949); (c) S. J. Cristol, R. P. Arganbright, G. D. Brindell, and R. M. Heitz, *ibid.*, **79**, 6035 (1957).

(8) R. F. Brookes, J. E. Cranham, D. Greenwood, and H. A. Stevenson, *J. Sci. Food Agr.*, **8**, 561 (1957).

TABLE III

PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR THE ADDUCTS

Compd	R	Yield, %	Bp (mm), °C	$n^{25}D$	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
6a	CH_3	80	119–120 (0.08)	1.5890	$C_{14}H_{18}O_2S$	67.18	7.25	66.89	6.99
6b	C_6H_5	59	168–169 (0.08)	1.5960	$C_{19}H_{20}O_2S$	73.06	6.45	72.89	6.73
7a	CH_3	77	131–132 (0.03)	1.5819	$C_{16}H_{16}O_2S$	70.57	5.92	70.39	6.21
7b	C_6H_5	66	189–190 (0.08)	1.6248	$C_{21}H_{18}O_2S$	75.43	5.43	75.15	5.39
8		59	100–101 (0.09)		$C_{12}H_{16}O_3S$	59.99	6.71	60.14	6.74

τ 3.93 assigned to the $C_\beta H$ proton of **7b** was shifted high field 1.55 ppm in **9**, indicating that the benzoyloxy group of **7b** is attached to the β carbon.

Finally, reactions of mercuric thiolates were investigated. Treatment of mercuric benzenethiolate or thiobenzoate with 2 equiv of **5** at room temperature afforded 89 or 82% of mercuric chloride and 97% of diphenyl disulfide or 80% of benzoyl phenyl disulfide, respectively. In addition, it was found that mercuric benzenethiolate reacted readily with **1** at room temperature to give **2** (95%) and diphenyl disulfide (98%), as expected.

$$(RS)_2Hg + 2C_6H_5SCl \longrightarrow HgCl_2 + 2RSSC_6H_5 \quad (8)$$

$$R = C_6H_5,\ C_6H_5C(=O)$$

$$(C_6H_5S)_2Hg + (Et_2NCS)_2 \longrightarrow Hg(SCNEt_2)_2 + (C_6H_5S)_2 \quad (9)$$

In conclusion, it is of special interest to note that there are essential differences in behavior between mercuric compounds containing the Hg–O bond and those containing the Hg–S bond toward sulfenyl chloride **5** or disulfide **1**.

Experimental Section[9]

Materials.—Cadmium, lead, mercuric, silver, and zinc acetates were commercial materials and used without further purification. The other mercuric carboxylates,[10] cupric benzoate,[11] silver benzoate,[12] and mercuric benzenethiolate[13] were prepared as previously described. Diphenyl disulfide, dibenzoyl disulfide, bis(diethylthiocarbamoyl) disulfide (**1**), benzenesulfenyl chloride (**5**), and the related sulfenyl compounds were prepared in the usual manner.

Preparation of Mercuric Thiobenzoate.—This compound was prepared from mercuric acetate and 2 equiv of thiobenzoic acid[14] in methylene chloride and recrystallized from ethanol to give white needles: mp 140–141°; ν_{max}^{KBr} 1625, 1610, 1200, and 900 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}O_2S_2Hg$: C, 35.41; H, 2.12. Found: C, 35.14; H, 2.08.

Reaction of Mercuric Acetate and Disulfide 1.—Mercuric acetate (6.38 g, 0.02 mol) was added to a solution of **1** (5.95 g, 0.02 mol) in 40 ml of benzene with stirring at room temperature over a period of 5 min. An exothermic reaction took place immediately and a pale yellow precipitate was formed. This decomposed to a fine black solid in about 20 min at room temperature. The black reaction mixture was concentrated, cooled at 0°, and treated with ether. The black crystalline material was collected by filtration and extracted with methylene chloride. The filtrate was distilled to give acetic anhydride (1.34 g, 68%), bp 51–52° (25 mm), $n^{25}D$ 1.3898, whose infrared spectrum was identical with that of an authentic sample. The residue was extracted with methylene chloride. The combined extracts were evaporated *in vacuo* to give **2** (7.51 g, 75%), mp 132–134°. Recrystallization from acetonitrile gave an analytically pure yellow crystal: mp 138–139°; ν_{max}^{KBr} 1495, 1425, 1270, and 1200 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_2S_4Hg$: C, 24.17; H, 4.05; N, 5.64. Found: C, 24.33; H, 3.92; N, 5.81.

By a similar procedure, propionic, butyric, and benzoic anhydrides were obtained (see Table I).

Reaction of Mercuric Phthalate with 1.—To a stirred solution of **1** (2.96 g, 0.01 mol) in 30 ml of benzene was added mercuric phthalate (3.65 g, 0.01 mol) at room temperature. After stirring was continued for 10 min, 1.45 g of a pale yellow precipitate (**3**) was collected by filtration. The infrared spectrum showed bands at 1700, 1510, 1430, and 1280 cm^{-1}. Except for acetonitrile, DMF, DMSO, and pyridine, compound **3** was insoluble in most organic solvents. Recrystallization from acetonitrile gave analytically pure yellow crystals (**4**): mp 159–160°; ν_{max}^{KBr} 1495, 1420, 1275, and 1200 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_2O_6S_4Hg$ or $C_{10}H_{20}N_2O_4S_5Hg$: C, 20.25; H, 3.39; N, 4.72. Found: C, 20.06; H, 3.22; N, 4.73.

The filtrate was concentrated and treated with ethanol. The resulting crystals of **2** (3.80 g, 76%), mp 133–135°, were filtered. Evaporation of ethanol from the filtrate gave phthalic anhydride (0.85 g, 57%), mp 127–128°, whose infrared spectrum was identical with that of an authentic sample. The mixture melting point with an authentic sample showed no depression.

By a similar procedure, anhydrides of carbobenzyloxyglycine and succinic acid were obtained (see Table I).

Reaction of Mercuric Benzoate with 1 in the Presence of Water.—To a stirred mixture of mercuric benzoate (4.45 g, 0.01 mol) and water (0.4 g, 0.02 mol) in 30 ml of methylene chloride was added **1** (2.96 g, 0.01 mol) at room temperature. A slightly exothermic reaction was observed. After stirring was continued for 10 min, a small amount of a pale yellow precipitate was removed by filtration. The filtrate was concentrated and treated with ether. The yellow crystals of **2** (4.81 g, 96%), mp 135–137°, were collected by filtration. Evaporation of ether from the filtrate gave benzoic acid (2.32 g, 95%), mp 112–115°, whose infrared spectrum was identical with that of an authentic sample.

Similarly, propionic acid (66%) and **2** (86%) were obtained by the reaction of mercuric propionate with **1** in the presence of water.

Reaction of Di-*p*-anisylmercury and Benzoic Acid with 1.—A mixture of di-*p*-anisylmercury (4.15 g, 0.01 mol) and benzoic acid (2.45 g, 0.02 mol) in 20 ml of benzene was refluxed for 20 min. To this was added a solution of **1** (2.96 g, 0.01 mol) in 10 ml of benzene, and the mixture was refluxed for 30 min. A black solid precipitated. Work-up of the reaction mixture as described above gave benzoic anhydride (1.63 g, 72%) and **2** (2.49 g, 50%).

Reaction of Mercuric Succinate with Sulfenyl Chloride 5.—To a stirred suspension of mercuric succinate (3.17 g, 0.01 mol) in 20 ml of methylene chloride was added dropwise a reddish orange solution of **5** (2.90 g, 0.02 mol) in 10 ml of methylene chloride over a period of 20 min at room temperature. An immediate reaction took place as indicated by decolorization of **5**. A white precipitate of mercuric chloride (2.50 g, 92%) was collected by filtration. The filtrate was evaporated *in vacuo* to dryness and treated with ether. The resulting crystals of succinic anhydride (0.91 g, 91%), mp 117–118°, were filtered. The infrared spectrum was identical with that of an authentic sample. The filtrate was concentrated and chromatographed on alumina (80 g) to remove residual mercuric chloride. Elution with ether gave diphenyl disulfide (1.63 g, 75%), mp 59–60°.

(9) All melting points and boiling points were uncorrected.

(10) T. Mukaiyama, H. Nambu, and I. Kuwajima, *J. Org. Chem.*, **28**, 917 (1963).

(11) W. W. Kaeding and A. T. Shulgin, *ibid.*, **27**, 3551 (1962).

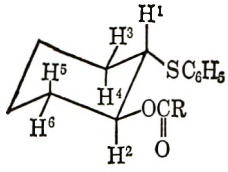
(12) R. A. Zingaro, J. E. Goodrich, J. Kleinberg, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **71**, 575 (1949).

(13) H. Lecher, *Chem. Ber.*, **48**, 1425 (1915).

(14) P. Noble, Jr., and D. S. Tarbell, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 924.

By a similar procedure, the other acid anhydrides were obtained from the corresponding mercuric and silver carboxylates (see Table II).

General Procedure for the Preparation of the Adducts (6–8).—To a stirred mixture of an olefin (0.02 mol) and a mercuric carboxylate (0.01 mol) in 20 ml of methylene chloride was added a solution of **5** (0.02 mol) in 10 ml of methylene chloride at room temperature over a period of 20 min. A slightly exothermic reaction took place soon. Stirring was continued for 20 min at room temperature. A white precipitate of mercuric chloride (1.8–2.2 g, 67–76%) was collected by filtration. The filtrate was concentrated and chromatographed on alumina (80 g) using ether as an eluent. After removal of ether, the residual oil was distilled to give the corresponding adduct. Yields, physical properties, and analytical data are listed in Table III. The infrared spectra of **6a**, **6b**, **7a**, **7b**, and **8** showed carbonyl absorptions at 1740, 1720, 1740, 1725, and 1740 cm^{-1}, respectively. The nmr[15] spectrum of **6a** showed peaks at τ 7.6–8.9 (complex,



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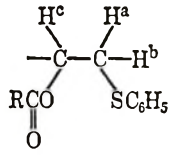

7, 8

8 H), 5.25 (sextet, 1 H, CH),[16] and 6.88 (sextet, 1 H, CH);[16] that of **6b** showed peaks at τ 7.6–8.9 (complex, 8 H), 5.01 (sextet, 1 H, CH),[16] and 6.71 (sextet, 1 H, CH).[16] The nmr spectrum of **7a** showed peaks at τ 6.73 (quartet, 1 H, CH_2),[17] 6.97 (quartet, 1 H, CH_2),[17] and 4.16 (quartet, 1 H, CH);[17] that of **7b** showed peaks at τ 6.57 (quartet, 1 H, CH_2),[17] 6.84 (quartet, 1 H, CH_2),[17] and 3.93 (quartet, 1 H, CH);[17] that of **8** showed peaks at τ 6.92 (doublet, 2 H, J = 6 cps, CH_2) and 4.13 (triplet, 1 H, J = 6 cps, CH).

Hydrolysis of 7b.—A solution of **7b** (3.34 g, 0.01 mol) and sodium hydroxide (0.60 g, 0.015 mol) in 25 ml of water and 25 ml of ethanol was heated on the steam bath for 10 hr. After removal of ethanol, the residue was diluted with 30 ml of water, extracted repeatedly with ether, and dried over anhydrous sodium sulfate. After removal of ether, the residual oil was distilled to give **9** (1.60 g, 70%): bp 138–139° (0.06 mm) [lit.[8] bp 168° (2 mm)]; ν_{max} 3410 (OH) cm^{-1}; nmr (CCl_4), two quartets centered at τ 7.00 (1 H) and 7.06 (1 H) with J_{ab} = 13 cps, a singlet at 6.45 (1 H, OH), a quartet at 5.48 (1 H, J_{ac} and J_{bc} = 5 and 8 cps), a multiplet centered at 2.88 (10 H, aromatic protons).

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.02; H, 6.13. Found: C, 73.26; H, 6.00.

The aqueous, alkaline solution was acidified with dilute hydrochloric acid to give benzoic acid (1.00 g, 82%), mp 118–120°.

Reaction of Mercuric Thiobenzoate with 5.—To a stirred suspension of mercuric thiobenzoate (4.75 g, 0.01 mol) in 20 ml of methylene chloride was added a solution of **5** (2.90 g, 0.02 mol) in 10 ml of methylene chloride at room temperature. After stirring was continued for 10 min, a white precipitate of mercuric chloride (2.22 g, 82%) was filtered off. The filtrate was concentrated and distilled to give benzoyl phenyl disulfide[18] (3.96 g, 80%): bp 147–148° (0.1 mm); ν_{max} 1695, 1200, 885, 690, and 680 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}OS_2$: C, 63.36; H, 4.09. Found: C, 63.65; H, 4.18.

Similarly, mercuric chloride (89%) and diphenyl disulfide (97%) were obtained from the reaction of mercuric benzenethiolate with **5**.

Reaction of Mercuric Benzenethiolate with 1.—To a stirred suspension of mercuric benzenethiolate (4.19 g, 0.01 mol) in 20 ml of methylene chloride was added **1** (2.96 g, 0.01 mol) at room temperature. A reaction took place immediately, and a clear yellow solution was formed. The reaction mixture was concentrated *in vacuo* to dryness and treated with ether. The yellow crystal of **2** (4.76 g, 95%), mp 134–136°, was collected by filtration. The filtrate was evaporated and chromatographed on alumina (80 g) to remove residual **2**. Elution with ether gave diphenyl disulfide (2.10 g, 98%), mp 59–60°.

Registry No.—**1**, 97-77-8; **2**, 16162-55-3; **5**, 931-59-9; **6a**, 16162-54-2; **6b**, 16162-48-4; **7a**, 16162-49-5; **7b**, 16162-50-8; **9**, 16162-51-9; benzoyl phenyl disulfide, 5718-98-9; mercuric thiobenzoate, 16162-53-1.

(15) The nmr spectra were measured at 100 Mcps in CCl_4 solution with TMS as an internal standard, and these data were obtained by first-order analysis.

(16) $J_{12} = J_{14} = J_{26} = 8$ cps, $J_{13} = J_{26} = 4$ cps.

(17) $J_{ab} = 14$ cps, J_{ac} and $J_{bc} = 6$ and 8 cps.

(18) H. Böhme and M. Clement, *Ann.*, **576**, 61 (1952).

Steric Rate Enhancement in the Chapman Rearrangement

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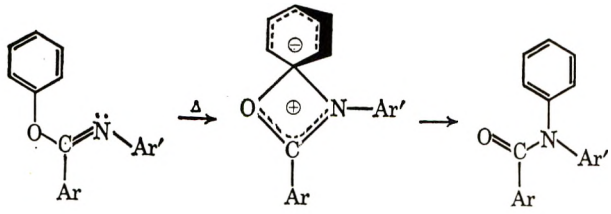
N-Phenylbenzimidates of 2,6-dimethyl-, 2,6-di-*t*-butyl-, 2,6-diphenyl-, and 2-methyl-6-phenylphenol have been prepared and have been found to undergo the Chapman rearrangement to give the corresponding N-arylbenzanilides. Kinetic measurements have been obtained and are discussed in terms of the competition between steric acceleration and steric deceleration of the rates of rearrangement.

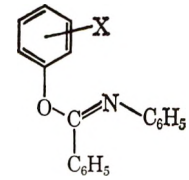
An elegant study by Wiberg and Rowland[1] indicated that the Chapman rearrangement[2] obeyed first-order kinetics and that the mechanism involved an intramolecular, nucleophilic–aromatic substitution.



(1) K. B. Wiberg and B. I. Rowland, *J. Amer. Chem. Soc.*, **77**, 2205 (1955).

(2) For a recent review, see J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).

It was also reported[1] that the ratios of the rate constants for corresponding *ortho*- and *para*-substituted compounds (Ia–d) were greater than unity. It was assumed that the *ortho* substituent hindered free ro-



Ia, X = $CH(CH_3)_2$
b, X = CH_3
c, X = Cl
d, X = OCH_3
e, X = $C(CH_3)_3$
f, X = H

tation of the aromatic ring to which it was attached; the restriction of this mode of rotation was precisely that which was required for the formation of the four-membered ring in the transition state. That is, the introduction of an *ortho* substituent lessens the entropy decrease on proceeding from the reactant to the transition state. Indeed, it was found that the entropies of activation for *p*-Ib and *o*-Ib were −9.7 and −3.6 eu, respectively. In the case of Ie, k_{ortho}/k_{para} was 0.60. Here it was suggested that the steric requirement of the *o*-*t*-butyl group was large enough to overcome the rate-enhancing effect resulting from hindered rotation. The $\Delta S^{\ddagger}$ value for *o*-Ie was indeed about 8 eu more negative than that for *o*-Ib.

An extension of these arguments predicts that the rate of the Chapman rearrangement should be greater with two *ortho* substituents on the migrating aromatic ring than with one, provided that overriding steric compression is not attained. Successful Chapman rearrangements, in which the migrating aromatic ring contained two *ortho* substituents, have been reported[2] only in cases where the substituents were halogens, and no kinetic data were reported. Even if a kinetic study revealed that these di-*o*-halo compounds rearranged faster than the corresponding mono-*o*-halo compounds, it would be difficult to separate the rate enhancement due to the hindrance to rotation in the reactant and that due to the inductive electron-withdrawing effect of the halogens.

A study of the Chapman rearrangement of imidates of some 2,6-disubstituted phenols, in which the substituents were not electron-withdrawing groups, was expected to provide an increased understanding of the competition between steric acceleration and steric deceleration of rates. Therefore, four aryl N-phenylbenzimidates (II, III, IV, V) were prepared from N-phenylbenzimidoyl chloride and the corresponding phenol in the presence of base. The rearrangement of these imidates occurred readily at 300° and the corresponding amides (VI, VII, VIII, IX) were obtained in high yield (Scheme I).

In order to compare the rates of rearrangement of II–V with literature values[1] for other imidates, samples of II–V were dissolved in diphenyl ether and heated at 258.0°. The rearrangements of II, III, and IV were followed by nuclear magnetic resonance spectroscopy; the rearrangement of V was followed by an infrared method. The semiquantitative results are given in Table I.[3-5] The $\Delta H^{\ddagger}$ values[1] for the Chapman rearrangement of five very different aryl N-phenylbenzimidates range from 36.7 to 39.5 kcal/mol. The average of these values was used to calculate the rate constants at 255° corresponding to those given in Table I. These are listed in Table II together with some other rate constants selected from the literature[1] for comparison.

SCHEME I

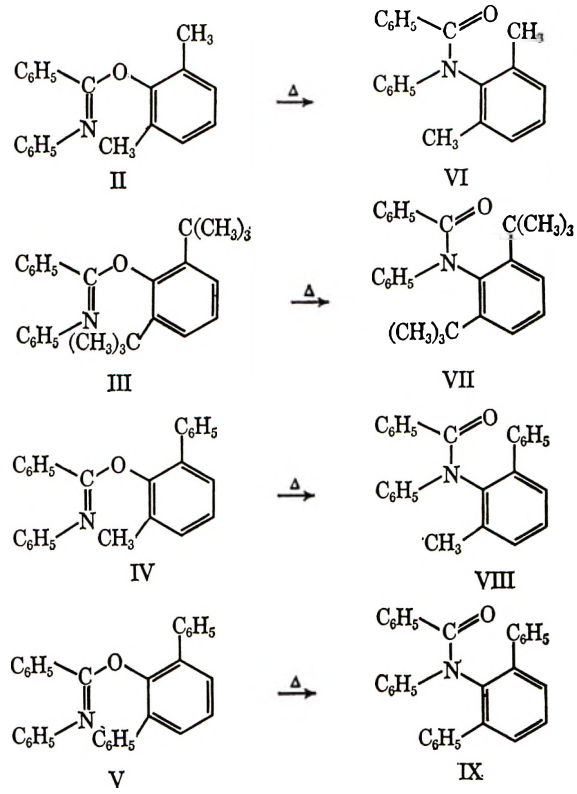


TABLE I

RATE CONSTANTS OF CHAPMAN REARRANGEMENTS AT 258.0° IN DIPHENYL ETHER

Imidate	Substituent[a]	Concn, M[b]	$k \times 10^5$, sec^{-1}
II	2,6-di-CH_3	0.303	15.1 ± 0.1
III	2,6-(*t*-C_4H_9)$_2$	0.303	0.38 ± 0.04
IV	2-CH_3-6-C_6H_5	0.301	19.0 ± 2.2
V	2,6-(C_6H_5)$_2$	0.302	23.1 ± 1.1

[a] In O-aryl ring. [b] Concentrations of the solutions at 25°.

TABLE II

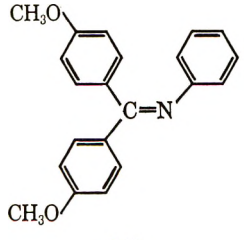
RATE CONSTANTS FOR CHAPMAN REARRANGEMENTS AT 255° IN DIPHENYL ETHER

Imidate	Substituent[a]	$k \times 10^5$, sec^{-1}	k/k_{If}
II	2,6-di-CH_3	12.3	1.61
III	2,6-(*t*-C_4H_9)$_2$	0.31	0.040
IV	2-CH_3-6-C_6H_5	15.5	2.02
V	2,6-(C_6H_5)$_2$	18.8	2.45
If	H	7.66[b]	1.00
o-Ib	2-CH_3	8.87[b]	1.16
p-Ib	4-CH_3	3.55[b]	0.46
o-Ie	2-*t*-C_4H_9	2.30[b]	0.30
p-Ie	4-*t*-C_4H_9	3.82[b]	0.50

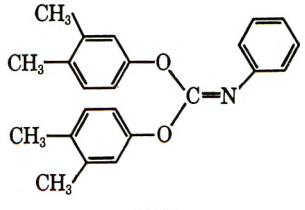
[a] In O-aryl ring. [b] Obtained from 0.3 M solutions of the imidate in diphenyl ether at 255° by a perchloric acid titration method.[1]

From the rate constants for If and *o*-Ib, it is apparent that the combined polar and steric decelerating effects of an added *o*-methyl group on the rearrange-

(3) Implicit in a discussion of the Chapman rearrangement and its kinetics is that, regardless of which form (*syn* or *anti*) of the imidate reacts, the equilibrium between these forms is rapid compared to the rate of rearrangement. This assumption is quite credible since XII and XIII have been shown[4,5] to have rate constants for inversion of nitrogen (pseudo-*syn*–*anti* isomerizations) at 60° of 10.9 and *ca.* 1.6 × 10^{-3} sec^{-1}, respectively.



XII



XIII

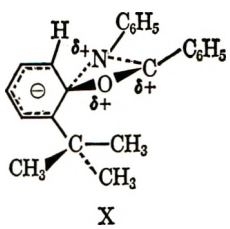
(4) D. Y. Curtin and C. G. McCarty, *Tetrahedron Lett.*, 1269 (1962).

(5) N. P. Marullo and E. H. Wagener, *J. Amer. Chem. Soc.*, **88**, 5034 (1966).

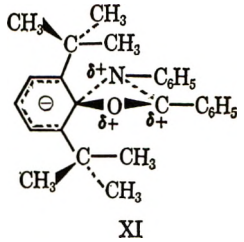
ment are outweighed by the steric acceleration due to hindered rotation (SAHR) effect. The combination of these factors leads to a 16% increase in k. More striking is the observed 61% increase in k in placing two *o*-methyl groups on the migrating aryl ring (compare k's for If and II). If all substituent effects were additive,[6] a 35% rate increase would have been expected. Since all polar and steric effects, other than the SAHR effect, should inhibit the rearrangement (compare k's for If and *p*-Ib), the large rate enhancement observed must be due to the fact that two *o*-methyl groups exhibit more of an SAHR effect than would be predicted from the effect of one *o*-methyl group alone. That is, two *o*-methyl groups hinder free rotation around the ether linkage of II more than twice as much as the methyl group in *o*-Ib.

On the other hand, with one *o*-*t*-butyl group (*o*-Ie), the steric compression which is introduced on proceeding to the transition state is slightly more important than the SAHR effect (assuming approximately the same polar effect for an *o*- and a *p*-*t*-butyl group) since the rate constant for *o*-Ie is slightly less than that for *p*-Ie.[7]

From the rate constants for If and *o*-Ie, if all substituent effects were additive, one would predict that the addition of another *o*-*t*-butyl group, giving III, would depress the rearrangement rate constant to *ca.* 0.69×10^{-5} sec^{-1}. The fact that the observed rate constant was 0.31×10^{-5} sec^{-1} indicates that the decelerating effect of steric compression is more than twice as important for two *o*-*t*-butyl groups as for one. A possible structural explanation for this more than cumulative effect is that bond-angle distortion occurs to relieve nonbonded strain in the rearrangement of *o*-Ie (see X) but cannot occur in III because of the presence of the second *o*-*t*-butyl group (see XI).



X



XI

From the available data, it is not possible at present to discuss the magnitude of the SAHR effect on the rates of the Chapman rearrangement of IV and V. It can be seen, however, that the combination of resonance, inductive, and SAHR effects, enhancing the rates of rearrangement of these two compounds over that of If, was apparently much more than enough to offset the rate-depressing effect arising from steric compression in the transition state.

Experimental Section

N-Phenylbenzimidoyl Chloride.—A mixture of 105 g (0.532 mol) of benzanilide and 100 ml of thionyl chloride was stirred and heated at reflux for 1.5 hr. Gas evolution began almost immediately. After the resulting black solution had been allowed to stand at room temperature overnight, the excess thionyl chloride was removed by distillation at atmospheric pressure. Further distillation under reduced pressure afforded 112.6 g (98%) of N-phenylbenzimidoyl chloride: bp 119–121° (0.15 mm); mp 41–42° [lit. bp 115–120° (0.3 mm);[9] mp 40°[10]].

2,6-Dimethylphenyl N-Phenylbenzimidate (II).—Exactly 6.097 g (0.0500 mol) of 2,6-xylenol was dissolved in 50 ml of 1.02 *M* sodium ethoxide in ethanol. Then, 10.774 g (0.0500 mol) of N-phenylbenzimidoyl chloride in 45 ml of ethyl ether was added with continuous stirring. A slight exotherm was noted and a precipitate appeared. After the system had been stirred at room temperature for 5 hr, it was mixed with 250 ml of ethyl ether. This ether solution was extracted three times with water and dried with anhydrous sodium sulfate. Removal of the solvent on a steam bath gave 14.91 g of a viscous, orange oil which soon became entirely crystalline. Three recrystallizations from hexane afforded 6.17 g (41%) of pure V, mp 93–94.5°. The nuclear magnetic resonance (nmr) spectrum (CCl_4) consisted of a multiplet for the aromatic protons (τ 2.35–3.60; integral 13.0) and a single peak for the methyl protons (7.72; integral 6.1). The infrared spectrum[11] ($CHCl_3$) displayed C=N absorption at 1670 cm^{-1} and aryl ether absorption at 1253 cm^{-1}.

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.9; H, 6.0; N, 4.6.

N-(2,6-Dimethylphenyl)benzanilide (VI).—A sample of 1.935 g (0.00643 mol) of V was sealed in a partially evacuated Carius tube under nitrogen and then heated at 300° for 30 min. The very slightly yellow material thus obtained was shown spectroscopically and by thin layer chromatography to be devoid of any starting material (II). The nmr spectrum (CCl_4) displayed a complex multiplet, entirely different from that of II, between τ 2.44 and 3.30 (integral 13.0) and a single sharp peak at 7.85 (integral 5.8). The infrared spectrum[11] ($CHCl_3$) showed a tertiary amide carbonyl absorption at 1645 and a tertiary phenyl amine band at 1345 cm^{-1} and none of the characteristic bands of II. The spectra are consistent with the structure of VI. One recrystallization from hexane (starting with 1.66 g) gave 1.21 g (73%) of pure VI, mp 95–97°.

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.6; H, 6.4; N, 4.5.

Identical results were obtained (as indicated by the nmr spectrum) when the reaction was carried out in air or in nitrogen (in Carius tubes sealed at atmospheric pressure). Interestingly, the nmr spectrum of VI was found to be temperature dependent. As the sample temperature was decreased below 38°, the peak for the methyl protons (w_h = 1.4 cps at 38°) gradually broadened and at *ca.* 7.5° two broad peaks appeared and these became sharper as the temperature was lowered. At −31°, the width at half-height for each was 1.5 cps. The ratio of the areas of the low-field and high-field peaks was 56:44. This phenomenon is undoubtedly the result of hindered rotation around the C—N amide bond.

2,6-Di-*t*-butylphenyl N-Phenylbenzimidate (III).—Exactly 10.00 g (0.0486 mol) of 2,6-di-*t*-butylphenol and 0.1 g of triphenylmethane were dissolved in 150 ml of tetrahydrofuran. While the solution was stirred under nitrogen, *ca.* 31 ml of 1.6 *M* butyllithium in hexane was added whereupon the red color of the triphenylmethyl carbanion just appeared. Then 10.47 g (0.0486 mol) of N-phenylbenzimidoyl chloride in 75 ml of tetrahydrofuran was added and the system was stirred overnight at room temperature under nitrogen. After the reaction mixture was combined with 400 ml of ethyl ether, it was extracted with water, dried with anhydrous magnesium sulfate, and freed of solvent on a rotary evaporator. A viscous, red oil (19.35 g) was thus obtained. Chromatography on 400 g of alumina, using hexane as elution solvent, afforded some 2,6-di-*t*-butylphenol and another impure compound which exhibited infrared absorption at 1670 and 1270 cm^{-1}, typical of 2,6-disubstituted phenyl N-phenylbenzimidates. Two recrystallizations from methanol afforded 4.28 g (23%) of colorless plates, mp 127.5–128.5°. The spectra of this material were consistent with the structure of III.

(6) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 575, 576.

(7) It is possible that a considerable SAHR effect is operating in *o*-Ie since the rate depression, in the absence of this effect, would have been very large; a rate constant 1/200 of that for If would not have been unreasonable.[8]

(8) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 72 (1963) [entry no. 1 in Table 12: partial rate factors for *ortho* and *para* substitution in *t*-butylbenzene (*ortho*/*para* = 4.97:806)].

(9) J. W. Schulenberg and S. Archer, *J. Amer. Chem. Soc.*, **82**, 2035 (1960).

(10) J. von Braun and W. Pinkernelle, *Ber.*, **67**, 1218 (1934).

Infrared bands were present for the C–N vibration[11] (1670 cm^{-1}) and for the aryl ether vibration[11] (1263 cm^{-1}). The nmr spectrum consisted of a complex multiplet for the aromatic protons (τ 2.32–3.57; integral 12.4) and a single sharp peak for the *t*-butyl protons (8.56; integral 18.4).

Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.11; N, 3.63. Found: C, 84.5; H, 7.8; N, 3.5.

N-(2,6-Di-*t*-butylphenyl)benzanilide (VII).—A 1.00-g sample of III was sealed in a glass tube in air and heated at 305° for 30 min. The resulting cooled mass was sampled (removed 0.10 g) and examined by nmr spectroscopy (CCl_4). Besides complicated changes that had occurred in the aromatic region, two new single peaks appeared at τ 8.88 and 8.67, and the *t*-butyl-proton peak of III at 8.56 had diminished proportionately. The nmr integration indicated that 55% of the starting material (III) was still present. Vapor phase chromatography (vpc) (2 ft, 10% polyphenyl ether; helium flow = 72 cc/min; 275°, isothermal) indicated that III (retention time = 10.0 min) and one other compound (retention time = 18.0 min) were present in the approximate ratio of 53:47.

The remaining 0.90 g of the reaction mixture was sealed in the glass tube again and heated at *ca.* 310° for 6 hr more and then cooled to room temperature. The nmr spectrum (CCl_4) of this material showed only a trace of III, two major peaks at τ 8.88 and 8.68, and a minor peak at 8.52. Vpc showed that the previously observed long retention time peak now accounted for greater than 90% of the reaction mixture while less than 5% was residual III. Two impurities were also observed in the vpc.

The infrared spectrum of the crude reaction mixture showed strong absorptions at 1640 and 1345 cm^{-1}, typical of carbonyl and tertiary phenyl amine bands, respectively, of the other tertiary amides reported herein.

When III was heated at 258 or 275° in diphenyl ether (c = 0.303 *M* or 0.5 *M*, respectively), only the τ 8.88 and 8.68 peaks appeared, besides complex changes in the aromatic region. The ratio of these two peaks (*ca.* 2.2) remained constant as the peak for the *t*-butyl protons of III (τ 8.56) diminished with time. This was the same ratio as observed previously for these two peaks which arose when III was heated at 310° without solvent.

The nmr spectrum of a diphenyl ether solution of III (originally 0.5 *M*) that had been heated at 275° for 11.75 hr (only 27% of III left) was recorded at various temperatures, ranging from 29 to 166°. On heating, the τ 8.88 and 8.68 peaks (w_h = 1.3 and 1.4 cps, respectively, at 29°) gradually broadened and overlapped. Coalescence occurred at 138°; the single peak became sharper as the temperature was raised; and, at 166°, the width at half-height was 1.9 cps. On cooling to room temperature, the original spectrum was regenerated. Thus, it appears that the expected product (VII) is obtained and it exists at room temperature as two rotational isomers which interconvert slowly enough to be distinguished by nmr spectroscopy.

The crude product, obtained by heating 0.90 g of III at 310° (see above), was chromatographed on activity I Woelm alumina. After eluting with pentane (nothing obtained) and 95:5 pentane–diethyl ether (recovered less than 5% of III), 60:40 pentane–diethyl ether afforded 0.71 g (79% isolated yield) of a colorless, viscous oil which was homogeneous by vpc. The nmr spectrum (CCl_4) showed aromatic protons (τ 2.2–3.4; integral 12.6) and two *t*-butyl peaks at 8.68 and 8.89 for the two different rotamers (total integral 18.0).

After several days, the viscous oil had completely crystallized; the broad melting point, 129–133.5°, was not unexpected for a mixture of isomers. The infrared spectrum of this product showed 1640- and 1343-cm^{-1} bands to be expected from the carbonyl and tertiary phenyl amine bands of VII.

Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.11; N, 3.63. Found: C, 83.9; H, 8.0; N, 3.4.

2-Methyl-6-phenylphenyl N-Phenylbenzimidate (IV).—To 70 ml of 0.76 *M* sodium ethoxide in ethanol was added 9.203 g (0.0500 mol) of 2-methyl-6-phenylphenol. After the phenol had dissolved, 10.775 g (0.0500 mol) of N-phenylbenzimidoyl chloride in 45 ml of ethyl ether was added with continuous stirring. A precipitate formed and the system warmed slightly. After 15 hr of stirring at room temperature, the entire system was added to 250 ml of ether, extracted with water, and dried with anhydrous sodium sulfate. Removal of the ether gave 18.082 g of a solid material which was subsequently recrystallized three times from hexane to give 8.14 g (45%) of IV, mp 90–92.5°. The infrared spectrum ($CHCl_3$) showed C=N absorption[11] (1670 cm^{-1}) and aryl ether absorption[11] (1253 cm^{-1}). The nmr spectrum consisted of a complex aromatic proton multiplet (τ 2.17–3.82; integral 18.0) and a single sharp peak for the methyl protons (7.63; integral 2.9). One more recrystallization from ethanol gave an analytical sample, mp 95–97°.

Anal. Calcd for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.86. Found: C, 85.6; H, 5.8; N, 3.8.

N-(2-Methyl-6-phenylphenyl)benzanilide (VIII).—A sample of IV (1.045 g, 0.00288 mol) was sealed in a nitrogen atmosphere in a Carius tube and heated at 300° for 30 min. The nmr spectrum ($CDCl_3$) of the solid product was then recorded. This spectrum showed a broad single peak for the methyl protons (τ 7.59; integral 2.6) and a complex multiplet, entirely different in complexity from that of IV, for the aromatic protons (2.21–3.86; integral 18.0). The infrared spectrum of this unpurified product displayed a tertiary amide carbonyl absorption[11] (1635 cm^{-1}) and a tertiary phenyl amine absorption[11] (1345 cm^{-1}) and indicated that IV was completely absent.

Identical results were obtained when IV was heated at 300° for 30 min in air in a sealed tube.

The products from both the nitrogen and the air runs (see above) were combined (total 1.66 g) and recrystallized from ethanol to afford 1.44 g (87%) of pure amide (VIII), mp 187–189°.

Anal. Calcd for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.86. Found: C, 85.5; H, 5.6; N, 3.7.

The nmr spectrum of VIII was found to be temperature dependent. At 60°, there was one peak for the methyl protons having a width at half-height of 2 cps; at 38°, this single peak had a width at half-height of 3.6 cps; at 18°, two broad peaks began to appear; and at −39°, two sharp peaks, both having a width at half-height of 1.5 cps, were present. (The ratio of the low-field and high-field peaks was 85:15.)

Again, as in the cases of VI and VII, hindered rotation around the C—N amide bond seems evident.

2,6-Diphenylphenyl N-Phenylbenzimidate (V).—A solution of 12.301 g (0.0500 mol) of 2,6-diphenylphenol in 70 ml of 0.76 *M* sodium ethoxide in ethanol was prepared. While this solution was stirred, 10.774 g (0.0500 mol) of N-phenylbenzimidoyl chloride in 45 ml of ethyl ether was added, whereupon heat was evolved and a precipitate appeared. Stirring was continued for 15 hr at room temperature. Then the reaction mixture was poured into ether, extracted with water, and dried with anhydrous sodium sulfate. Removal of the solvent gave 19.90 g of a viscous residue which crystallized when stirred with a little hexane. Attempted recrystallization from hexane gave two distinct types of crystals, irregularly shaped white ones and orange prisms. All of the solvent was removed from the recrystallization systems, the residue was dissolved in a minimum of chloroform, and the chloroform solution was placed on a column of 760 g of alumina in hexane. Elution with 50:50 (v/v) hexane–ether gave 15.86 g of a white solid. Recrystallization from hexane gave 12.88 g (61%) of V, mp 117.5–120.5°. The infrared spectrum ($CHCl_3$) showed a C=N absorption[11] (1670 cm^{-1}) and an aryl ether absorption[11] (1249 cm^{-1}). The nmr spectrum ($CDCl_3$) showed only aromatic protons as a complex multiplet (τ 2.19–3.97).

Anal. Calcd for $C_{31}H_{23}NO$: C, 87.50; H, 5.45; N, 3.29. Found: C, 87.3; H, 5.5; N, 3.2.

N-(2,6-Diphenylphenyl)benzanilide (IX).—An amount of V (1.23 g) was heated in air in a sealed Carius tube at 300° for 30 min. The product was recrystallized from ethanol to give 0.89 g (72%) of IX, mp 159–160.5°. The infrared spectrum showed a tertiary amide carbonyl absorption[11] (1645 cm^{-1}) and a tertiary phenyl amine band[11] (1350 cm^{-1}). The nmr spectrum showed only a complex aromatic proton multiplet, entirely different in complexity from that of V, between τ 2.45 and 4.12. The use of an internal standard indicated that this product (IX) contained the required number of aromatic protons (*i.e.*, 23) per molecule.

Anal. Calcd for $C_{31}H_{23}NO$: C, 87.50; H, 5.45; N, 3.29. Found: C, 87.8; H, 5.6; N, 3.1.

Kinetic Runs.—Approximately 0.3 *M* solutions of II, III, IV, and V in diphenyl ether were prepared. Samples of II, III, and IV were sealed in nmr tubes and heated in a refluxing diphenyl ether bath at 258.0°. The samples were withdrawn periodically and cooled to room temperature, and the diminution in the amount of starting material was determined by nmr spectros-

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 115, 205, 249, and 263.

copy. Several samples of the same 0.3 *M* solution of V were sealed in Pyrex tubes, all of which were placed into the 258.0° bath simultaneously. Samples were removed at various times, cooled to room temperature, and diluted with chloroform, and the amount of V remaining was determined by infrared spectroscopy. By these semiquantitative methods, rate constants for the rearrangements of these imidates could be determined and are given in Table I.

Registry No.—II, 16240-81-6; III, 16240-82-7; IV, 16240-83-8; V, 16240-84-9; VI, 16240-85-0; VII, 16240-86-1; VIII, 16240-87-2; IX, 16240-88-3.

Acknowledgment.—The author acknowledges many encouraging and stimulating thoughts contributed to this work by A. S. Hay.

Steric Rate Enhancement in the Newman–Kwart Rearrangement. A Comparison with the Chapman Rearrangement

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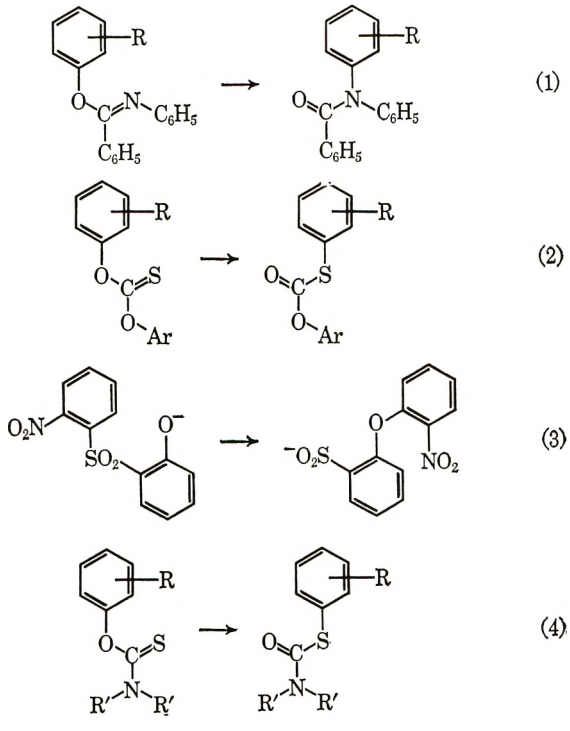
A series of O-aryl dimethylthiocarbamates have been prepared and their rates of rearrangement to the corresponding S-aryl dimethylthiocarbamates have been determined. Steric acceleration of rates due to hindered rotation (as found also in the Chapman rearrangement) appeared to be present in the *ortho*-substituted compounds in this series. A correlation of the rates with substituent constants and a separation of polar and steric effects were achieved.

Intramolecular migration of aryl groups between adjacent atoms occurs quite commonly in organic chemistry. Much less common, however, are intramolecular migrations between nonadjacent atoms. Some examples of this latter type of reaction are the Chapman rearrangement[1] (reaction 1), the Schönberg rearrangement[2] (reaction 2), the Smiles rearrangement[3] (reaction 3), and the recently reported conversion of O-aryl dialkylthiocarbamates into S-aryl dialkylthiocarbamates[4] (reaction 4), hereinafter referred to as the Newman–Kwart rearrangement. The present paper is concerned mainly with the Newman–Kwart and Chapman rearrangements.



(1)

(2)

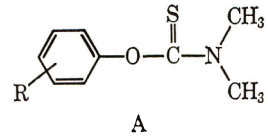
(3)

(4)

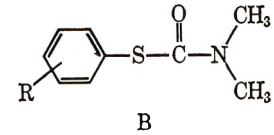
It has been reported[5] that the Chapman rearrangement is an intramolecular nucleophilic–aromatic substitution reaction and that *ortho* substituents in the migrating aromatic ring enhance the rate[5–7] (steric acceleration due to hindered rotation (SAHR) effect[6]). The apparent similarity between this reaction and the Newman–Kwart rearrangement prompted a kinetic investigation of the latter in order to determine whether or not the postulated SAHR effect in the Chapman rearrangement was evident in the Newman–Kwart rearrangement also.

Results

The O-aryl dimethylthiocarbamates (A1–A13) used in the present study were prepared from the corresponding phenols by the method of Newman and Karnes.[4] The previously unknown materials (A2, A4–A10, A12, and A13) were identified by their nmr and infrared spectra and by their elemental analyses.



A



B

1, R = 4-OCH_3
2, R = 4-CH_3
3, R = 4-t-C_4H_9
4, R = H
5, R = 4-Br
6, R = 4-C_6H_5
7, R = 2-CH_3

8, R = 2,6-$(CH_3)_2$
9, R = 2-t-C_4H_9
10, R = 2-t-C_4H_9-4-CH_3
11, R = 2,6-(t-C_4H_9)$_2$-4-CH_3
12, R = 2-C_6H_5
13, R = 2,6-$(C_6H_5)_2$
14, R = 4-NO_2

These same previously unkown compounds were each heated neat at 258° for times necessary for

(1) For a recent review, see J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).

(2) H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Amer. Chem. Soc.*, **77**, 2479 (1955); D. H. Powers and D. S. Tarbell, *ibid.*, **78**, 70 (1956).

(3) J. F. Bunnett and T. Okamoto, *ibid.*, **78**, 5363 (1956).

(4) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966); H. Kwart and E. R. Evans, *ibid.*, **31**, 410 (1966).

(5) K. B. Wiberg and B. I. Rowland, *J. Amer. Chem. Soc.*, **77**, 2205 (1955).

(6) H. M. Relles, *J. Org. Chem.*, **33**, 2245 (1968).

(7) Conversely, in *inter*molecular nucleophilic–aromatic substitution reactions, *ortho* substituents sterically cause rate depressions (absence of SAHR effect). See, for example, (a) A. M. Porto, L. Altiere, A. J. Castro, and J. A. Brieux, *J. Chem. Soc., Sect. B*, 963 (1966); (b) N. E. Sbarbati, *J. Org. Chem.*, **30**, 3365 (1965); (c) P. Van Berk, J. O. M. Van Langen, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **75**, 1137 (1956); (d) P. J. C. Fierens and A. Halleux, *Bull. Soc. Chim. Belges*, **64**, 696 (1955).

their complete rearrangement to the corresponding S-aryl dimethylthiocarbamates (B2, B4–B10, B12, and B13, respectively). In every case, the product was found to be essentially pure by nmr spectroscopy. Each was recrystallized and identified by its elemental analysis and nmr and infrared spectra. The conversions of A1, A3, A11, and A14 into B1, B3, B11, and B14, respectively, have been reported[4] previously.

In agreement with the recent study of Neuman, Roark, and Jonas,[8] it was observed that the nmr spectrum of each A isomer displayed a well-resolved doublet at room temperature for the $(CH_3)_2N$ group, whereas each corresponding B isomer showed, for this group, a single sharp peak shifted upfield somewhat from the doublet of A. This type of nmr spectral difference was also noted by Newman and Karnes[4] for the isomeric pairs which they prepared. This difference provided a relatively simple method for following the rates of rearrangement of the A isomers to the corresponding B isomers in diphenyl ether. The observed rate constants are listed in Table I.

TABLE I

RATE CONSTANTS FOR THE NEWMAN–KWART REARRANGEMENT IN A 0.3 *M* SOLUTION OF DIPHENYL ETHER AT 258.2°

Compd	$k \times 10^4$, sec^{-1}
A1	1.09 ± 0.05
A2	2.80 ± 0.10
A3	3.25 ± 0.05
A4	5.70 ± 0.20
A5	11.3 ± 0.2
A6	7.95 ± 0.15
A7	5.45 ± 0.25
A8	4.75 ± 0.05
A9	1.09 ± 0.03
A10	0.595 ± 0.005
A11	0.0390 ± 0.0010
A12	4.80 ± 0.05
A13	4.70 ± 0.10

In one case, A9 → B9, a fourfold increase in the initial concentration gave no change in the k value, thus indicating that the rearrangement was first order in A9. Newman and Karnes found[4] that the rearrangement of A14 was also unimolecular. It, therefore, does not seem unreasonable to assume that the other A isomers studied herein rearranged by unimolecular processes also.[9]

The rates of rearrangement of A2, A4, A7, and A8 were similarly determined at 232.3°. These k values are similarly determined at 232.3°. These k values are listed in Table II along with the calculated enthalpy and entropy of activation.

Discussion

Evidence that (at least) A2, A4, A7, and A8 rearrange by a common mechanism is provided by the excellent straight-line plot of log $k_{258.2°}$ against log $k_{232.3°}$ (correlation coefficient = 0.990), which fulfills Exner's criterion.[10]

(8) R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, **89**, 3412 (1967).

(9) Powers and Tarbell showed[2] that the structurally similar Schönberg rearrangement of bis(4-chlorophenyl)thioncarbonate to bis(4-chlorophenyl)-thiolcarbonate displayed first-order kinetics. Furthermore, Wiberg and Rowland found[6] that the Chapman rearrangement proceeded by first-order kinetics.

TABLE II

ACTIVATION PARAMETERS AND RATE CONSTANTS FOR THE NEWMAN–KWART REARRANGEMENT IN 0.3 *M* SOLUTIONS OF DIPHENYL ETHER AT 232.3°

Compd	$k \times 10^5$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
A2	4.35 ± 0.15	37.3 ± 1.5	−6.0 ± 2.5
A4	8.0 ± 0.25	39.5 ± 1.5	−0.4 ± 2.5
A7	7.9 ± 0.20	38.8 ± 1.5	−1.7 ± 2.5
A8	6.60 ± 0.10	39.7 ± 1.5	−0.2 ± 2.5

It is apparent from a comparison of the rate constants for A2, A7, and A8 that there is a rate-enhancing effect present in A7 and A8 which is considerably more important than the rate-depressing inductive and steric-compressive effects of methyl groups. This is most likely the SAHR effect previously found[5,6] to be of importance in the Chapman rearrangement. Although there is considerable uncertainty involved, the trend in the $\Delta S^{\ddagger}$ values for A2, A7, and A8 (Table II) indicates that the rate enhancements of A7 and A8 arise from decreased $\Delta S^{\ddagger}$. That is, the *o*-methyl substituents cause an entropy loss in A7 and A8, relative to A2, even before rearrangement occurs by hindering free rotation around the carbon–oxygen bonds. The restriction of this mode of rotation is precisely that which is required for the formation of the four-membered ring during rearrangement.

Also as in the Chapman rearrangement, steric compression apparently overrides the SAHR effect for *t*-butyl groups in the Newman–Kwart rearrangement. Thus, A9 rearranges only one-third as fast as A3.

The above discussion serves to indicate somewhat qualitatively that the same sort of effects are operative in the Chapman and Newman–Kwart rearrangement. However, the separation of polar and steric contributions to *ortho* substituent constants in both rearrangements can be achieved by a more quantitative approach, as follows.

Since direct attack occurs on a ring carbon during the rearrangements, the use of a set of substituent parameters other than σ seems desirable. Indeed, when the logarithms of the rate constants for A1–A6 (in which no steric effects are involved) were plotted against the corresponding σ values,[11] a least-squares line was obtained which had a correlation coefficient of only 0.839. Similarly, in the Chapman rearrangement, the plot of log k's for C1–C9 *vs.* σ gave a correlation coefficient of 0.925.

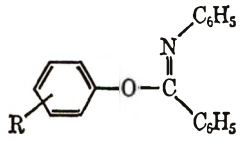
Intermolecular nucleophilic-aromatic substitution reactions resemble the Chapman and Newman–Kwart rearrangements in that they also involve direct attack on a ring carbon and placing of negative charge in the ring. From the kinetics of four different series of these reactions, Brieux and coworkers[7a,12] were able to calculate *para* substituent constants by using the ρ values obtained from plots of log k's of *meta*-substituted compounds against σ values obtained from the literature. Where comparisons could be made, the *para* substituent constants obtained in this way much more closely resembled σ^- (Hammett's constants obtained from the reactions of anilines and phenols)

(10) O. Exner, *Collect. Czech. Chem. Commun.*, **29**, 1094 (1964).

(11) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 89 (1963).

(12) W. Greizerstein, R. A. Bonelli, and J. A. Brieux, *J. Amer. Chem. Soc.*, **84**, 1026 (1962).

than σ. For the present discussion, Brieux's series of substituent constants have been desginated as "σ^-" constants.



C1, R = 4-OCH_3	C9, R = 3-CH_3
2, R = 4-CH_3	10, R = 2-CH_3
3, R = 4-t-C_4H_9	11, R = 2,6-$(CH_3)_2$
4, R = H	12, R = 2-t-C_4H_9
5, R = 4-C_2H_5	13, R = 2,6-$(t$-$C_4H_9)_2$
6, R = 4-i-C_3H_7	14, R = 2,6-$(C_6H_5)_2$
7, R = 4-Cl	15, R = 2-CH_3-6-C_6H_5
8, R = 4-Br	16, R = 2-i-C_3H_7

When these σ^- values were plotted against the log k's for the Newman–Kwart rearrangement of A1–A6, the correlation coefficient was found to be 0.954 and $\rho = 1.62$[13] (see Figure 1). For the Chapman rearrange-

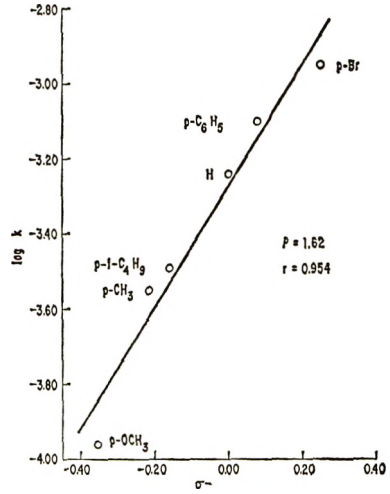


Figure 1.—Least-squares plot of log k for the Newman–Kwart rearrangement of 4-substituted A at 258.2° *vs.* σ^-.

ment of C1–C4 and C7–C9,[5,14] the correlation coefficient was 0.970 and $\rho = 1.63$[13] (see Figure 2). (No improvement in these correlations was found when log k's were plotted against linear combinations of σ^- and σ.[15]) From these ρ values, it was possible to calculate the substituent constants for the *ortho*-substituted compounds in the Newman–Kwart (A7–A13) and in the Chapman (C10–C16) rearrangements. Furthermore, according to Taft[16]

$$\sigma^{-\,\text{polar}}_{ortho} \cong \sigma^{-\,\text{polar}}_{para} \qquad (5)$$

Using this same approximation for σ^- values, it was possible to calculate *steric* substituent constants for the two rearrangements. These results are tabulated in Tables III, IV, and V.

(13) The similarity in the ρ values further supports the proposal that the mechanisms for the two rearrangements are the same.

(14) C5 and C6 were omitted from the plot because σ^- values for p-C_2H_5 and p-i-C_3H_7 are not available.

(15) The use of linear combinations of substituent constants for improved rate correlations has been reported: (a) A. A. Humffray and J. J. Ryan, *J. Chem. Soc., Sect. B*, 468 (1967); (b) J. J. Ryan and A. A. Humffray, *ibid.*, 842 (1966); (c) Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **32**, 960 (1959); (d) Y. Tsuno and Y. Tukawa, *ibid.*, **32**, 965, 971 (1959).

(16) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 556.

TABLE III

SEPARATION OF POLAR AND STERIC EFFECTS IN THE NEWMAN–KWART REARRANGEMENT IN 0.3 *M* SOLUTIONS OF DIPHENYL ETHER AT 258.2°

Compd	Log k	σ^-_{para}[a]	$\sigma^{-\,\text{polar}\ a}_{para}$	$\sigma^{-\,\text{steric}}_{para}$
A1	−3.96	−0.354	−0.354	0.0
A2	−3.55	−0.216	−0.216	0.0
A3	−3.49	−0.160	−0.160	0.0
A4	−3.24	0.0	0.0	0.0
A5	−2.95	0.251	0.251	0.0
A6	−3.10	0.078	0.078	0.0
		Newman–Kwart σ^-_{ortho}[b]	$\sigma^{-\,\text{polar}\ a,c}_{ortho}$	Newman–Kwart $\sigma^{-\,\text{steric}}_{ortho}$
A7	−3.26	−0.012	−0.216	0.204
A8	−3.32	−0.049	−0.432	0.383
A9	−3.96	−0.444	−0.160	−0.284
A10	−4.23	−0.611	−0.376[d]	−0.235
A11	−5.41	−1.340	−0.536[d]	−0.804
A12	−3.32	−0.049	0.078	−0.127
A13	−3.33	−0.056	0.156	−0.212

[a] Average values for four intermolecular reactions; see ref 7a and 12. [b] Calculated from $\rho = 1.62$. [c] Assume that total σ^- equals the sum of the individual σ^-'s; see ref 16; $\sigma^{-\,\text{polar}}_{ortho} \cong \sigma^{-\,\text{polar}}_{para}$. [d] Includes σ^-_{para} for 4-CH_3 group.

TABLE IV

SEPARATION OF POLAR AND STERIC EFFECTS IN THE CHAPMAN REARRANGEMENT IN 0.3 *M* SOLUTIONS OF DIPHENYL ETHER AT 255°

Compd	Log k	σ^-_{para}[a]	$\sigma^{-\,\text{polar}\ a}_{para}$	$\sigma^{-\,\text{steric}}_{para}$
C1	−4.80[b]	−0.354	−0.354	0.0
C2	−4.45[b]	−0.216	−0.216	0.0
C3	−4.42[b]	−0.160	−0.160	0.0
C4	−4.12[b]	0.0	0.0	0.0
C5	−4.43[b]	(−0.19)[c]	(−0.19)[c]	0.0
C6	−4.42[b]	(−0.19)[c]	(−0.19)[c]	0.0
C7	−3.86[b]	0.212	0.212	0.0
C8	−3.74[b]	0.251	0.251	0.0
C9	−4.15[b]	−0.069	−0.069	0.0
		Chapman σ^-_{ortho}[d]	$\sigma^{-\,\text{polar}\ a,e}_{ortho}$	Chapman $\sigma^{-\,\text{steric}}_{ortho}$
C10	−4.05[b]	0.043	−0.216	0.259
C11	−3.91[f]	0.129	−0.432	0.561
C12	−4.64[b]	−0.319	−0.160	−0.159
C13	−5.51[f]	−0.853	−0.320	−0.533
C14	−3.73[f]	0.239	0.156	0.083
C15	−3.81[f]	0.190	−0.138	0.328
C16	−4.17[b]	−0.031	(−0.19)[c]	(0.16)[c]

[a] Average values for four intermolecular reactions, see ref 7a and 12. [b] Data from ref 5. [c] No data reported in ref 7a and 12. Assumed that values would be intermediate between CH_3 and t-C_4H_9 to a first approximation. [d] Calculated from $\rho = 1.63$. [e] Assume that total σ^- equals the sum of the individual σ^-'s (see ref 16); $\sigma^{-\,\text{polar}}_{ortho} \cong \sigma^{-\,\text{polar}}_{para}$. [f] Data from ref 6.

TABLE V

COMPARISON OF STERIC EFFECTS IN THE NEWMAN–KWART AND CHAPMAN REARRANGEMENTS

ortho substituent(s)	Newman–Kwart $\sigma^{-\,\text{steric}}_{ortho}$	Chapman $\sigma^{-\,\text{steric}}_{ortho}$
2-CH_3	0.204	0.259
2,6-$(CH_3)_2$	0.383	0.561
2-t-C_4H_9	−0.284, −0.235	−0.159
2,6-$(t$-$C_4H_9)_2$	−0.804	−0.533
2-C_6H_5	−0.127	
2,6-$(C_6H_5)_2$	−0.212	0.083
2-CH_3-6-C_6H_5		0.328
2-i-C_3H_7		(0.16)

TABLE VI

O-ARYL DIMETHYLTHIOCARBAMATES

Compd	Mp, °C	Proton nmr τ values (no. of protons) Aromatic multiplet	$N(CH_3)_2$ Doublet	$Ar-CH_3$ singlet	$Ar-C(CH_3)_3$ singlet	Characteristic ir bands,[a] cm^{-1}
A2	86–88[b]	2.72–3.22 (4 H)	6.63, 6.74 (6 H)	7.77 (3 H)		1539, 1200
A4[c]	170–175 (0.25)[d]	2.47–3.1 (5 H)	6.68, 6.80 (6 H)			1527, 1200
A5	84–86[b]	2.23–3.16 (4 H)	6.60, 6.74 (6 H)			1542, 1208
A6	139–141[b]	2.27–3.01 (9 H)	6.55, 6.67 (6 H)			1534, 1205
A7[c]	163–168 (0.2)[d]	2.68–3.18 (4 H)	6.63, 6.77 (6 H)	7.92 (3 H)		1528, 1212
A8	80–82[b]	2.94 (3 H)	6.55, 6.64 (6 H)	7.83 (6 H)		1535, 1172
A9	63–65[b,e]	2.53–3.28 (4 H)	6.60, 6.67 (6 H)		8.66 (9 H)	1533, 1193
A10	72–74[b]	2.72–3.1 (3 H)	6.52, 6.63 (6 H)	7.67 (3 H)	8.65 (9 H)	1522, 1208
A12	102–104[b]	2.47–2.9 (9 H)	6.72, 6.94 (6 H)			1533, 1194
A13	132–133[b,f]	2.40–2.85 (13 H)	7.08, 7.13 (6 H)			1535, 1197

[a] Characteristic bands were reported to be 1530–1560 and 1190–1230 cm^{-1} for a series of 29 compounds (see ref 4). [b] Recrystallized from ethanol. [c] Some S-aryl compound was formed on distillation and remained as a small impurity in the O-aryl compound. Its presence was taken into account in the kinetic runs but did not affect the elemental analysis. [d] Boiling point (millimeter). [e] Recrystallized after distilling; the boiling point was 174–182° (0.13 mm). [f] Recrystallized after eluting from an alumina column with 1:3 hexane–benzene.

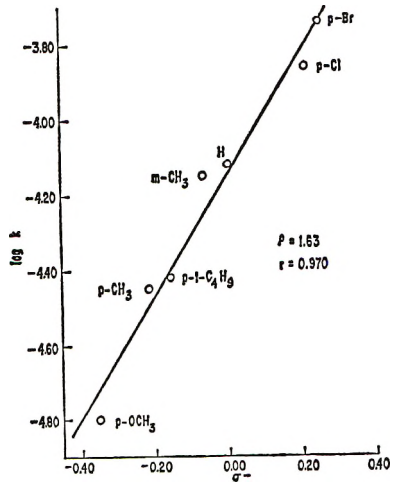


Figure 2.—Least-squares plot of log k for the Chapman rearrangement of 4-substituted C at 255° *vs.* σ^-.

Despite the approximations made above, the values for $\sigma^{-\,\text{steric}}_{ortho}$[17] in both rearrangments are in agreement with the previously discussed (*vide supra*) competition between rate enhancement (SAHR effect) and rate depression. The rate-enhancing steric effect of a single *o*-methyl group is almost the same in both rearrangements and, in each case, addition of a second *o*-methyl group causes further *steric* rate enhancement by a factor of approximately two (see Table V).

Steric compression during rearrangement would be expected to be much more severe with *t*-butyl groups than with methyl groups and the negative sign of the $\sigma^{-\,\text{steric}}_{ortho}$ values for the *t*-butyl compounds shows that this rate-retarding compression overrides the SAHR effect. Although the $\sigma^{-\,\text{steric}}_{ortho}$ values for the *t*-butyl compounds are not the same in the two rearrangements, the ratio of the values for two *t*-butyl groups and one *t*-butyl group in both cases is *ca.* 3. This more-than-cumulative effect has been discussed previously[6] and given a tentative structural interpretation.

A single isopropyl group has a $\sigma^{-\,\text{steric}}_{ortho}$ value between those for methyl and *t*-butyl in agreement with the expected order of steric compression for the three groups (*t*-butyl > *i*-propyl > methyl). The positive sign of this $\sigma^{-\,\text{steric}}_{ortho}$ indicates that here, as in the methyl case, the SAHR effect is more important than steric compression.

It is probable that the compounds containing *o*-phenyl substituents give rise to small $\sigma^{-\,\text{steric}}_{ortho}$ values because of the approximate balance between steric compression and the SAHR effect. But the errors incurred through the approximations used are apparently magnified in these cases since the sign of the $\sigma^{-\,\text{steric}}_{ortho}$ cannot even be stated.

There is another internal consistency which arises from the $\sigma^{-\,\text{steric}}_{ortho}$ values for the Chapman rearrangement. The calculated value for 2-CH_3-6-C_6H_5 is 0.328. This is very close to that which is obtained, 0.301, by adding the value for 2-CH_3 to one-half of the value for 2,6-$(C_6H_5)_2$ (see Table V).

Experimental Section

All new compounds gave satisfactory elemental analysis and molecular weight determinations consistent with the assigned structures. Known compounds gave correct melting points and the expected spectral data.

Preparation of O-Aryl Dimethylthiocarbamates.—These compounds (A1–A13) were prepared under nitrogen from the appropriate phenol by the sodium hydride–DMF–dimethylthiocarbamoyl chloride method of Newman and Karnes.[4] Their corrected melting points (or boiling points) and spectral data are given in Table VI. Infrared spectra were recorded as KBr pellets or in chloroform or carbon disulfide solution. Nmr spectra were taken in CCl_4 or $CDCl_3$ using tetramethylsilane as an internal standard.

Preparation of S-Aryl Dimethylthiocarbamates.—These compounds were all obtained in high yield by heating the corresponding O-aryl dimethylthiocarbamate at 258° for the appropriate time (determined in the kinetic runs). Their physical constants and spectral data are given in Table VII. Infrared and nmr spectra were recorded as described for the O-aryl dimethylthiocarbamates.

Kinetic Runs.—A 0.3 *M* solution of each A isomer in diphenyl ether was prepared, sealed in an nmr tube, and heated in a refluxing diphenyl ether bath at 258.2° (cor.). The nmr tube was removed at various intervals and its nmr spectrum was recorded at room temperature. The relative amounts of A and B isomers present as a function of time at 258.2° were thus determined. Control experiments showed that no changes in the

(17) It should be noted that these steric substituent constants can only apply to *intramolecular* reactions of the types shown in eq 1–4 since they include SAHR effects. SAHR effects would not be expected to occur in *intermolecular* nucleophilic–aromatic substitutions.

TABLE VII

S-ARYL DIMETHYLTHIOCARBAMATES

Compd	Mp, °C	Proton nmr τ values (no. of protons) Aromatic multiplet	$N(CH_3)_2$ Singlet	$Ar-CH_3$ singlet	$Ar-C(CH_3)_3$ singlet	Thiol ester carbonyl ir band, cm^{-1} [a]
B2	31–33[b]	2.50–2.96 (4 H)	6.97 (6 H)	7.65 (3 H)		1669
B4	c	2.50–2.67 (5 H)	6.98 (6 H)			1668
B5	81–83[d]	2.40–2.77 (4 H)	6.97 (6 H)			1660
B6	136–137.5[d]	2.32–2.83 (9 H)	6.98 (6 H)			1665
B7	c	2.73 (4 H)	6.94 (6 H)	7.67 (3 H)		1668
B8	35–37[b]	2.86 (3 H)	7.00 (6 H)	7.59 (6 H)		1664
B9	75–77[b]	2.45–3.00 (4 H)	7.07 (6 H)		8.53 (9 H)	1662
B10	70–73[d]	2.68–2.98 (3 H)	6.95 (6 H)	7.67 (3 H)	8.56 (9 H)	1662
B12	83–85[d]	2.68 (9 H)	7.19 (6 H)			1663
B13	127–129[d]	2.56–2.91 (13 H)	7.42 (6 H)			1660

[a] Reported as occurring near 1675 cm^{-1} by L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 188. [b] Recrystallized from 30–60° petroleum ether. [c] Liquid. [d] Recrystallized from ethanol.

TABLE VIII

REARRANGEMENT OF (2-*t*-BUTYL-4-METHL)PHENYL DIMETHYLTHIOCARBAMATE (A10) AT 258.2°

Time at 258.2° min	% of A10 remaining	$k \times 10^5$ [a] sec^{-1}
0	100	
30	89.4	6.2
90	74.0	5.6
150	58.6	6.0
210	48.5	5.7
270	39.6	5.7
450	19.3	6.1
1350	*ca.* 0	Av $k = 5.9 \pm 0.2$

[a] Calculated from the equation $k = 2.303/t \times \log a/(a - x)$ where t = seconds, a = initial concentration, and $(a - x)$ = concentration at time t.

amounts of A and B isomers occurred over a period of days at room temperature. Duplicate runs in each case agreed within 4% (the precision of the nmr integrator). The rearrangements were followed kinetically to at least 75% completion and no drifts in the rate constants were noted. The results are listed in Table I.

In every case, after many half-lives, no O-aryl compound could be detected by nmr.

The results of a typical kinetic run are illustrated in Table VIII.

Registry No.—A2, 16241-02-4; B2, 7322-85-2; A4, 16241-04-6; B4, 7304-68-9; A5, 16241-06-8; B5, 7305-13-7; A6, 16241-08-0; B6, 16241-09-1; A7, 10345-39-8; B7, 7305-14-8; A8, 16241-12-6; B8, 16241-13-7; A9, 16241-14-8; B9, 16241-15-9; A10, 16214-91-8; B10, 16214-92-9; A12, 10345-41-2; B12, 16241-17-1; A13, 16241-18-2; B13, 16241-19-3.

Hydrolysis Kinetics for *p*-Dimethylaminophenyl Isocyanate in Aqueous Solutions

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p-Dimethylaminophenyl isocyanate hydrolyzes, giving *p*-dimethylaminoaniline. The rate-limiting reaction at pH <9 is hydration of the isocyanate to give the carbamic acid (or carbamate ion). Rate data for the hydration indicate three reaction paths which are first order in unprotonated isocyanate: (1) pH independent; (2) first order in $[H^+]$; (3) first order in $[OH^-]$. Approach of the rate to pH independence as the pH is lowered is attributed to protonation of the isocyanate. The rate decreases with increasing acetate buffer concentration. In phosphate buffers, fast reaction of the phosphate with the isocyanate competes with hydration. An interpretation of the yields of *p*-dimethylaminoaniline in phosphate buffers indicates that there is no important catalysis of isocyanate hydrolysis by phosphate. The yield experiments also gave the rate constant for the reaction of the isocyanate with *p*-dimethylaminoaniline to form 1,3-bis(*p*-dimethylaminophenyl)urea. Arsenate reacts with the isocyanate even more rapidly than does phosphate. The product goes to *p*-dimethylaminoaniline very rapidly. Above pH 9, decarboxylation of the carbamate ion is the rate-limiting reaction in the hydrolysis of the isocyanate. It is proposed that decarboxylation proceeds *via* protonation of the nitrogen of the carbamate group.

Hydrolysis kinetics for organic isocyanates in aqueous solution appear not to have been reported. The present communication describes the hydrolysis kinetics for *p*-dimethylaminophenyl isocyanate in aqueous solutions containing 1% acetonitrile. This isocyanate gave a product (*p*-dimethylaminoaniline) that could be monitored conveniently at a rotating platinum anode, and reaction rates were not prohibitively high. Since the rotating electrode is a very sensitive analytical probe, low isocyanate concentrations could be used. It was thus possible to avoid almost completely the reaction of the isocyanate with *p*-dimethylaminoaniline to give 1,3-bis(*p*-dimethylaminophenyl)urea.[1] Eliminating this reaction simplified the kinetics.

Results and Discussion

Below pH 11, reactions were monitored with the rotating platinum electrode. At higher pH values, reactions were slow and were best followed spectrophotometrically. Observed pseudo-first-order rate constants, k_{obsd}, were calculated from slopes of log $(X_\infty$

(1) H. Staudinger and R. Endle, *Ber.*, **50**, 1042 (1917); C. Naegeli, A. Tyabji, L. Conrad, and F. Litwan, *Helv. Chim. Acta*, **21**, 1100 (1938).

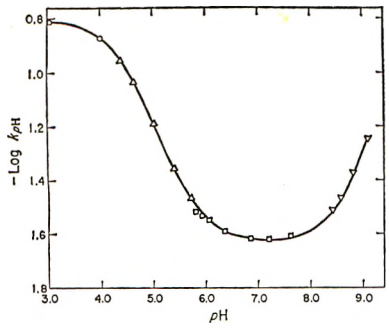

Figure 1.—pH dependence for the hydration of *p*-dimethylaminophenyl isocyanate at 25° and ionic strength 0.1 *M*: ○, hydrochloric acid solutions; △, acetate buffers; □, phosphate buffers; ▽, borate buffers.

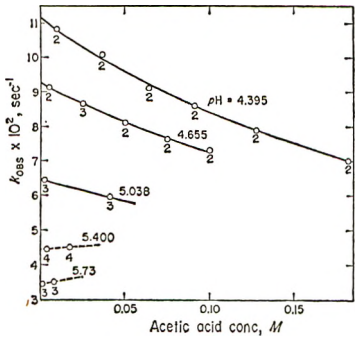

Figure 2.—Pseudo-first-order rate constants for the formation of *p*-dimethylaminoaniline from *p*-dimethylaminophenyl isocyanate in acetate buffers at 25° and ionic strength 0.1 *M*. Each point gives the average value of k_{obsd} for the number of kinetic runs indicated beneath the point. The solid lines were calculated with eq 2. The maximum acetate concentration at each pH was 0.1 *M*.

minus X_t) *vs.* time plots, where X is the experimental variable monitored.

Near pH 9 there was a change in the rate-limiting step, resulting in nonlinear induction periods in the first-order plots. In these cases, k_{obsd} values were obtained from the slopes of the linear portions of the plots following the induction periods. Below pH 9, the rate-limiting reaction is hydration of the isocyanate to give carbamic acid or carbamate ion ($RNHCOOH$ or $RNHCOO^-$). Above pH 9, decarboxylation of the carbamate ion is rate limiting. The accumulation of carbamate as an intermediate in the conversion of phenyl isocyanate into aniline has been described by Mohr.[2]

pH Dependence of Isocyanate Hydration.—Reactions were run at 25° in dilute hydrochloric acid solutions and in acetate, phosphate, arsenate, and borate buffers. Ionic strength was adjusted to a calculated value of 0.1 *M*. The values of k_{obsd} depended on the concentrations of the buffers. Extrapolation of k_{obsd} to zero buffer concentration gave values designated k_{pH} (for the hydrochloric acid solutions, k_{obsd} is identical in meaning with k_{pH}). The log k_{pH}–pH profile is shown in Figure 1. A theoretical model that can duplicate this profile consists of three parallel reactions, each first-order in unprotonated isocyanate. The first is pH independent, the second is first-order in hydrogen ion, and the third is first-order in hydroxide ion. The approach toward pH independence as pH is lowered is associated with substantial protonation of the isocyanate. This model leads to eq 1 where k_1, k_2, and k_3 are the rate constants for the three parallel reactions, K_1 is the acid dissociation constant for the protonated isocyanate, and K_w is the ion product for water. Values for the parameters of eq 1, determined by nonlinear regression, are given in Table I. The value found for K_1 does not seem unreasonable for the acid dissociation constant of the protonated isocyanate. Calculated and experimental k_{pH} values agree well. The standard error of fit of log k_{pH} (calcd) to log k_{pH} (exptl) is 0.0089 log unit. The maximum deviation is 0.019 log unit.

$$k_{pH} = (k_1 + k_2 10^{-pH} + k_3 K_w 10^{pH})(1 + K_1^{-1} 10^{-pH})^{-1} \quad (1)$$

TABLE I
PARAMETER VALUES FOR 25° AND IONIC STRENGTH 0.1 *M* (OR 0.5 *M* AS INDICATED)

Eq	Parameter	pH[a]	Value[b]	Units
1	k_1		$(2.31 \pm 0.02) \times 10^{-2}$	sec^{-1}
1	k_2		$(7.35 \pm 0.08) \times 10^{3}$	$M^{-1}\ sec^{-1}$
1	k_3k_w		$(2.78 \pm 0.08) \times 10^{-11}$	$M\ sec^{-1}$
1	K_1		$(2.17 \pm 0.09) \times 10^{-5}$	*M*
2	*a*	4.395	29.3 ± 1.5	M^{-1} sec
2	*a*	4.655	29.6 ± 1.8	M^{-1} sec
2	*a*	5.038	32.0 ± 5.9	M^{-1} sec
3, 4	K_2		$\sim 3 \times 10^{-6}$	*M*
3, 5	K_3		~ 0.7	M^{-1}
6	k_4		0.692 ± 0.031	$M^{-1}\ sec^{-1}$
6	k_5		$(1.231 \pm 0.039) \times 10^{6}$	$M^{-2}\ sec^{-1}$
7	*b*	5.823	63.5 ± 1.0	M^{-1}
7	*b*	6.860	32.3 ± 0.6	M^{-1}
7	*b*	7.202	28.8 ± 0.4	M^{-1}
7	*b*	7.616	27.8 ± 0.4	M^{-1}
7	*c*	5.823	$(1.12 \pm 0.06) \times 10^{3}$	M^{-1}
7	*c*	6.860	$(4.87 \pm 0.07) \times 10^{3}$	M^{-1}
7	*c*	7.202	$(6.34 \pm 0.09) \times 10^{3}$	M^{-1}
7	*c*	7.616	$(6.57 \pm 0.13) \times 10^{3}$	M^{-1}
8	k_4		0.657 ± 0.016	$M^{-1}\ sec^{-1}$
8	k_5		$(0.920 \pm 0.050) \times 10^{6}$	$M^{-2}\ sec^{-1}$
9	k_6	5.823	35.9	$M^{-1}\ sec^{-1}$
9	k_6	6.860	118	$M^{-1}\ sec^{-1}$
9	k_6	7.202	152	$M^{-1}\ sec^{-1}$
9	k_6	7.616	161	$M^{-1}\ sec^{-1}$
10	k_7		172	$M^{-1}\ sec^{-1}$
10	K_4		3.7×10^{-7}	*M*
14, 15	$k_w[H_2O]$		$(5.134 \pm 0.096) \times 10^{-5}$	sec^{-1}
			$(5.198 \pm 0.125) \times 10^{-5}$ [c]	sec^{-1}
14, 15	k_{H^+}		$(1.501 \pm 0.014) \times 10^{8}$	$M^{-1}\ sec^{-1}$
			$(1.097 \pm 0.016) \times 10^{8}$ [c]	$M^{-1}\ sec^{-1}$
14, 15	$k_{H_2CO_3}/K_5$		$(4.49 \pm 0.29) \times 10^{8}$	$M^{-2}\ sec^{-1}$
14, 15	$k_{HCO_3^-}$		0.1326 ± 0.0078	$M^{-1}\ sec^{-1}$
14	K_5/k_{10}		0.875×10^{-9} [d]	*M* sec
			$(1.137 \pm 0.040) \times 10^{-9}$ [c]	*M* sec

[a] No entry means that the parameter is theoretically independent of pH. [b] Limits are estimates of the standard errors. [c] Ionic strength, 0.5 *M*. [d] Fixed at this value.

Hydration of the Isocyanate in Acetate Buffers.—Observed pseudo-first-order rate constants are plotted *vs.* acetic acid concentration in Figure 2. In the lower part of the pH range, there is significant inhibition of the reaction by the buffers. At the upper end of the pH range, there may be a barely perceptible catalysis. The inhibition can be accounted for quantitatively by assuming that (a) an acetic acid–isocyanate adduct forms in a reversible reaction; (b) equilibrium with respect to this reaction is maintained during the course of the isocyanate hydration; (c) the adduct is basic, *i.e.*, it can be protonated; (d) the only reaction of the adduct is its dissociation to give back the isocyanate; and (e) there is no catalysis by acetate buffers of *p*-dimethylaminoaniline formation. The theoretical rela-

(2) E. Mohr, *J. Prakt. Chem.*, **73**, 177 (1906).

tionship between the observed rate constants and the acetic acid concentration is given in eq 2. The param-

$$k_{obsd}^{-1} = k_{pH}^{-1} + a[HOAc]. \quad (2)$$

eter a is given by eq 3 where K_3, the formation con-

$$a = K_3(1 + 10^{-pH}K_2^{-1})(k_1 + k_2 10^{-pH} + k_3 K_w 10^{pH})^{-1} \cong K_3(1 + 10^{-pH}K_2^{-1})(k_1 + k_2 10^{-pH})^{-1} \quad (3)$$

stant for the acetic acid–isocyanate adduct is given by K_3 = [unprotonated adduct][HOAc]$^{-1}$ [unprotonated isocyanate]$^{-1}$, K_2 is the acid dissociation constant for the protonated adduct, and the other constants have the same significance and values as in eq 1. For the acetate buffers, the term headed by k_3 in the expression for a is very small and can be omitted.

Equation 2 predicts that at constant pH the reciprocal of the observed rate constant is linearly related to the acetic acid concentration, a prediction in accord with the experimental results. Values for the parameter a, determined by regression, are given in Table I. The value of a is approximately independent of pH. This result is not a necessary consequence of the theoretical model. Rather, it indicates the fortuitous relationship in eq 4. Substitution of approximation 4

$$K_2 \cong k_1/k_2 \quad (4)$$

in eq 3 and solving for K_3 give the relationship in eq 5.

$$K_3 \cong k_1 a \quad (5)$$

Values for K_2 and K_3 calculated with approximations 4 and 5 and with the known values of k_1, k_2, and a are given in Table I.

Consider now the structure of the proposed acetic acid–isocyanate adduct. Naegeli and Tyabji believed that the more stable of the adducts formed from isocyanates and carboxylic acids in inert solvents are mixed anhydrides, RNHCOOCOR′.[3] However, they did not accept this structure for the adducts that formed reversibly. Two structures that can be considered for the adduct proposed here to explain the kinetic data are a hydrogen-bonded complex and a mixed anhydride. Comparison of the values of K_2 and K_1 indicates that the adduct is a stronger base than the isocyanate. This is not the result expected for a hydrogen-bonded complex of the isocyanate with acetic acid. Therefore, the mixed anhydride structure is preferred. If the interpretation of the kinetics in the acetate buffers is correct, we have an example of a mixed carbamic carboxylic anhydride that forms rapidly and reversibly. Thus, Naegeli and Tyabji may not have been entirely justified in rejecting the mixed anhydride structure for certain carboxylic acid–isocyanate adducts just on the basis of the looseness of the adducts.

Hydration of the Isocyanate in Phosphate Buffers.—As shown by measurements of *p*-dimethylaminoaniline yields, hydration was not the only reaction of the isocyanate in phosphate buffers. A competing reaction of the isocyanate with the phosphate gave a product that went only very slowly to *p*-dimethylaminoaniline. This product is presumably a mixed phosphoric carbamic anhydride resulting from nucleophilic attack of phosphate at the carbon of the isocyanate group. Cramer and Winter have isolated such products from acetonitrile solution.[4]

(3) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **18**, 142 (1935).
(4) F. Cramer and M. Winter, *Chem. Ber.*, **92**, 2761 (1959).

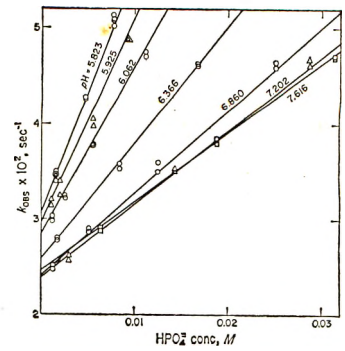

Figure 3.—Pseudo-first-order rate constants for the formation of *p*-dimethylaminoaniline from *p*-dimethylaminophenyl isocyanate in phosphate buffers at 25° and ionic strength 0.1 *M*. The lines were calculated with eq 6.

The observed pseudo-first-order constants, k_{obsd}, for the hydration of the isocyanate are given in Figure 3. These k_{obsd} values obey eq 6, where k_{pH} is given by eq 1.

$$k_{obsd} = k_{pH} + (k_4 + k_5 10^{-pH})[HPO_4^{2-}] \quad (6)$$

The values of k_4 and k_5 are given in Table I. Interpretation of *p*-dimethylaminoaniline yields shows that the term containing HPO_4^{2-} in eq 6 can be accounted for on the basis of the isocyanate–phosphate reaction just mentioned. There is no important contribution to this term by catalytic reaction paths leading to *p*-dimethylaminoaniline. The form of this term shows that there is more than one path involved in the isocyanate–phosphate reaction.

Yields of *p*-dimethylaminoaniline, based on initial isocyanate, are given in Tables II and III. These yields were measured after the reaction of the isocyanate had gone essentially to completion but before noticeable hydrolysis of the phosphoric carbamic anhydride had occurred. The competitive reaction of the phosphate with the isocyanate shows itself in the decreasing yields with increasing buffer concentration. The analytical method used in these experiments dictated higher initial isocyanate concentrations than sufficed in the kinetic experiments. Consequently, there was appreciable reaction of *p*-dimethylaminoaniline with the isocyanate to give 1,3-bis(*p*-dimethylaminophenyl)-urea. For this reason, the yields of *p*-dimethylaminoaniline do not extrapolate to 100% at zero buffer concentration.

The yields have been interpreted on the basis of the model shown in Scheme I where A and P represent

SCHEME I

$$A \xrightarrow{k_{pH}} P$$

$$A + HPO_4^{2-} \xrightarrow{k_4 + k_5 10^{-pH}} \text{mixed anhydride}$$

$$A + P \xrightarrow{k_6} \text{symmetrical urea}$$

the isocyanate and *p*-dimethylaminoaniline, respectively (protonated and unprotonated). This model leads to eq 7 where the values for b and c are calculated in eq 8 and 9 and Y is the per cent yield of *p*-dimethyl-

$$1 + 0.01Y + \frac{2 + b[HPO_4^{2-}]}{c[A]_0} \ln\left(1 - \frac{0.01Yc[A]_0}{1 - c[P]_0}\right) = 0 \quad (7)$$

$$b = (k_4 + k_5 10^{-pH})/k_{pH} \quad (8)$$

$$c = k_6/k_{pH} \quad (9)$$

TABLE II

YIELDS OF *p*-DIMETHYLAMINOANILINE FROM *p*-DIMETHYLAMINOPHENYL ISOCYANATE IN PHOSPHATE BUFFERS AT 25° AND IONIC STRENGTH 0.1 *M*. INITIAL CONCENTRATION OF *p*-DIMETHYLAMINOANILINE = 0

pH	$10^5[A]_0$,[a] *M*	$10^2[HPO_4^{2-}]$, *M*	Yield, % Found	Yield, % Calcd
5.823	4.23	0.1523	87.3	87.60
		0.266	81.4	82.46
		0.380	77.8	77.90
		0.494	73.8	73.80
		0.646	68.7	68.95
	7.44	0.1523	84.6	85.11
		0.1523	85.5	85.11
		0.228	82.0	81.87
		0.266	81.0	80.32
		0.304	78.8	78.84
		0.380	76.0	76.02
		0.494	72.1	72.14
		0.646	67.5	67.54
		0.761	64.8	64.42
6.860	3.09	0.248	80.9	81.95
		0.619	74.3	74.95
		0.992	68.8	68.98
		1.487	61.8	62.33
		1.98	57.1	56.85
		2.48	52.7	52.18
	5.86	2.48	49.3	49.52
	6.42	0.248	72.7	73.36
		0.618	67.2	67.90
		0.992	62.8	63.10
		1.487	57.8	57.65
		1.98	53.2	53.03
		2.48	49.3	49.02
	12.6	0.248	61.3	61.86
		0.619	57.3	58.10
		0.992	54.3	54.71
		1.487	50.3	50.72
		1.98	47.3	47.24
		2.48	44.7	44.13
7.202	2.90	0.283	80.3	79.92
		0.934	69.6	69.98
		2.83	51.6	51.10
	5.86	0.1415	72.6	72.58
		0.283	70.9	70.70
		0.934	62.8	63.07
		1.70	55.5	55.85
		2.83	47.6	47.65
7.616	4.23	0.623	70.0	70.48
		1.09	64.6	64.94
		1.555	59.4	60.16
		2.02	55.8	56.03
		2.65	51.1	51.21
		3.11	48.2	48.17
	7.44	0.623	62.8	62.70
		0.623	62.9	62.70
		1.09	58.6	58.41
		1.555	54.7	54.65
		2.33	49.4	49.27
		3.11	45.8	44.77

[a] Initial isocyanate concentration.

aminoaniline, $[A]_0$ is the initial isocyanate concentration, and $[P]_0$ is the concentration of *p*-dimethylaminoaniline added at the beginning of the reaction. A computer was used to find values for the parameters *b* and *c* for each of the four experimental pH levels. The program involved solving eq 7 for *Y* by a reiterative procedure and adjusting *b* and *c* to minimize the sum of the squares of the differences between experimental and calculated *Y* values. The values of *b* and *c* are given

TABLE III

YIELDS OF *p*-DIMETHYLAMINOANILINE FROM *p*-DIMETHYLAMINOPHENYL ISOCYANATE (6.42×10^{-5} *M*) IN THE PRESENCE OF ADDED *p*-DIMETHYLAMINOANILINE. PHOSPHATE BUFFER AT pH 6.860, 25°, AND IONIC STRENGTH 0.10 *M*

$10^5[P]_0$,[a] *M*	$10^2[HPO_4^{2-}]$, *M*	Yield, % Found	Yield, % Calcd
2.02	0.248	65.3	62.47
	0.992	56.0	54.05
3.78	0.248	53.5	53.87
	0.992	45.7	46.81
6.30	0.248	43.2	42.81
	0.992	37.4	37.48

[a] Initial *p*-dimethylaminoaniline concentration.

in Table I. The *Y* values calculated with these parameters and eq 7 are shown in Tables II and III, where they may be compared with the experimental yields.

The intercept and slope of the regression line for a plot of $k_{pH}b$ *vs.* 10^{-pH}, where k_{pH} was calculated with eq 1, gave values for k_4 and k_5 (see eq 8). These values are shown in Table I. The rather good agreement between these constants derived partly from yield measurements and those obtained entirely from kinetic measurements supports the validity of the theoretical model for the yield experiments. The success of this model, which does not incorporate phosphate catalysis, is the basis for the earlier statement that phosphate catalysis is unimportant.

Values for k_6, the second-order rate constant for the reaction of the isocyanate with protonated plus unprotonated *p*-dimethylaminoaniline, were obtained with eq 9, the k_{pH} values being calculated with eq 1. This rate constant decreases with decreasing pH (see Table I). If it is assumed that this decrease is associated with protonation of the *p*-dimethylaminoaniline and that the rate for the protonated amine is zero, and, if any effect of the small degree of protonation of the isocyanate in the phosphate buffers is ignored, then k_6 is given theoretically by eq 10 where k_7 is the rate

$$k_6 = k_7K_4/(K_4 + 10^{-pH}), \quad (10)$$

constant for the reaction of unprotonated *p*-dimethylaminoaniline with the isocyanate, and K_4 is the acid dissociation constant for the protonated *p*-dimethylaminoaniline. Values for k_7 and K_4, determined from the k_6 values and eq 10 by regression, are given in Table I. The agreement between the value of K_4 and the value determined independently by spectrophotometry ($K_4 = 3.2 \times 10^{-7}$ *M* at 25° and μ 0.1 *M*) indicates that the assumptions leading to eq 10 are valid.

As mentioned, hydrolysis of the phosphoric carbamic anhydride was very slow in the phosphate buffers. The rate was independent of buffer concentration and of pH in the range 6.88–7.63. The reaction is first order and has a half-time of 0.97 day at 25°.

The theoretical model used above in the analysis of the yield experiments leads to the expression given in eq 11 for the per cent yield, based on isocyanate, of

$$Y_{anh} = b(100 + Y)[HPO_4^{2-}]/(2 + b[HPO_4^{2-}]), \quad (11)$$

the phosphoric carbamic anhydride where *Y* and *b* have the same significance as in eq 7. Values of Y_{anh} calculated with eq 11 and with *Y* and *b* values taken

TABLE IV

THEORETICAL YIELDS, Y_{anh}, OF PHOSPHORIC CARBAMIC ANHYDRIDE IN pH 6.86 PHOSPHATE BUFFERS. YIELDS, Y_{slow}, OF p-DIMETHYLAMINOANILINE FORMED IN THE SLOW HYDROLYSIS OF THE PHOSPHORIC CARBAMIC ANHYDRIDE

$10^2[HPO_4^{2-}]$, M	$10^5[A]_0$, M[a]	Y_{anh}, %[b]	Y_{slow}, %[a]
0.248	6.42	6.7	6.8
0.618	6.42	15.3	15.7
1.487	6.42	30.5	29.5
2.48	5.86	42.8	41.0

[a] Initial isocyanate concentration. [b] Yields based on the initial isocyanate concentration.

from Table I are given in Table IV along with experimental yields, also based on isocyanate, of p-dimethylaminoaniline formed in the slow hydrolysis of the phosphoric carbamic anhydride. Comparison of the two sets of yield values indicates that conversion of the anhydride into the amine was close to quantitative.

Hydration of the Isocyanate in Arsenate Buffers.—Because of an experimental difficulty apparently associated with the arsenate buffers (high background current at the rotating platinum electrode), only one kinetic run was made (0.00125 M $H_2AsO_4^-$; 0.0025 M $HAsO_4^{2-}$; 25°; μ 0.1 M; pH 7.06). The formation of p-dimethylaminoaniline was close to pseudo first order (k_{obsd} = 0.0357 sec^{-1}). This rate constant is substantially larger than k_{pH} (0.0239 sec^{-1} at pH 7.06). This difference is probably not due to general acid–base catalysis by arsenate, since such catalysis was not important in solutions of $H_2PO_4^-$–HPO_4^{2-}, a couple having very nearly the same pK_a as $H_2AsO_4^-$–$HAsO_4^{2-}$. Therefore, augmentation of k_{obsd} by arsenate must result from a reaction of arsenate with the isocyanate, perhaps leading to an arsenate carbamate anhydride.

It was of interest to see if the arsenate–isocyanate product is as long lived as the phosphoric carbamic anhydride. Measurements of p-dimethylaminoaniline yields indicated that the arsenate–isocyanate product is very short lived. As in the yield experiments with phosphate buffers, the initial isocyanate concentration (6.38×10^{-5} M) was high enough to give noticeable diminution of yield owing to the reaction of the p-dimethylaminoaniline with the isocyanate. Yields were measured shortly after the initial fast reaction of the isocyanate and then at times up to a day later. There was no slow increase in yield, as when phosphate buffers were used, and the yield increased with increasing arsenate buffer concentration (Table V). These

TABLE V

YIELDS OF p-DIMETHYLAMINOANILINE FROM p-DIMETHYLAMINOPHENYL ISOCYANATE IN ARSENATE BUFFERS AT pH 7.062, 25°, AND IONIC STRENGTH 0.1 M

$10^2[AsO_4^{2-}]$, M	Yield, %
0.125	77.7
0.25	79.9
0.50	83.3
0.825	86.7
1.50	91.0
2.50	94.0

observations show that the arsenate–isocyanate product had gone to p-dimethylaminoaniline prior to the earliest yield measurement. In the single kinetic experiment, there was no indication of any further formation of the amine following the initial fast first-order reaction. Apparently the arsenate–isocyanate product went to and amine about as fast as it formed. In effect, then, arsenate catalyzes the conversion of the isocyanate into p-dimethylaminoaniline.

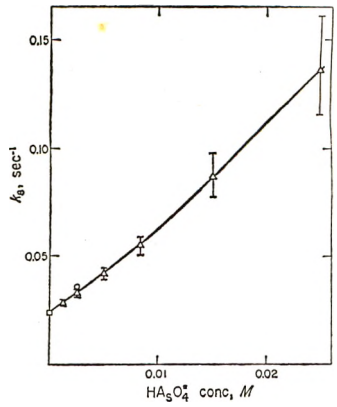

Figure 4.—Pseudo-first-order rate constants for the formation of p-dimethylaminoaniline from p-dimethylaminophenyl isocyanate in arsenate buffers at pH 7.06, 25°, and ionic strength 0.1 M: ○, observed kinetically; △, calculated from p-dimethylaminoaniline yields with eq 12 and 10 (the limits show the effect on the calculated rate constants of ±1% errors in the yields); □, calculated with eq 1.

The yields have been interpreted on the basis of the model which is shown in Scheme II where A and P

SCHEME II

$$A \xrightarrow{k_8} P$$

$$A + P \xrightarrow{k_6} \text{symmetrical urea}$$

represent the isocyanate and p-dimethylaminoaniline, respectively, k_8 is the pH- and arsenate-dependent pseudo-first-order rate constant for conversion of A into P, and k_6 is given by eq 10. Equation 12

$$(1 + 0.01Y)[A]_0 = -2(k_8/k_6) \ln \{1 - 0.01Y[A]_0(k_8/k_6)^{-1}\} \quad (12)$$

was derived for this model where Y is the per cent yield of p-dimethylaminoaniline based on isocyanate, and $[A]_0$ is the initial concentration of isocyanate.

Equation 12 was solved by reiteration to obtain values of k_8/k_6 corresponding to the Y values of Table V. These k_8/k_6 values were multiplied by k_6 (eq 10 gives k_6 = 139 for pH 7.06) to obtained k_8. A plot of k_8 *vs.* $HAsO_4^{2-}$ concentration is shown in Figure 4. The plot is not linear, possibly owing to errors in Y. As shown in the figure, small errors in Y can give large errors in k_8. As expected, the plot extrapolates to a value close to k_{pH} from eq 1. It also passes close to the observed rate constant for the single kinetic experiment. If one assumes that the nonlinearity of the plot is an artifact, k_8 can be expressed in a form analogous to eq 6 for reactions in phosphate buffers. See eq 13 where k_9 is the rate constant, of unknown pH

$$k_8 = k_{pH} + k_9[HAsO_4^{2-}] \quad (13)$$

dependence, for the reaction of $HAsO_4^{2-}$ with the isocyanate at pH 7.06. The value of k_9 from the slope of the k_8 *vs.* $[HAsO_4^{2-}]$ plot is approximately 5.0 M^{-1} sec^{-1}. An idea of the relative nucleophilicities of arsenate and phosphate toward the isocyanate can be

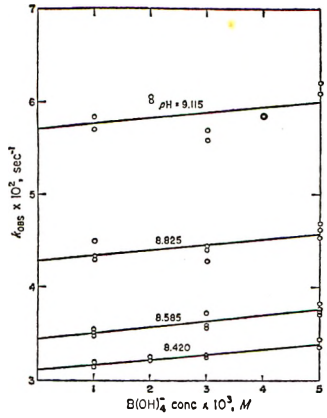

Figure 5.—Pseudo-first-order rate constants for the formation of *p*-dimethylaminoaniline from *p*-dimethylaminophenyl isocyanate in borate buffers at 25° and ionic strength 0.1 *M*.

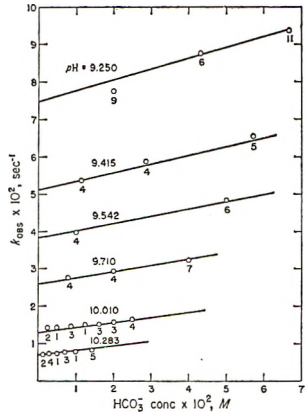

Figure 6.—Pseudo-first-order rate constants for the decarboxylation of *p*-dimethylaminophenylcarbamate ion in carbonate buffers at 25° and ionic strength 0.1 *M*. Each point gives the average value of k_{obsd} for the number of kinetic runs indicated beneath the point. The lines were calculated with eq 14.

gained by comparing k_9 with the coefficient of $[HPO_4^{2-}]$ in eq 6. At pH 7.06, the value of this coefficient is 0.80 M^{-1} sec^{-1}. Thus, arsenate is more nucleophilic than phosphate. A similar difference was observed for the attack of arsenate and phosphate on *p*-nitrophenyl acetate.[5]

Hydration of the Isocyanate in Borate Buffers.—Very dilute buffers were used to avoid significant polymerization of the borate ion. Owing to this precaution, the maximum observed effect of buffer dilution on pH was only 0.025 units (for the pH 9.115 buffer). To obtain k_{obsd}, the experimental rate constants were corrected for the small changes in pH accompanying dilution. The largest correction amounted to 2.5%. The others were less than 1%. The positive slopes of the k_{obsd} *vs.* $[B(OH)_4^-]$ plots (Figure 5) may indicate a reaction of the borate ion with the isocyanate having a rate constant of about 0.6 M^{-1} sec^{-1}.

Decarboxylation of the Carbamate Ion.—Observed pseudo-first-order rate constants for the decarboxylation in carbonate-buffered solutions and in sodium hydroxide solutions are given in Figures 6 and 7. Over much of the pH range, the reaction of the carbamate ion is close to first order in hydrogen ion. The data for the carbonate-buffered solutions indicate acid catalysis of the reaction by H_2CO_3 and HCO_3^-.

(5) W. P. Jencks and J. Carriulo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

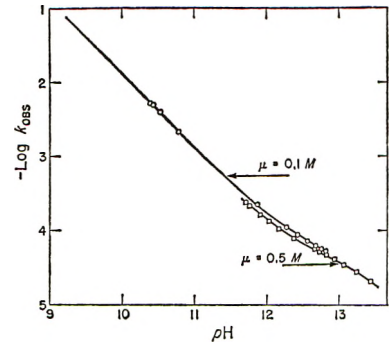

Figure 7.—pH dependence for the decarboxylation of *p*-dimethylaminophenylcarbamate ion at 25°. The points are for runs in sodium hydroxide solutions. The lines were calculated with eq 14.

To extend the pH to higher values than available at ionic strength 0.1 *M*, experiments were also run at ionic strength 0.5 *M* in unbuffered sodium hydroxide solutions. The log k_{obsd}–pH profile has an inflection at pH ~ 12.5 (Figure 7). The rate constants measured by Christenson for the decarboxylation of phenyl carbamate ion in sodium hydroxide solutions (μ not held constant) also give such an inflection.[6] Spectrophotometry revealed no change in the molar extinction of the substrate throughout the experimental pH range. Therefore, the inflection is not associated with an acid–base reaction of the substrate.

The experimental results can be explained on the basis of the acid catalysis mechanism discussed by Bell[7]

$$S^- + \Sigma_i A_i \underset{k_r}{\overset{k_f}{\rightleftharpoons}} SH + \Sigma_i B_i$$

$$SH \xrightarrow{k_{10}} p\text{-dimethylaminoaniline}$$

where S^- is the carbamate ion, SH is protonated carbamate ion, and $\Sigma_t A_t$ and $\Sigma_t B_t$ represent all the acids and their conjugate bases, respectively. The pseudo-first-order constants k_f and k_r are given by $k_f = \Sigma_i k_i[A_i]$ and $k_r = \Sigma_t k_i'[B_i]$, where k_i is the rate constant for proton transfer from acid A_i to S^-, and k_i' is the rate constant for proton transfer from SH to base B_i.

If $k_f \ll k_r$, the steady-state approximation for SH can be used, giving eq 14 where K_5 is the acid dissocia-

$$1/k_{obsd} = 1/\Sigma_i k_i[A_i] + K_5/(k_{10}10^{-pH}) \quad (14)$$

tion constant for SH. For the kinetic experiments eq 15 applies, where $K_6 = 10^{-pH}[HCO_3^-]/[H_2CO_3]$. Of

$$\Sigma_i k_i[A_i] = k_w[H_2O] + k_H{}^+10^{-pH} + k_{H_2CO_3}[H_2CO_3] + k_{HCO_3^-}[HCO_3^-] = k_w[H_2O] + k_H{}^+10^{-pH} + [(k_{H_2CO_3}/K_6)10^{-pH} + k_{HCO_3^-}][HCO_3^-] \quad (15)$$

course, the last term of eq 15 is zero for experiments in the unbuffered sodium hydroxide solutions. Regression with a computer was used to fit eq 14 to the 13 k_{obsd} values for ionic strength 0.5 *M*. The resulting constant parameter values are given in Table I. Calculated and experimental k_{obsd} values agree closely. The standard error of fit of log k_{obsd} (calcd) to log k_{obsd} (exptl) is only 0.0069 log unit. The largest deviation is 0.0109 log unit. Multiple regression (both pH and $[HCO_3^-]$ varied) was used to fit eq 14 to k_{obsd} for ionic strength 0.1 *M*. All the 108 k_{obsd} values for

(6) I. Christenson, *Acta Chem. Scand.*, **18**, 904 (1964).

(7) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 136, 137.

carbonate-buffered solutions and unbuffered sodium hydroxide solutions were included in this one regression. In this regression, the value of K_5/k_{10} was fixed, since the data did not extend to high enough pH to allow evaluation of this parameter from the data. The value of K_5/k_{10} was set equal to 0.77 times the value of this parameter for ionic strength 0.5 M. The factor 0.77 is an estimate of the salt effect for K_5/k_{10} in going from ionic strength 0.5 to 0.1 M. Parameter values resulting from the regression are given in Table I. The standard error of fit of log k_{obsd} (calcd) to log k_{obsd} (exptl) for ionic strength 0.1 M is 0.0115 log unit. The maximum deviation for any k_{obsd} is 0.0299 log unit. The deviation exceeds 2σ for only 4 out of the 108 k_{obsd} values.

As expected for a reaction involving an uncharged reactant (H_2O), the value of k_w is insensitive to change in ionic strength. The value of k_{H^+}, on the other hand, decreases with increasing ionic strength, consistent with the reaction of oppositely charged species (carbamate anion and hydronium cation). The change in k_{H^+} is close to that predicted by the empirical expression[8] given below.

$$\Delta \log k_{H^+} = -\Delta[\sqrt{\mu}/(1 + \sqrt{\mu}) - 0.20\,\mu]$$

Bell[7] has pointed out an interesting prediction based on the mechanism for acid catalysis described above. The mechanism predicts that k_{obsd} will not approach k_w [H_2O], the water-catalyzed rate, as the hydrogen-ion concentration approaches zero. Rather, the rate will go to zero, as is apparent from eq 14. That this prediction is borne out for carbamate decarboxylation is shown more clearly in the k_{obsd} *vs.* 10^{-pH} plot of Figure 8 than in the logarithmic plot of Figure 7. Lacking data for the lower hydrogen-ion concentrations, as in the case of the experiments at ionic strength 0.1 M, one might erroneously assume k_{obsd} to be given by the linear eq 16 which is the equation for general acid

$$k_{obsd} = \pi_w[H_2O] + \pi_{H^+}10^{-pH}, \qquad (16)$$

catalysis when water and hydrogen ion are the only acids present. The intercepts and slopes of straight lines through those k_{obsd} values showing near-linear dependence on 10^{-pH} give $\pi_w[H_2O]$ and π_{H^+} values that differ from the values of $k_w[H_2O]$ and k_{H^+} resulting from the fitting of eq 14 to the k_{obsd} values. The proper choice of mechanism is important if correct values for the catalytic constants are desired.

In the mechanism leading to eq 14, the position of protonation in SH is not specified and is a matter of conjecture. In the derivation of eq 14, the conversion of SH into *p*-dimethylaminoaniline was assumed to be a pH-independent, irreversible reaction. Of the sites available for protonation in the carbamate ion, the carbamate nitrogen is the one whose protonation would seem most likely to lead to such a reaction. Owing to the very low concentration of CO_2 in the experiments, the position of the equilibrium in Scheme III, part b, is assumed to lie far to the right. In effect, then, the reaction is considered to be irreversible.

Experimental Section

p-Dimethylaminophenyl isocyanate was prepared by the method of Staudinger and Endle.[1] The material distilled at

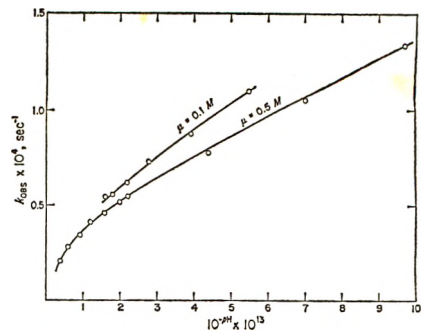

Figure 8.—Dependence of decarboxylation rate on 10^{-pH} at 25°.

SCHEME III

$$RNHCO_2^- + \Sigma_i A_i \rightleftharpoons \overset{+}{R}NH_2CO_2^- + \Sigma_i B_i \qquad (a)$$

$$\overset{+}{R}NH_2CO_2^- \rightleftharpoons \left[\begin{array}{ccc} & H & O \\ & \delta^+ | & \| \\ R & -N\cdots & C \\ & H & \ddots \\ & & O_\delta^- \end{array}\right] \rightleftharpoons RNH_2 + CO_2 \qquad (b)$$

100° (~3 mm) and solidified in the receiver, mp 35–36.5° uncor. Reagent grade or Acculate[9] standard volumetric solutions were used for the buffers. The acetate and borate buffers were prepared from the respective acids and sodium hydroxide. The phosphate and carbonate buffers were prepared from the appropriate sodium salts, and the arsenate buffer was made with Na_2HAsO_4 and hydrochloric acid. Sodium sulfate was employed to maintain the ionic strength at 0.1 M for the diluted buffers and for the sodium hydroxide solutions. Sodium nitrate was used to maintain the ionic strength for the hydrochloric acid solutions. Sodium hydroxide solutions were brought to ionic strength 0.5 M with sodium chloride.

In the kinetic experiments, the temperature was held at 25.0 ± 0.2°. The apparatus used to follow the formation of *p*-dimethylaminoaniline electrochemically was designed by W. R. Ruby, of these laboratories. A water-jacketed beaker was fitted with a Teflon cover, nitrogen inlet tube and exit port, and the conventional configuration of rotating platinum-disk working electrode and platinum-disk auxiliary electrode. The external saturated calomel reference electrode was connected through an agar-saturated sodium nitrate bridge. A modified version of the Adams potentiostat was used to supply constant voltage to the cell and to amplify the current.[10] The amplified current was recorded *vs.* time with a Moseley Autograf Model 2D-2 X-Y recorder. The potential applied to the working electrode was between 200 and 430 mV *vs.* the S. C. E. higher potential was needed at the lower pH values to give adequate current.

Over the course of a number of kinetic runs, there was a gradual downward drift in the current associated with a given concentration of *p*-dimethylaminoaniline. This effect was due to a change in the electrode surface that could be reversed by polishing the electrode. The change in the electrode during a kinetic experiment was of no apparent consequence, provided the total time that voltage was applied to the cell did not exceed about 15 min. For the slow reactions in the vicinity of pH 10.5, the voltage was interrupted after about two half-lives and reestablished after about ten half-lives. The electrochemical method was not used for pH values higher than 10.78.

The buffer (75 ml) was placed in the cell and purged with nitrogen. The working voltage was applied to the cell until the current was constant, and then 0.75 ml of a stock solution of the isocyanate (~6×10^{-4} M) in Eastman Spectro Grade acetonitrile was added rapidly with a syringe. The stirring of the solution by the rotating electrode gave complete mixing in 2 sec or less. Nitrogen was passed over the surface of the solution during the reaction. Although no special precautions were taken to remove or exclude water from the acetonitrile stock solutions of the isocyanate, these solutions were surprisingly stable. There was no indication of change in a week.

(8) C. W. Davies, "Progress in Reaction Kinetics," Vol. 1, Pergamon Press Inc., New York, N. Y., 1961, p 161.

(9) Obtained from Anachemia Chemicals, Ltd.

(10) J. R. Alden, J. Q. Chambers, and R. N. Adams, *J. Electroanal. Chem.*, **5**, 152 (1963).

Preliminary experiments with the acetate buffers gave results indicating that an impurity was oxidizing or catalyzing the oxidation of the *p*-dimethylaminoaniline. This reaction was prevented by adding 0.1–0.2 ml of 0.03 *M* Na_2EDTA to the reaction mixtures. The oxidation was apparently not a serious problem; eliminating it caused only a small decrease in the measured rate constants.

The increase in rate with decreasing acetate buffer concentration was not associated with the use of sodium sulfate to maintain the ionic strength. Sodium nitrate gave the same result.

The reaction product in the kinetic experiments was not isolated. That *p*-dimethylaminoaniline was formed was confirmed by determination of the polarographic wave at the end of the reaction at pH 10.28.

Kinetic runs at pH values higher than 10.78 were monitored spectrophotometrically. The reaction vessel was a Teflon beaker with a tight-fitting Teflon cover having nitrogen inlet and exit tubes and a port for removing samples. The sodium hydroxide solution (100 ml) was purged with nitrogen that had been passed through 0.1 *M* sodium hydroxide solution and 0.1 *M* sodium chloride solution. Reaction was started by adding 1 ml of a stock solution ($\sim 6 \times 10^{-3}$ *M*) of the isocyanate in Eastman Spectro Grade acetonitrile. Nitrogen was passed through the solution during the course of the reaction. Samples were removed and absorbances were measured at 260 and 274 mμ with the Beckman DU spectrophotometer. The absorbances decreased with time, making a first-order approach to values very close to those of *p*-dimethylaminoaniline. Rate constants were calculated for both the 260- and 274-mμ data and averaged. Agreement between the constants for the two wavelengths was generally excellent.

Reactions were monitored spectrophotometrically for as long as 4 days. Simply passing nitrogen through the solutions did not suffice to protect the very labile *p*-dimethylaminoaniline from noticeable autoxidation during such a long time. Consequently, 0.04 g of sodium sulfite was included in each reaction mixture. This agent very effectively inhibited the autoxidation. The *p*-dimethylaminoaniline in turn would have been expected to inhibit the autoxidation of the sulfite, an important point, since this oxidation is accompanied by a change in absorbance at 260 and 274 mμ. As an extra precaution against oxidation of the sulfite, 0.03 g of Na_4EDTA was included in the solutions.

Measurements of the pH values of the reaction mixtures were made at the end of each kinetic experiment. A Corning Model 12 pH Meter was used. For pH values below 11, a Beckman glass electrode (Cat. No. 1190-80) was employed, and the Corning Triple-Purpose electrode was used for higher pH values. A Beckman reference calomel electrode was used. The electrodes were calibrated with 0.01 *M* sodium tetraborate, and their linearity was checked with Corning pH 7.00 buffer. Dilute sodium hydroxide solutions were protected from atmospheric CO_2 during the pH measurements with nitrogen. Sodium ion corrections were made.

The following relationships exist between the sodium hydroxide concentrations and the corrected experimental pH values greater than 11: pH = 13.829 + 0.979 log[NaOH] for ionic strength 0.1 *M*; pH = 13.746 + 0.994 log[NaOH] for ionic strength 0.5 *M*. The standard error of fit of the experimental to the calculated pH values is 0.004 pH unit. The maximum deviation is 0.008 pH unit. The fact that the coefficients of log NaOH are close to unity indicates that ion activity coefficients remained almost unchanged as sodium hydroxide concentration was varied at constant ionic strength.

For the experiments in which yields of *p*-dimethylaminoaniline were determined, reactions were carried out in rubber-stoppered glass bottles fitted with nitrogen inlet and exit tubes and a port for sampling. Isocyanate stock solution (Eastman Spectro Grade acetonitrile) (1 ml) was delivered from a calibrated volumetric pipet into 100 ml of nitrogen-purged buffer. Analysis for *p*-dimethylaminoaniline was carried out as follows. A 5-ml sample of the reaction mixture was added to a mixture of 2 ml of a buffer designed to give pH ~7 and *v* ml of 5×10^{-4} *M* aqueous 1-naphthol solution. Then there was added *v* ml of 2×10^{-3} *M* aqueous potassium ferricyanide solution, followed by 1 ml of 15% Triton X-100 solution. Finally, the solution was made up to a total weight of 10.00 g with water. The volume *v* was chosen to be about 0.2 ml in excess of the volume theoretically required to convert the *p*-dimethylaminoaniline into the blue indoaniline dye. If *v* was much larger, significant amounts of colored 1-naphthol oxidation products were formed. Owing to the Triton X-100, the dye followed Beer's law in the solutions.[11] The amount of *p*-dimethylaminoaniline in the sample was calculated from the absorbance at 600 mμ. The calculations were based on the results of calibration experiments. Analyses were generally carried out in duplicate and sometimes in triplicate. The values given in Tables II–V are the averages.

In the yield experiments having the highest initial isocyanate concentration (1.26×10^{-4} *M*), traces of crystalline solid formed in the reaction mixtures. The amount of this material, estimated visually, decreased with increasing phosphate concentration, and therefore it correlated with the expected yields of 1,3-bis(*p*-dimethylaminophenyl)urea. The material melted partially in the 250–260° range. Staudinger and Endle give 258–259° dec for the melting point of the urea.[1]

Registry No.—*p*-Dimethylaminophenyl isocyanate, 16315-59-6; *p*-dimethylaminoaniline, 99-98-9.

Acknowledgment.—The author wishes to thank Mr. E. A. Sylvestre, of the Eastman Kodak Co., for carrying out the computations.

(11) L. K. J. Tong and M. Carol Glesmann, *J. Amer. Chem. Soc.*, **79**, 4305 (1957).

Mass Spectral Studies of Alkyl Methanesulfonates

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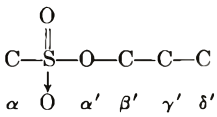
Received August 10, 1967

The mass spectral fragmentation patterns of several alkyl, cycloalkyl, and aryl methanesulfonates have been recorded and studied. Deuterium-labeling experiments have been conducted to determine the origin of the hydrogens involved in several interesting rearrangements to sulfonyl oxygen. The mechanistic implications of these data are discussed in terms of the stereochemistry of the transition state and the stability of the product ion formed through rearrangement.

In continuing studies on the mass spectral fragmentation patterns of tetracoordinated sulfur compounds, a series of alkyl methanesulfonates was prepared and examined under mass spectral conditions. It was of interest to determine if rearrangements analogous to those involving the alkane portion of the sulfonate esters would also occur with involvement of the alkyl moiety of the ester.[2]

The mechanisms suggested for the observed rearrangements are supported by deuterium-labeling studies. In discussing the rearrangements and fragmentations of these esters, the position of the atoms will be designated as



An α cleavage will mean cleavage of the C–S bond and an α' cleavage of the S–OR bond, etc. A substituent referred to as an α substituent will be borne on the α carbon. The convention proposed by Budzikiewicz, Djerassi, and Williams[3] for denoting electron shifts will be used. A fishhook (↷) will indicate the movement of a single electron; an arrow (⇝) will denote the movement of an electron pair. Table I indicates the esters that have been studied and will be discussed. Mass spectra are given in Figures 1–7.

TABLE I
CH_3SO_3R

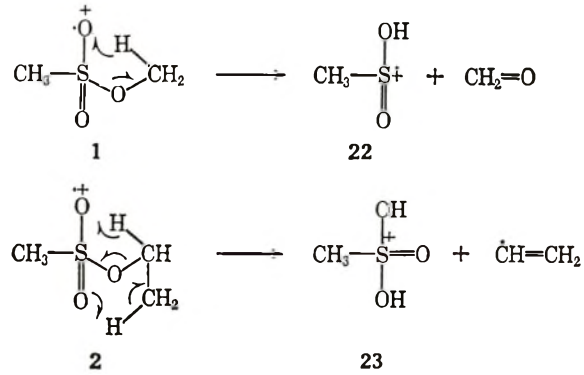
	R	Registry no.	Bp, °C (mm)
1	CH_3	66-27-3	78 (10)
2	CH_2CH_3	62-50-0	78 (7.5)
3	$CH_2CH_2CH_3$	1912-31-8	120 (28)
4	$CH_2(CH_2)_2CH_3$	1912-32-9	96 (4.1)
5	$CH_2(CH_2)_3CH_3$	6968-20-3	93–94 (2.5)
6	$CH_2(CH_2)_4CH_3$	16156-50-6	86 (1.5)
7	$CH_2(CH_2)_5CH_3$	16156-51-7	94–95 (1.0)
8	$CH_2(CH_2)_6CH_3$	16156-52-8	95–96 (0.50)
9	$CH(CH_3)_2$	3409-44-7	54–55 (0.75)
10	$CH_2CH(CH_3)_2$	16156-53-9	63–64 (1.0)
11	$CH(CH_3)CH_2CH_3$	16156-54-0	57–58 (1.0)
12	$CH_2CH_2CH(CH_3)_2$	16156-55-1	60–61 (0.65)
13	Cyclohexyl	16156-56-2	84 (0.77)
14	Cyclopentyl	16156-57-3	70–71 (0.75)
15	$CH_2—C\equiv CH$	16156-58-4	67 (1.0)
16	Phenyl	16516-59-5	Mp 59°
17	*o*-Tolyl	1009-01-4	80.5 (0.20)
18	*m*-Tolyl	1077-02-7	84 (0.55)
19	$CD_2CH(CH_3)_2$	16156-60-8	76 (2.6)
20	$CD_2CH_2CH_3$	16156-61-9	76–77 (2.6)
21	$CH_2CD_2CH_3$	16156-62-0	76–77 (2.6)
22	$CH_2CH_2CD_3$	16156-63-1	58–59 (0.60)

(1) L. W. C. thesis contains the complete spectra of those esters not presented here.

(2) W. E. Truce, R. W. Campbell, and G. D. Madding, *J. Org. Chem.*, **32**, 308 (1967).

Results and Discussions

It has been found that, in addition to hydrogen migrations from the alkane portion of methyl alkanesulfonates, hydrogen is also transferred from the alkyl portion of both methyl and ethyl methanesulfonate to the sulfonyl oxygens with simultaneous α' or β' cleavage. Methyl methanesulfonate (1) and ethyl methanesulfonate (2) give prominent ions at *m/e* 80 (22) and *m/e* 97 (23), respectively. The following mechanisms were proposed and supported by labeling experiments.



The McLafferty rearrangement to give ion 23 is postulated to go through a 3,2,1-bicyclic transition state. Precedence for this type of transition state can be found in the proposed transfer of two hydrogens in propyl and higher esters of aliphatic and aromatic carboxylic acids.[4] It was of interest to determine if results similar, with regard to site specificity, to those obtained for double hydrogen rearrangement from the alkyl portion of carboxylic acid esters would be obtained for methanesulfonic acid esters. For one of the most characteristic fragmentation processes for carboxylic acid esters, *i.e.*, transfer of two hydrogens from the alkyl portion of the ester with loss of the alkyl residue, it had originally been thought, as a result of work on *sec*-butyl acetate, that β and γ hydrogens were exclusively involved.[5] However, McFadden[6] as well as Benz and Biemann[7] concluded, using deuterium-

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 3.

(4) F. W. McLafferty and T. S. Gohlke, *Anal. Chem.*, **31**, 2076 (1959).

(5) F. W. McLafferty and M. C. Hamming, *Chem. Ind.* (London), 1366 (1958).

(6) D. R. Black, W. H. McFadden, and J. W. Corse, *J. Phys. Chem.*, **68**, 1237 (1964).

(7) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964).

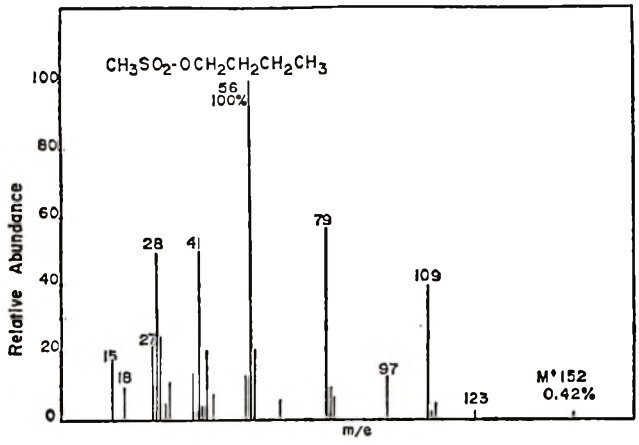


Figure 1.—*n*-Butyl methanesulfonate.

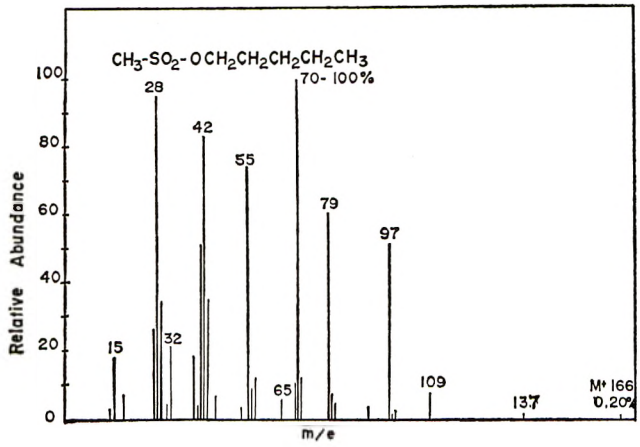


Figure 2.—*n*-Pentyl methanesulfonate.

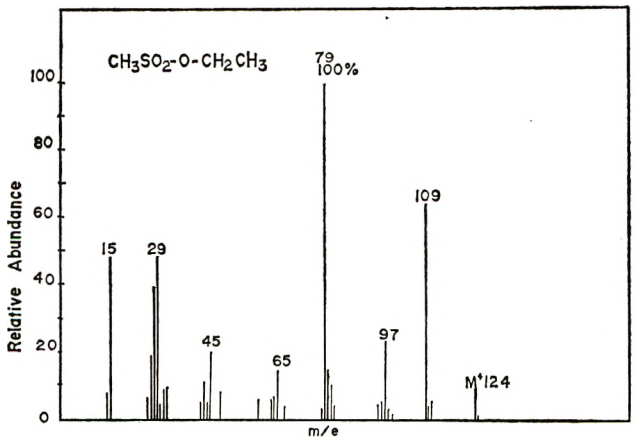


Figure 3.—Ethyl methanesulfonate.

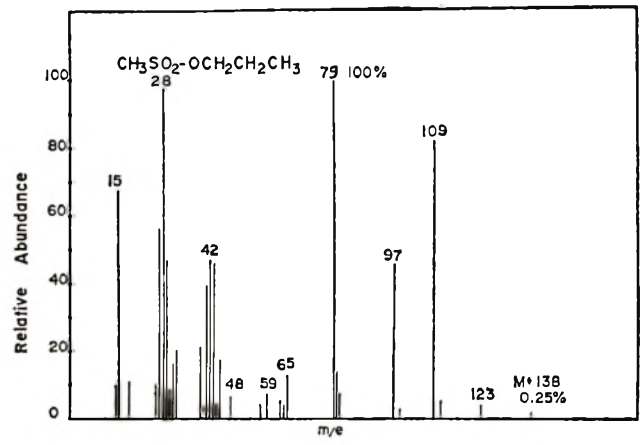


Figure 4.—*n*-Propyl methanesulfonate.

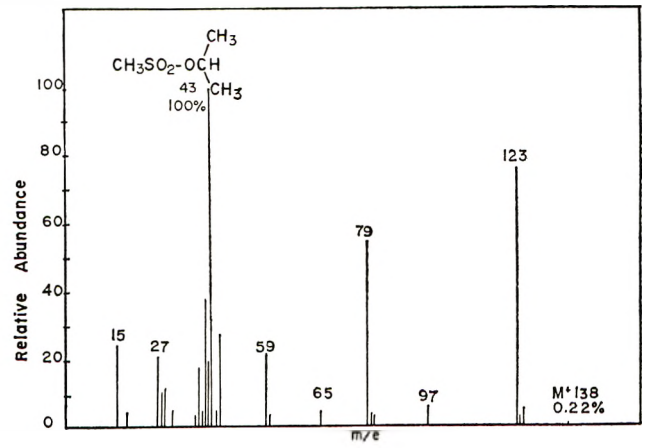


Figure 5.—2-Propyl methanesulfonate.

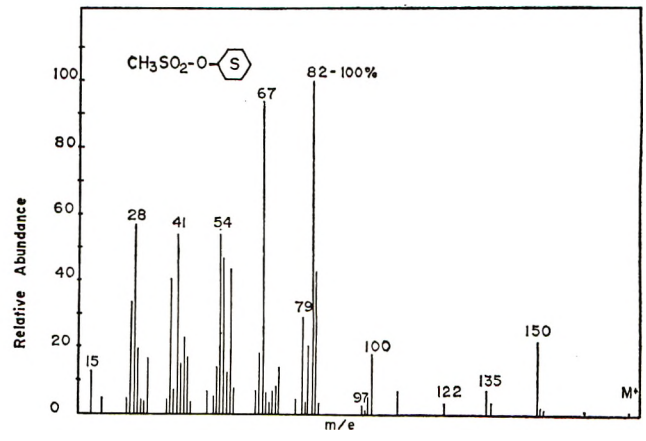
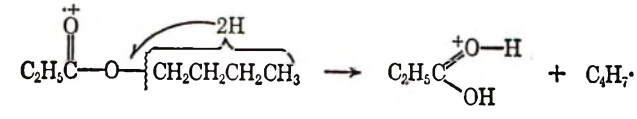


Figure 6.—Cyclohexyl methanesulfonate.

labeled *n*-butyl and *n*-amyl esters, that the first proton in this rearrangement comes specifically from the γ position and the second proton is abstracted in a random manner from the other possible positions. Djerassi and Fenselau have since shown conclusively that the itinerant hydrogens come mostly, but not entirely, from C-2 and C-3 in butylcarboxylic acid esters.[8]



(8) C. Djerassi and C. Fenselau, *J. Amer. Chem. Soc.*, **87**, 5756 (1965).

In the present work it was indeed found that all of the unbranched primary alkyl esters (**2**–**8**) gave the double hydrogen rearrangement ion **23**, in relative abundance of 13–53%. Deuterium labeling shows that hydrogens from other than the β' and γ' positions are involved which is similar to the conclusions reached by Djerassi[8] for carboxylic acid esters. The deuterium-labeled compounds (**20**–**22**) indicate that a different mechanism is operative for hydrogen transfer with the propyl ester compared with the ethyl ester since the β' and γ' hydrogens are not exclusively involved in the rearrangement. Indeed, Table II shows that in *n*-propyl methanesulfonate (**3**) the hydrogens involved

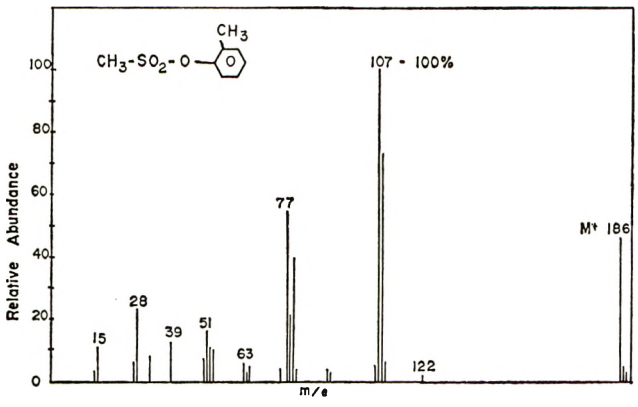


Figure 7.—*o*-Methyl benzene methanesulfonate.

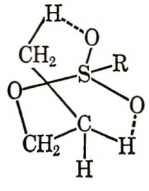
TABLE II

Compound[a]	*m/e* 97	*m/e* 98	*m/e* 99	Σ
$CH_3SO_3CH_2CH_2CH_3$	45.7	1.27	2.72	49.7
$CH_3SO_3CD_2CH_2CH_3$	28.2	19.2	3.78	51.2
$CH_3SO_3CH_2CD_2CH_3$	20.7	27.4	2.79	50.9
$CH_3SO_3CH_2CH_2CD_3$	2.54	42.6	1.73	46.8

[a] Base peak ion (**25**), *m/e* 79.

in the rearrangement to give ion **23** come approximately 38% of the time from the β',δ' carbons, 56% of the time from the γ',δ' carbons, and less than 5% of the time from the β',γ' carbons. The low abundance of the ion at *m/e* 99 eliminates any substantial contribution to ion **23** by way of transfer of two hydrogens from the same carbon. It can be concluded therefore that sulfonic acid esters like carboxylic acid esters do not transfer hydrogen only through five- and six-membered-ring transition states, but substantial contributions are made by hydrogen transfer through seven-membered-ring transition states. Molecular models show that the conformation for the γ',δ'-hydrogen transfer through a 3,2,2-bicyclic transition state is neither badly eclipsed nor strained (Chart I). Hence, it is feasible even though it involves a seven-membered ring which is infrequently found in mass spectral literature.[5,8-10]

CHART I
γ',δ'-HYDROGEN MIGRATION
via 3,2,2-BICYCLIC TRANSITION STATE



A difference, however, should be noted in the behavior of ethylcarboxylic acid esters and ethyl alkanesulfonates. The results of deuterium-labeling experiments for carboxylic ethyl esters show that almost complete scrambling of the ethoxyl hydrogens occurs for both the single and double hydrogen rearrangement.[11,12] However, with ethyl methanesulfonate scrambling was not observed.[2]

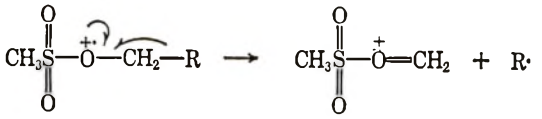
(9) W. H. McFadden, L. E. Boggs, and R. G. Buttery, *J. Phys. Chem.*, **70**, 3516 (1966).
(10) N. C. Rol, *Rev. Trav. Chim.*, **84**, 413 (1965).
(11) A. G. Harrison and E. G. Jones, *Can. J. Chem.*, **43**, 960 (1965).
(12) E. V. Godbole and P. Kebarle, *Trans. Faraday Soc.*, **58**, 1897 (1962).

A comparison of the mass spectra of ethyl methanesulfonate and *n*-propyl methanesulfonate (Figures 3 and 4) indicates a general trend, *i.e.*, as the alkyl group becomes longer in going from **2** to **8**, ion **22** (single hydrogen transfer, α' cleavage) becomes less abundant and ion **23** (double hydrogen transfer, β' cleavage) becomes more abundant.

s-Alkyl methanesulfonates (**9**, **11**) do not show abundant ions (<6%) at either *m/e* 80 (**22**) or *m/e* 97 (**23**) (Figure 5). Presumably β' cleavage to form the secondary carbonium ion becomes more favorable than any process involving hydrogen transfer. Indeed, *m/e* 43 from β' cleavage is the base peak (R.A. = 100) for isopropyl methanesulfonate (**9**).

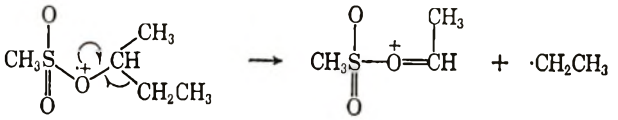
$$[CH_3SO_3CHMe_2]^{\cdot+} \longrightarrow Me_2\overset{+}{C}H \ (m/e\ 43) + CH_3SO_3\cdot$$

Another mode of fragmentation which may give rise to hydrogen rearrangement is γ' cleavage.[13]



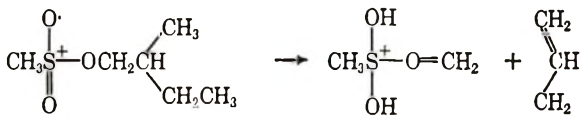
24 (*m/e* 109)

Ion **24**, *m/e* 109, occurs in all primary esters, while in the secondary esters such as 2-butyl methanesulfonate (**11**) the largest alkyl chain is lost preferentially to give the corresponding ion at *m/e* 123.[14] Ion **25** is the base peak in the spectrum of **11**. However, with



11 **25** (*m/e* 123)

a branched primary ester such as isobutyl methanesulfonate (**10**), not only is ion **24** present (R.A. = 25%), but also an ion appears as *m/e* 111 (R.A. = 77%).



10 **26** (*m/e* 111)

The mass spectrum of **19** in which the two β' hydrogens of isobutyl methanesulfonate are replaced by deuterium shows that the two β' hydrogens are retained in ion **24** (Table III).

A seven-membered-ring transition state is presumably involved in the rearrangement to form ion **26**. However, deuterium labeling to establish firmly the origin of this ion has not been carried out. In addition isobutyl methanesulfonate (**10**) gives an

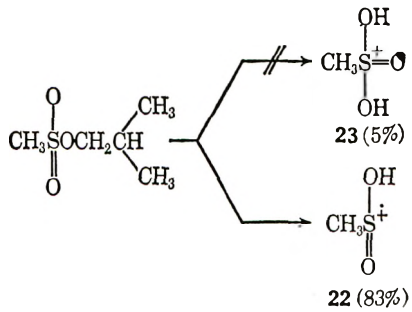
(13) See, for example, ref 3, Chapters 4 and 6.
(14) F. W. McLafferty, *Anal. Chem.*, **29**, 1782 (1957).

TABLE III

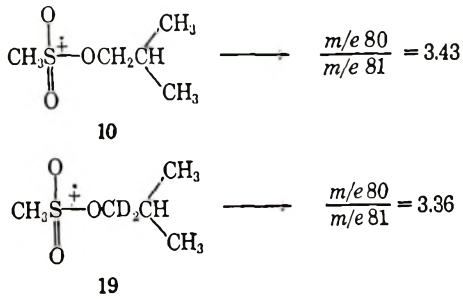
Compound[a]	m/e 109	110	111	112	113	Σ
$CH_3SOCH_2CH(CH_3)_2$	25.2	15.7	77.1	2.63	3.71	123.4
$CH_3SOCD_2CH(CH_3)_2$	1.02	1.36	33.8	18.2	33.0	87.4

[a] Base peak at m/e 43 for each ester.

abundant ion at m/e 80 (**22**) but very little ion **23**, m/e 97. Comparing isobutyl methanesulfonate (**10**)

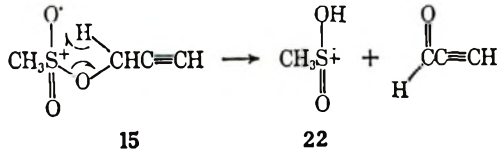


with its β'-deuterated analog (**19**) indicates, by the constant ratio of m/e 80 to m/e 81, that the β' hydrogens are not predominantly involved in the rearrangement to give ion **22** for this ester. This is in contrast



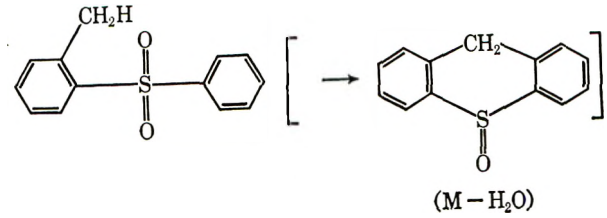
to methyl methanesulfonate which gives ion **22** by transfer of one β' hydrogen.[2]

One unsaturated ester was examined, propargyl methanesulfonate (**15**), which gave a m/e 80 ion (R.A. = 57%).

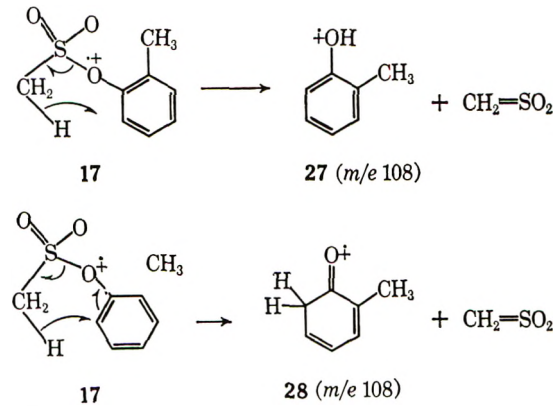


The two cycloalkyl methanesulfonates investigated, **13** and **14**, did not show ions corresponding to hydrogen migration to sulfonyl oxygen. If a model is constructed of cyclohexyl methanesulfonate (**13**), it would appear that the stereochemical requirements for the transfer of two hydrogens from the 2 and 6 positions of the cyclohexyl ring are adequately met. However, this rearrangement does not take place to any appreciable extent (Figure 6). Rupture of the β' bond to form the secondary cyclohexyl ion and subsequent fragmentation of the ring itself must be energetically favorable. The main fragmentation patterns then for the cycloalkyl esters arise from the fragmentation of the cycloalkyl ring itself.[15,16]

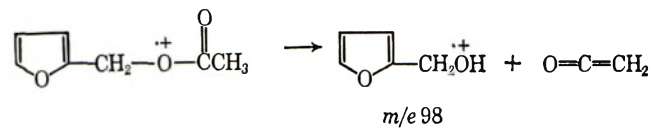
Finally, several aryl methanesulfonates were prepared and their mass spectra examined. These esters were examined for possible hydrogen transfer from *ortho* methyl substituents. This type of rearrangement has been observed for several diaryl sulfones, where migration occurred through a six-membered-ring transitions state.[17] However, in *o*-methyl-



phenyl methanesulfonate rearrangement of an *o*-methyl hydrogen would have to proceed through a seven-membered-ring transition state. No specific hydrogen rearrangements to give either an ion at m/e 80 (hydrogen transfer with α' cleavage) or an ion at m/e 96 (hydrogen transfer with β' cleavage) occurred. An examination of Figure 7, however, reveals an ion at m/e 108 (R.A. = 75%) which could be the molecular ion of *o*-cresol. This ion could arise by either of the following mechanistic pathways, involving a four- or six-membered-ring transition state, respectively. Either



mode of rearrangement would involve the novel elimination of a neutral molecule of sulfene.[18] An analogy to this mode of rearrangement would be the postulated elimination of ketene in the following ester.[19] With



(15) R. I. Reed, "Applications of Mass Spectrometry to Organic Chemistry," Academic Press Inc., London, 1966, Chapter 3.

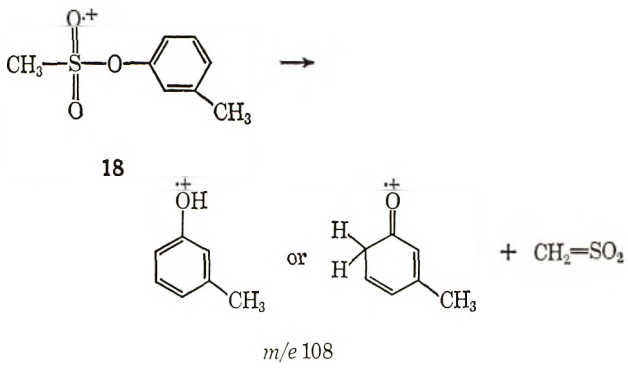
(16) J. H. Beynon, "Mass Spectrometry and its Application to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960.

(17) S. Meyerson, H. Drews, and E. K. Fields, *Anal. Chem.*, **36**, 1294 (1964).

(18) (a) G. Opitz, M. Kleeman, D. Bucher, G. Walz, and K. Reith, *Angew. Chem. Intern. Ed. Engl.*, **5**, 594 (1966); (b) J. F. King and T. Durst, *J. Amer. Chem. Soc.*, **87**, 5684 (1965); (c) W. E. Truce and R. W. Campbell, *ibid.*, **88**, 3599 (1966).

(19) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 111, 112.

m-tolyl methanesulfonate (**18**) the corresponding *meta* isomer at *m/e* 108 is the base peak in the spectrum.



18

m/e 108

Aside from this rearrangement, the main fragmentation pattern for aryl methanesulfonates arises from simple β' cleavage with retention of charge on the aromatic moiety and subsequent fragmentation of the aryl ring itself.[15]

Experimental Section

We are indebted to Professor F. W. McLafferty and his staff for determining and helping us to interpret the mass spectra which were recorded on a Hitachi RMU-6A instrument using a heated inlet system, ionization energy of 80 eV, inlet temperature of 185°. Also, several representative compounds were run at an inlet temperature of 50° and source temperature of 60°, and the spectra were compared to those taken at the higher temperatures to determine if these compounds were thermally stable. All of the esters thus tested proved to be thermally stable. All esters gave physical constants consistent with literature values and were purified by vpc through a silicon S.E. 30 (150°) column when fractional distillation left purity in doubt. Nmr spectra were recorded on a Varian A-60 spectrometer with TMS as internal standard.

General Procedure for Preparation of Alkyl Methanesulfonates.—To a solution of 0.13 mol of triethylamine (Matheson Coleman and Bell reagent), and 0.13 mol of alcohol in 200 ml of benzene (Baker Spectrophotometric reagent) contained in a dry 500-ml three-neck flask equipped with an addition funnel, nitrogen inlet, calcium chloride drying tube, and a magnetic stirrer was slowly added with cooling and stirring a solution of 0.10 mol of methanesulfonyl chloride in 50 ml of benzene. The mixture was stirred overnight under nitrogen, and the precipitated triethylamine hydrochloride was filtered. The filtrate was washed several times with dilute hydrochloric acid and dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting ester was then distilled *in vacuo* through a 10-cm Vigreux column.

Modification of the Above Procedure for the Preparation of Secondary Alkyl Methanesulfonates.—The procedure was identical except that the esters were distilled under the lowest possible pressure in the presence of 0.5 g of $CaCO_3$ to minimize decomposition. The esters were then stored over 1 g of $NaHCO_3$ in which case they were reasonably stable.

Preparation of Propanol-1,1-d_2.—In a three-neck 500-ml flask equipped with a reflux condenser fitted with a calcium chloride drying tube, dropping funnel, and mechanical stirrer was mixed 200 ml of diethyl ether distilled from $LiAlH_4$ and 3.1 g (0.13 mol) of $LiAlD_4$. The resulting slurry was heated under reflux for 1 hr. Then 9.63 g (0.13 mol) of propanoic acid in 50 ml of Et_2O was added over a period of 2 hr with cooling. After addition was complete the reaction was allowed to run overnight under gentle reflux. The reaction mixture was cooled and an excess (25 ml) of methyl carbitol was added slowly. After this addition was complete the reaction mixture was distilled to give 4.3 g (81%) of n-$CH_3CH_2CD_2OH$, bp 99–101°.

Preparation of n-Propyl-β',β'-d_2 Methanesulfonate.—To a solution of 6.59 g (0.065 mol) of triethylamine and 4.3 g (0.069 mol) of propanol-1,1-d_2 in 100 ml of benzene was slowly added a solution of 5.72 g (0.05 mol) of methanesulfonyl chloride in 25 ml of benzene. The mixture was stirred for 8 hr and worked up in the usual manner to give 4.37 g (63%) of propyl-β',β'-d_2 methanesulfonate: bp 76–77° (2.6 mm); nmr ($CDCl_3$), τ 9.01 (t, 3), 8.30 (q, 2), 7.08 (s, 3).

Preparation of Propanol-2,2-d_2, $CH_3CD_2CH_2OH$.—A solution of 25.0 g (0.212 mol) of methylmalonic acid (Mallinckrodt), 20 g (1.0 mol) of deuterium oxide (Columbia Organic Chemicals, 99.7%), and 20 ml of dioxane (distilled from sodium) was stirred for 48 hr at room temperature. The solvent was then removed at room temperature *in vacuo*, and the residue dried *in vacuo* over phosphorus pentoxide. This procedure was repeated for a total of three times. The product was then decarboxylated by heating with stirring at 140° until the evolution of CO_2 stopped (about 24 hr). The crude acid was distilled *in vacuo* to give 15.5 g (0.204 mol) of propanoic-2,2-d_2 acid. This acid (10 g, 0.13 mol) was taken up in 10 ml of Ansul ether 141 (distilled from $LiAlH_4$) and slowly added with stirring to a cooled slurry of 4.94 g (0.130 mol) of lithium aluminum hydride in 100 ml of Ansul ether 141. The mixture was stirred overnight, and then excess methyl carbitol (25 ml) was added. The product was distilled from the reaction mixture. This material was redistilled to give 6.38 g (79%) of propanol-2,2-d_2, bp 100–101°.

Preparation of Propyl-2,2-d_2 Methanesulfonate.—To a solution of 4.35 g (0.043 mol) of triethylamine and 2.67 g (0.043 mol) of propanol-2,2-d_2 in 75 ml of dry benzene was slowly added 4.35 g (0.038 mol) of methanesulfonyl chloride in 10 ml of benzene. The mixture was stirred overnight under nitrogen, and then worked up in the usual manner. The ester was distilled *in vacuo* and collected in the amount of 4.9 g (92%): bp 84–85° (6.0 mm); nmr, τ 9.05 (s, 3), 7.10 (s, 3), and 5.98 (s, 2).

Preparation of Propanol-3,3,3-d_3.—A solution of 104 g (1.0 mol) of malonic acid (Mallinckrodt), 50 g (2.50 mol) of deuterium oxide (98%), and 100 ml of dioxane (distilled from sodium) was stirred for 48 hr at room temperature. The solvent was removed at room temperature *in vacuo* and the residue dried *in vacuo* over phosphorus pentoxide. This procedure was repeated for a total of three times. This product was then decarboxylated by heating at 145° until CO_2 evolution stopped. The crude acetic-d_4 acid (18.9 g, 0.30 mol) was added slowly to 44.0 g (0.34 mol) of thionyl chloride cooled to 10–15°. After the addition was complete, the reaction mixture was heated gently for 0.5 hr and the product distilled. The original distillate was redistilled to give 20.3 g (84%) of CD_3COCl, bp 52–53° (760 mm).[20] CD_3COCl (16.3 g, 0.20 mol) was added slowly to a cold solution of diazomethane in ether (prepared from bis(N-methyl-N-nitroso)-terephthalamide).[21] A brisk evolution of nitrogen occurred, and the solution was allowed to stand at 0°.[22] The ether was removed from the reaction mixture at 5–10° *in vacuo* leaving a bright yellow liquid (diazo ketone) which was taken up in 200 ml of methanol. To this solution was added a few drops of a mixture prepared by adding 9.2 g (0.04 mol) of silver benzoate to 30 ml of triethylamine.[23] Nitrogen was evolved immediately and the solution turned black. When the nitrogen evolution slowed down, more of the silver benzoate solution was added. A total of 2.65 l. of nitrogen was evolved. The mixture was filtered and then distilled on a Todd column to give 11.6 g (0.110 mol) of methyl propionate-3,3,3-d_3, bp 78–79° (756 mm). This ester was reduced with $LiAlH_4$ in Ansul ether 141 to give 6.05 g (87%) of propanol-3,3,3-d_3, bp 100.5–101.5° (753 mm).

Preparation of Propyl-3,3,3-d_3 Methanesulfonate.—To a solution of 5.15 g (0.051 mol) of triethylamine and 3.22 g (0.051 mol) of propanol-3,3,3-d_3 in 100 ml of dry benzene was slowly added 4.81 g (0.042 mol) of methanesulfonyl chloride in 15 ml of benzene. The mixture was stirred overnight and worked up in the usual manner. Distillation *in vacuo* gave 3.78 g (64%) of ester: bp 110.5–111.5° (20.0 mm); nmr, τ 8.25 (q, 2), 7.10 (s, 3), 5.95 (q, 2).

Preparation of Isobutyl-1,1-d_2 Methanesulfonate.—To a slurry of 2.1 g (0.05 mol) of $LiAlD_4$ in 50 ml of Ansul ether 141 (distilled from $LiAlH_4$) was slowly added 4.4 g (0.05 mol) of isobutyric acid

(20) B. Helferich and W. Schaefer, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1964, p 147.

(21) Th. J. DeBoer and H. J. Backer, "Organic Syntheses," Coll. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 250.

(22) W. E. Bachman and W. S. Staure, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942.

(23) M. S. Newman and P. F. Beal, III, *J. Amer. Chem. Soc.*, **72**, 5163 (1950).

in 25 ml of Ansul ether 141. The reaction mixture was allowed to stir overnight at 70°. Excess methyl carbitol was added and the product distilled to give 2.3 g (61%) of isobutyl-1,1-d_2 alcohol, bp 108–109°.

To a solution of 3.04 g (0.030 mol) of triethylamine and 2.28 g (0.030 mol) of isobutyl-1,1-d_2 alcohol in 75 ml of dry benzene was added 2.86 g (0.025 mol) of methanesulfonyl chloride in 10 ml of benzene. The mixture was stirred overnight and worked up in the usual manner. The ester was distilled *in vacuo* giving 1.4 g (28%) of isobutyl-1,1-d_2 methanesulfonate: bp 58–59° (0.60 mm); nmr, τ 9.00 (d, 6), 8.00 (m, 1), 7.02 (s, 3).

Acknowledgment.—This investigation was supported by Public Health Service Grant No. CA-04536-08 and the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2949.

Mass Spectrometry in Structural and Stereochemical Problems. CLIV.[1] Electron Impact Promoted Fragmentation of Alkyl Tetrahydropyranyl Ethers and Thioethers[2]

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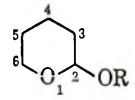
Received January 3, 1968

In view of the importance of tetrahydropyranyl ethers as protecting groups for alcohols, there was undertaken a study of the principal modes of fragmentation subsequent to electron impact of alkyl tetrahydropyranyl ethers and thioethers using specifically deuterated derivatives and high resolution mass spectrometry.

Tetrahydropyranyl ethers have been used in synthetic organic chemistry as base-stable, acid-labile protecting groups for hydroxylic functions. Although much research has been completed on the mass spectrometric fragmentation of alcohols,[3] ethers,[4] and thioethers,[5] only a preliminary description[6] of the processes following electron impact of alkyl tetrahydropyranyl ethers has been published. The present communication records the results of a detailed study, using specifically deuterated analogs supplemented by high resolution mass spectrometry, of the fragmentation of alkyl tetrahydropyranyl ethers and thioethers.

Discussion of Mass Spectra

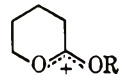
n-Alkyl Tetrahydropyranyl Ethers.—Ethyl and n-butyl tetrahydropyranyl ethers (I and II) were prepared



I, R = C_2H_5
II, R = n-C_4H_9

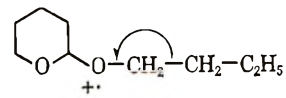
as typical representatives of this class of compound and their respective mass spectra are reproduced at both 70 and 12 eV in Figures 1, 1a, 2, and 2a. It was found necessary to use an all-glass heated inlet system in the determination of these spectra since we observed partial pyrolysis of these compounds to a mixture of dihydropyran (strong molecular ion at m/e 84) and the respective alcohol when using a metal heated inlet system.

The mass spectra (Figures 1 and 2) of ethyl and n-butyl tetrahydropyranyl ether (I and II) contain weak molecular ion peaks which are surpassed in intensity by an M − 1 species. Deuterium labeling established that the hydrogen atom eliminated in this process must originate from C-2 of the pyran ring as no loss of deuterium was observed in the analogs labeled in the alkyl chain or at C-3, C-4, or C-6 of the pyran ring. Therefore this ion can be represented by a.

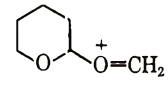


a, M − 1

α cleavage relative to the aliphatic ether oxygen atom is responsible (Table I) for the formation of the low abundance ion (represented by b) at mass 115 in the spectrum (Figure 2) of II and a metastable peak was recognized to verify this decomposition of the molecular ion.

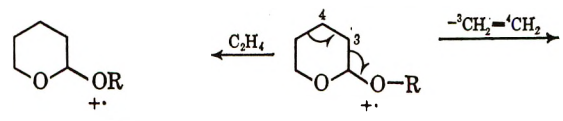


II



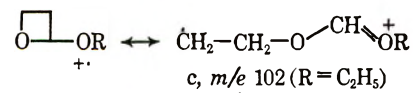
b, m/e 115

A peak of low abundance at m/e 102 (M − 28) in the spectrum (Figure 1) of ethyl tetrahydropyranyl ether (I) was shown by deuterium labeling to originate from loss of C-3 and C-4 of the pyranyl ring (c, 80%) supplemented by elimination of the alkyl chain less a terminal hydrogen atom (d, 20%). The analogous peak at m/e 130 in the spectrum (Figure 2) of the n-butyl homolog was less intense but 50% of its ion contribution arose from a process similar to I → c, the remainder of



d, m/e 102 (R = H)
d, m/e 130 (R = C_2H_5)

I, R = C_2H_5
II, R = n-C_4H_9



c, m/e 102 (R = C_2H_5)
c, m/e 130 (R = n-C_4H_9)

(1) For paper CLIII, see W. Carpenter, Y. M. Sheikh, A. M. Duffield, and C. Djerassi, *Org. Mass Spectry.*, **1**, 3 (1968).

(2) Financial assistance from the National Institutes of Health (Grants No. GM 11309 and AM 04257) is gratefully acknowledged.

(3) For a recent review of the mass spectrometry of alcohols, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 2.

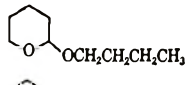
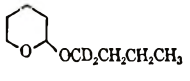
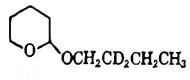
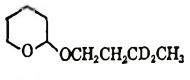
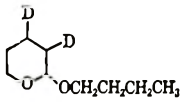
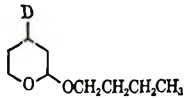
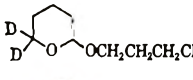
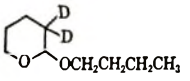
(4) See ref 3, Chapter 6.

(5) See ref 3, Chapter 7.

(6) See ref 3, pp 478, 479.

TABLE I

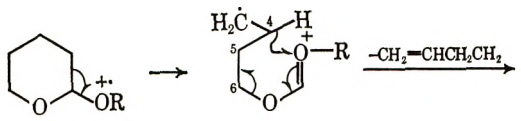
PRINCIPAL MASS SPECTRAL PEAKS IN *n*-BUTYL TETRAHYDROPYRANYL ETHER (FIGURE 2) AND DEUTERATED ANALOGS[a]

Compound	Isotopic purity	Relative abundance, % M	M − 1	M − 28	M − 43	M − 55	M − 58	M − 73	M − 74	M − 91	M − 101
	...	158	157	130	115	103	100	85	84	67	57
	98% d_2	160	159 (q)	130 (50%) 132 (50%)	117 (q)	105 (q)	102 (q)	85 (q)	84 (q)	67 (q)	59 (70%)
	98% d_2	160	159 (q)	130 (50%) 132 (50%)	115 (q)	105 (q)	102 (q)	85 (q)	84 (q)	67 (q)	59 (75%)
	98% d_2	160	159 (q)	132 (90%)	115 (q)	105 (q)	102 (q)	85 (q)	84 (q)	67 (q)	59 (70%)
	96% d_2	160	159 (q)	130 (50%) 132 (50%)	117 (q)	104 (15%) 103 (85%)	101 (q)	87 (q)	85 (~45%)	68 (50%) 69 (50%)	59 (25%)
	96% d_1	159	158 (q)	130 (50%) 131 (50%)	116 (q)	104 (15%) 103 (85%)	100 (q)	86 (q)	85 (~90%)	67 (90%) 68 (10%)	58 (25%)
	98% d_2	160	159 (q)	132 (q)	117 (q)	104 (25%) 103 (75%)	100 (q)	87 (q)	86 (q)	68 (60%) 69 (40%)	59 (30%)
	65% d_2 30% d_1	160	159 (q)	130 (50%) 132 (50%)	117 (q)	103 (10%) 104 (90%)	102 (q)	87 (q)	85 (~80%)	68 (~15%) 69 (~80%)	59 (25%)

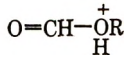
[a] Isotopic purities were calculated from precursor compounds in the synthetic sequence whenever possible and these values checked against the displacement of the peak (Figures 1 and 2) at *m/e* 85. Numerical values are considered accurate to ±5% for peaks in excess of 20% relative abundance. The symbol q refers to a quantitative shift (>95%) while the absence of a value in the table indicates that no accurate assessment was possible.

the expelled ethylene emanating from C-1 and C-2 of the alkyl chain—a process which must involve an ethyl migration.[7]

Peaks of 56 and 7% relative abundance corresponding to the loss of 55 mass units occur in the spectra of I and II (*m/e* 75 in Figure 1; *m/e* 103 in Figure 2). In the case of the ethyl homolog (I) a high resolution mass measurement established the composition $C_3H_7O_2$ for the fragment of mass 75 and it is noteworthy that at low ionizing voltage (12 eV) this ion attains still greater abundance (Σ_{40} 14% *vs.* Σ_{40} 8%). In the ethyl and butyl analogs (I and II) deuterium labeling showed that the ions at mass 75 and 103, respectively, arose from fragmentation of the pyran ring as demonstrated by the total label retention in those derivatives containing deuterium in the side chain. Furthermore, isotopic labeling of the pyran ring indicated that 25% of the hydrogen at C-6 in both I and II were included in the charged species. The compound containing deuterium at C-4 of the pyran ring of I was unavailable but in view of the significant transfer (30%, Table I) from this ring position in the butyl derivative XVIIb it is likely that some similar transfer occurs in the ethyl analog. The



I, R = C_2H_5
II, R = *n*-C_4H_9



e, *m/e* 75, R = C_2H_5
e, *m/e* 103, R = *n*-C_4H_9

(7) P. Brown and C. Djerassi, *Angew. Chem.*, **79**, 481 (1967).

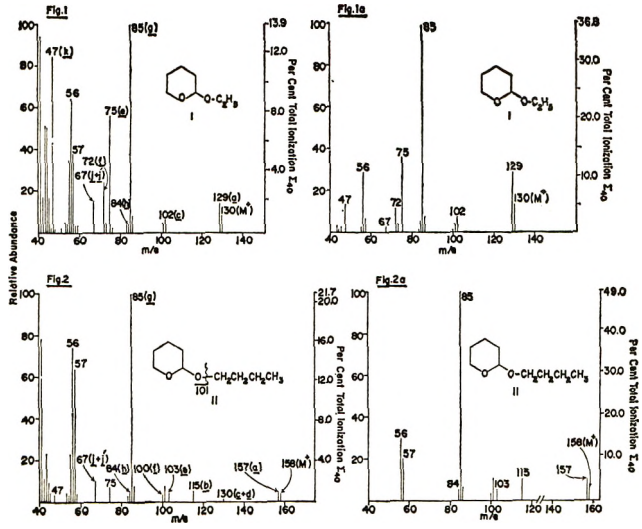


Figure 1.—Mass spectrum (70 eV) of ethyl tetrahydropyranyl ether (I).

Figure 1a.—Mass spectrum (12 eV) of ethyl tetrahydropyranyl ether (I).

Figure 2.—Mass spectrum (70 eV) of *n*-butyl tetrahydropyranyl ether (II).

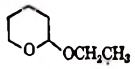
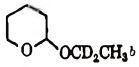
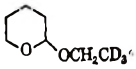
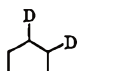
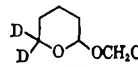
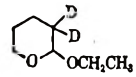
Figure 2a.—Mass spectrum (12 eV) of *n*-butyl tetrahydropyranyl ether (II).

remainder of the transferred hydrogen must embark from C-5 since no appreciable loss from C-3 (Tables I and II) was found. The general fragmentation sequence I → e (supplemented by hydrogen rearrangement from C-5 and C-6) is consistent with the observed results.

An ion equivalent to M − 58 (*m/e* 72, Figure 1; *m/e* 100, Figure 2) is present in the mass spectra of the tetra-

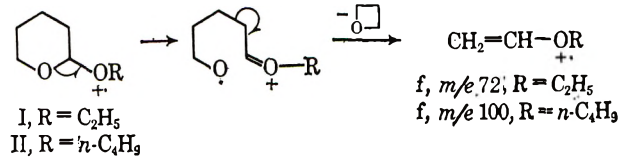
TABLE II

PRINCIPAL MASS SPECTRAL PEAKS IN ETHYL TETRAHYDROPYRANYL ETHER (FIGURE 1) AND DEUTERATED ANALOGS[a]

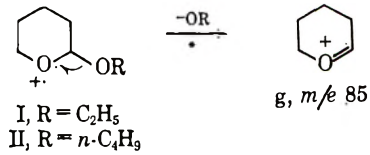
Compound	Isotopic purity	Relative abundance, % M+	M − 1	M − 28	M − 55	M − 58	M − 45	M − 46	M − 63	M − 73	M − 83
		130	129	102	75	72	85	84	67	57	47
	98% d_2	132	131 (q)	104 (80%) 102 (20%)	77 (q)	74 (q)	85 (q)	84 (q)	67 (q)	57 (q)	47 (80%) 48 (20%)
	98% d_3	133	132 (q)	105 (86%) 103 (14%)	78 (q)	75 (q)	85 (q)	84 (q)	67 (q)	57 (q)	47 (30%) 48 (70%)
	98% d_2	132	131 (q)	102 (80%) 104 (20%)	76 (20%) 75 (80%)	73 (q)	87 (q)	85 (~50%) 86 (~50%)	68 (30%) 69 (70%)	59 (~40%)	47 (75%) 48 (20%)
	98% d_2	132	131 (q)	104 (q)	75 (75%) 76 (25%)	72 (q)	87 (q)	86 (q)	68 (55%) 69 (45%)	59 (~70%)	47 (q)
	67% d_2 33% d_1	132	131 (q)	102 (85%) 104 (15%)	75 (90%) 76 (10%)	74 (q)	87 (q)	85 (~90%)	68 (~20%) 69 (~70%)	59 (~40%)	47 (90%) 48 (10%)

[a] See Table I, footnote *a*. [b] Registry no.: 16315-53-0. [c] Registry no.: 16315-54-1.

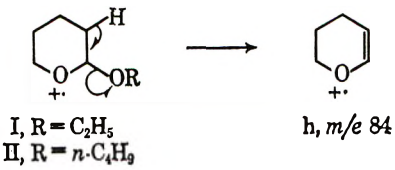
hydropyranyl ethers I and II and high resolution mass spectrometry identified the species in question as C_4H_8O in the case of the ethyl homolog. Deuterium labeling (Tables I and II) implicated the alkyl chain of both I and II with this ion and the rationalization depicted in I → f is consistent with the observed label retention.



The most abundant ion in the mass spectra (Figures 1 and 2) of ethyl and *n*-butyl tetrahydropyranyl ether (I and II) at both 70 and 12 eV occurs at mass 85 (C_5H_9O). The obvious representation for this ion is g and label retention in all the deuterated analogs examined supports this contention while the recognition of an appropriate metastable peak in the mass spectra of I and II testifies to the origin of this species by a single-step fragmentation of the parent ion.

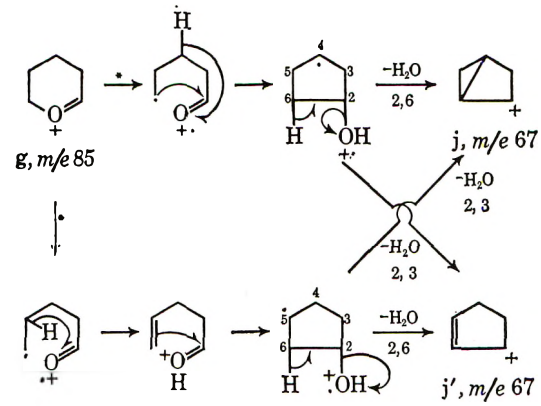


Whereas the elimination of an alkoxy radical from the molecular ion of I and II is a very important process in the electron impact promoted decomposition of these compounds, this loss accompanied by hydrogen abstraction from the pyranyl ring (M − ROH) assumes only minor importance (*m/e* 84, Figures 1 and 2). The major source of hydrogen in the butyl analog in this process is most likely C-3 of the ring (Table I) and this decomposition can be rationalized by the formation of dihydropyran (h, *m/e* 84). In view of our observation that alkyl tetrahydropyranyl ethers decomposed to dihydropyran when a metal heated inlet system was employed, we cannot eliminate the possibility that the low abundance of ion h observed actually arises from



pyrolytic cleavage during passage through the all-glass heated inlet system.

A metastable peak was present in the spectra of I and II corresponding to the loss of water from the ion of mass 85 (g) with the generation of the species of mass 67 (C_5H_7). Low ionizing energy (12 eV) resulted in the virtually complete suppression (Figures 1a and 2a) of this ion. Label retention in the deuterated analogs (XII, XVIb, XVIIb, and XXb) of the butyl homolog implicated the hydrogen atoms attached to C-4 (90%), C-6 (60%), and C-3 (~15%) of the pyranyl ring, the remainder possibly arising from C-5, the only position of the ring not tagged with deuterium. The following rationalization (g → j + j′, *m/e* 67) is consistent with the shifts of the peak at *m/e* 67 in the deuterated compounds examined.



The peaks at *m/e* 57 in the spectra (Figures 1 and 2) of ethyl and *n*-butyl tetrahydropyranyl ether (I and II) correspond to C_4H_9 and C_3H_5O, the percentage of hydrocarbon being 50% in I and 90% in II. In the butyl homolog approximately 70% of the C_4H_9 species arises

from the alkyl chain; the remainder arises from the pyranyl ring plus one hydrogen atom. This latter explanation also accounts for the C_4H_9 ion in the mass spectrum of the ethyl derivative I.

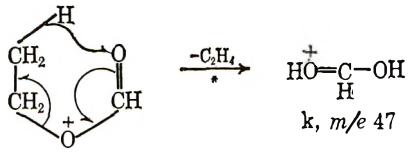
The oxygen containing species of mass 57 in the spectra (Figures 1 and 2) of I and II is formed, at least in part (since a metastable ion was recognized), by the loss of 28 mass units from g (*m/e* 85). Deuterium labeling in the ethyl homolog indicated that ethylene is possibly lost from g by multiple pathways and in view of the difficulty in calculating precise percentage shifts in the 3,4-d_2 derivative of I no accurate assessment can be given for this process. Loss of C-4 and C-5 as ethylene formally corresponds to an electron impact sponsored retro Diels–Alder process.[8]

g, *m/e* 85

High resolution mass spectrometry showed the peak at *m/e* 56 in the spectra (Figures 1 and 2) of the tetrahydropyranyl ethers I and II to be C_4H_8 (>90%). Deuterium labeling suggested that this ion arose from the pyranyl ring carbon atoms in ethyl tetrahydropyranyl ether (I) while in the *n*-butyl compound (II) approximately 70% arose in this fashion, the remainder originating from the butyl side chain.

The peak at *m/e* 55 in the spectra (Figures 1 and 2) of I and II is a doublet of composition C_4H_7 (80%), C_3H_3O (20%); and C_4H_7 (85%), C_3H_3O (15%), respectively. It was impossible to calculate precise shifts in the position of this peak in the isotopically labeled compounds studied but as anticipated for the ethyl compound (I) the pyranyl ring carbon atoms are the major source of the C_4H_7 ion while in the *n*-butyl analog better than 70% of this ion results from fragmentation of the alkyl side chain.

Because of its lack of adjacent neighbors the peak at *m/e* 47 in the mass spectra (Figures 1 and 2) of I and II is easily identified and high resolution mass spectrometry established its composition as CH_3O_2. In view of the presence of a metastable peak in the spectrum (Figure 1) of the ethyl analog I this ion must be formed, at least in part, by ejection of ethylene from e, (*m/e* 75). In this instance deuterium labeling was instrumental in determining that 20% of the hydrogen at C-1 and 70% of that at C-2 of the alkyl chain were involved with the charged species at mass 47. The following process will rationalize the formation of 70% of the ion current at mass 47 in the spectrum of ethyl tetrahydropyranyl ether (I).



e, *m/e* 75 k, *m/e* 47

***n*-Alkyl Tetrahydropyranyl Thioethers.**—Ethyl and *n*-butyl tetrahydropyranyl thioethers (III and IV) were

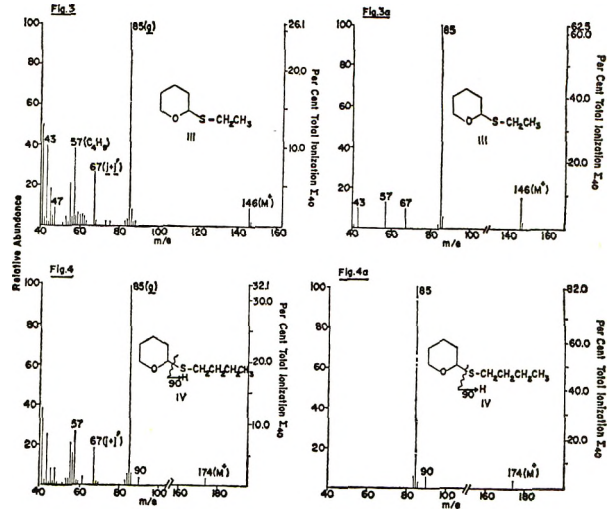
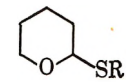


Figure 3.—Mass spectrum (70 eV) of ethyl tetrahydropyranyl thioether (III).

Figure 3a.—Mass spectrum (12 eV) of ethyl tetrahydropyranyl thioether (III).

Figure 4.—Mass spectrum (70 eV) of *n*-butyl tetrahydropyranyl thioether (IV).

Figure 4a.—Mass spectrum (12 eV) of *n*-butyl tetrahydropyranyl thioether (IV).



III, R = C_2H_5
IV, R = *n*-C_4H_9

examined as typical examples of this class of compound[9] and their mass spectra (Figures 3 and 4) determined. Over-all these spectra show a strong general resemblance to their oxygenated counterparts, two obvious differences being the anticipated[5] relative increase of the molecular ion in the butyl analog and especially the absence of an M − 1 species in both the thio compounds.

By far the most abundant peak in the mass spectra (Figures 3 and 4) of the tetrahydropyranyl thioethers (III and IV) examined occurs at *m/e* 85 and this species can be rationalized by g, the eliminated neutral entity being a thioalkyl radical. At low ionizing energy this ion remains as the dominant feature of the spectra (Figures 3a and 4a) of III and IV.

A metastable peak at *m/e* 53.0 in the spectra (Figures 3 and 4) of the thioethers III and IV demonstrated that at least some of the charged species of mass 67 arose from the expulsion of water from g, *m/e* 85. In the absence of extensive isotopic labeling one would expect that this process proceeds in a manner analogous to that described for *n*-butyl tetrahydropyranyl ether (II).

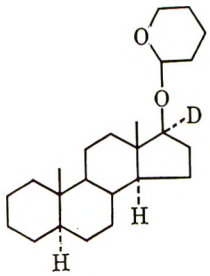
The prominent ions at mass 57 in the spectra (Figures 3 and 4) of the thioethers III and IV correspond to C_4H_9 in greater than 90% yield. In the butyl thioether, dideuterated at C-6 of the pyran ring, 90% of the ion current at mass 57 is displaced to 59 thus establishing that this ion results from fragmentation of the pyran ring supplemented by a hydrogen-transfer process. This result conflicts with the mechanism operative in formation of the ion of mass 57 (C_4H_9) in the spectrum of *n*-butyl tetrahydropyranyl ether (II) in which 70%

(8) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).

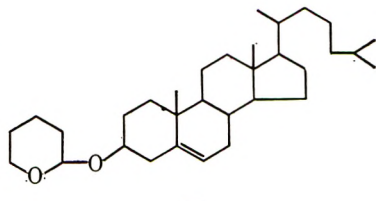
(9) E. L. Eliel, B. N. Nowak, and R. A. Daignault, *J. Org. Chem.*, **30**, 2448 (1965).

is generated from fragmentation of the butyl side chain. It is also noteworthy that there was no evidence of carbon–sulfur fission with charge retention on sulfur in any of the spectra, in marked contrast to the propensity of simple thioethers[10] for this type of cleavage.

Steroid Tetrahydropyranyl Ethers.—Tetrahydropyranyl ether derivatives of some steroids such as cholesterol and androstan-17β-ol were prepared and their mass spectra determined. A weak molecular ion peak was visible (0.3% relative abundance) in the spectrum of androstan-17β-ol tetrahydropyranyl ether (V) but a parent ion was absent in the cholesterol derivative VI. The only prominent ions in the mass spectra of these compounds corresponded to the product of elimination of 2-hydroxydihydropyran and the ubiquitous ion (g) of the tetrahydropyranyl ether at mass 85. From these results it would appear that tetrahydropyranyl ether derivatives are not the ones of choice for mass spectral identification of larger molecular weight hydroxylated compounds.



V

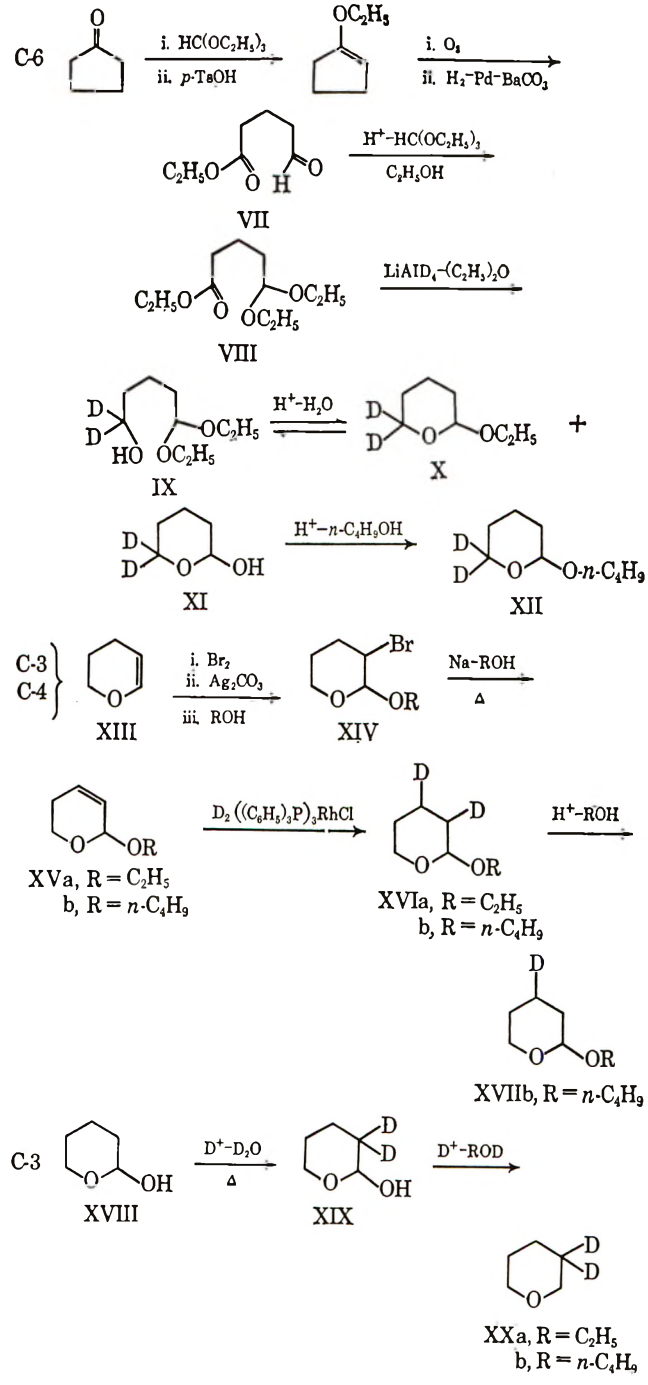


VI

In summary it can be stated that tetrahydropyranyl ethers and thioethers subsequent to electron impact cleave preferentially α to the ring oxygen atom (formation of g, m/e 85). The occurrence of a strong peak at m/e 84 in the mass spectrum of a tetrahydropyranyl ether is indicative of thermal fragmentation of the compound to dihydropyran and the corresponding alcohol in the heated inlet system (or ion source) of the mass spectrometer.

Synthesis of Deuterated Tetrahydropyranyl Ethers.—The compounds labeled in the alkyl chain were conveniently prepared by acid-catalyzed condensation of a specifically deuterated alcohol[11] with dihydropyran or alternatively by addition of the deuterated alcohol to 2-hydroxytetrahydropyran and azeotropic distillation with benzene of the water produced. Introduction of deuterium into the pyranyl ring at positions C-3, C-4, and C-6 was accomplished according to Scheme I.

SCHEME I



Experimental Section

Low resolution mass spectra were obtained with a CEC 103-C mass spectrometer (ion source temperature 250°) attached to a heated all-glass inlet system (100°) while high resolution mass measurements were determined on an MS-9 instrument (inlet temperature 120°) by Mr. R. G. Ross and were accurate to within 3 ppm. Low-voltage spectra refer to nominal electron volt values. Samples were purified by vpc on a 15% Apiezon L column and isotopic purities are included in Tables I and II.

Side Chain Labeled Tetrahydropyranyl Ethers.—Ethyl and *n*-butyl tetrahydropyranyl ethers (I and II) labeled in the side chain with deuterium were prepared from the labeled ethanol[11] or *n*-butyl alcohol[11] by acid-catalyzed condensation with 2-hydroxytetrahydropyran (Aldrich).

Ethyl and *n*-Butyl Tetrahydropyranyl-6,6-d_2 Ether (X and XII).—5,5-Diethoxyvaleric acid ethyl ester (VIII) was prepared according to the method of Schmidt and Grafen[12] and 3.4 g (15.6 mmol) reduced with lithium aluminum hydride (0.76 g, 18.2 mmol) in refluxing anhydrous ether solution for 2 hr followed by decomposition of excess reagent with saturated sodium sulfate solution to give 5,5-diethoxypentanol-1,1-d_2 (IX) (yield 2.4 g, 87%). Attempted hydrolysis of IX using 1 *N* aqueous hydrochloric acid (11 ml) at room temperature for 2.5 hr afforded ethyl tetrahydropyranyl-6,6-d_2 ether (X) as the major product which was purified by vpc. 2-Hydroxytetrahydropyran-6,6-d_2 (XI) was isolated by vpc as a minor constituent (100 mg) of the reaction mixture. This material (23 mg) was converted into *n*-butyl tetrahydropyranyl-6,6-d_2 ether (XII) by refluxing overnight with *n*-butyl alcohol containing 1 drop of concentrated hydrochloric acid in benzene and the product (XII) (yield 21 mg, 57%) purified by vpc.

(10) S. D. Sample and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 1937 (1966).

(11) For the preparation of specifically deuterated alcohols, see A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *ibid.*, **87**, 805 (1965).

(12) U. Schmidt and P. Grafen, *Ann.*, **656**, 97 (1962).

Ethyl and *n*-Butyl Tetrahydropyranyl-3,4-d_2 Ether (XVIa and XVIb).—2-Ethoxy- and 2-butoxy-Δ^3-dihydropyran (XVa and XVb) were prepared by the method of Woods and Sanders[13] and each was deuterated by homogenous catalysis[14] using $[(C_6H_5)_3P]_3RhCl$ (25 mg) in acetone (10 ml) at room temperature for 18 hr, the solvent and the labeled tetrahydropyranyl ethers (XVIa and XVIb) being separated by vpc.

***n*-Butyl tetrahydropyranyl-4-d_1 ether (XVIIb)** was prepared from *n*-butyl tetrahydropyranyl-3,4-d_2 ether (XVIb) by stirring overnight with *n*-butyl alcohol containing a trace of concentrated hydrochloric acid. The solvent alcohol was fractionally distilled and XVIIb isolated by preparative vpc.

(13) G. F. Woods and H. Sanders, *J. Amer. Chem. Soc.*, **68**, 2483 (1946).
(14) W. Voelter and C. Djerassi, *Chem. Ber.*, **101**, 58 (1968).

Ethyl and *n*-Butyl Tetrahydropyranyl-3,3-d_2 Ether (XXa and XXb).—2-Hydroxytetrahydropyran (XVIII, 0.5 g) was heated under reflux for 1.5 hr with deuterium oxide (15 ml) containing deuteriohydrochloric acid (8.8 *N*, 5 drops) and then continuously extracted with ether. Isolation by preparative vpc yielded 2-hydroxytetrahydropyran-3,3-d_2 (XIX, 0.27 g). Condensation of XIX (50 mg) with an excess of ethanol-O-*d* and deuterium oxide containing 3 drops of deuteriohydrochloric acid yielded ethyl tetrahydropyranyl-3,3-d_2 ether (XXa). Similar treatment of *n*-butanyl alcohol-O-*d* with 2-hydroxytetrahydropyran-3,3-d_2 (XIX) afforded *n*-butyl tetrahydropyranyl-3,3-d_2 ether (XXb).

Registry No.—I, 4819-83-4; II, 1927-68-0; III, 16315-51-8; IV, 16315-52-9; X, 16315-55-2; XVIa, 16315-56-3; XXa, 16315-57-4.

Mass Spectrometry in Structural and Stereochemical Problems. CLV.[1] Electron Impact Induced Fragmentations and Rearrangements of Some Trimethylsilyl Ethers of Aliphatic Glycols and Related Compounds[2]

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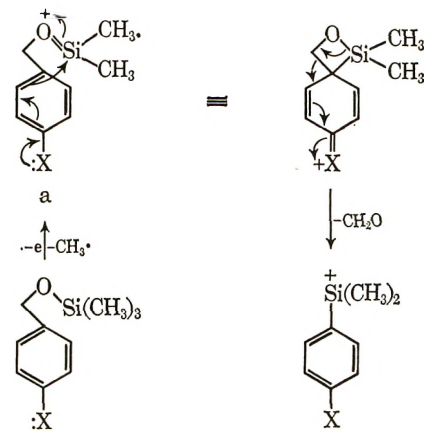
In view of the importance of trimethylsilyl ethers in gas chromatography, the basic fragmentation modes incurred upon electron bombardment of polymethylene glycol bistrimethylsilyl ethers (III, n = 2–8) were elucidated; in all cases (n = 2–8), there is encountered a characteristic rearrangement ion (g) of mass 147 involving expulsion of the central portion of the molecule. Electron bombardment of the corresponding methoxy- (XI, n = 2,4,5), ethoxy- (XIV), and phenoxy- (XVIII, n = 2–7) polymethylene trimethylsilyl ethers also produced intense rearrangement peaks analogous to g; and in all instances there was encountered a remarkable insensitivity toward ring size (five to eleven membered) in the cyclic transition state. Deuterium and oxygen-18 labeling was employed to elucidate the fragmentation patterns exhibited by XI, XIV, and XVIII. The trimethylsiloxy function of 2-phenoxyethyl trimethylsilyl ether (XVIII, n = 2) was replaced with the triethylsiloxy and trimethylgermanyl groups in order to assess their effect upon the mass spectral behavior of XVIII (n = 2). Likewise, the effect of substitution of nitrogen and sulfur atoms for both the phenoxy and trimethylsiloxy oxygen atoms was examined. Finally, deuterium labeling was employed to elucidate the electron impact induced fragmentation modes of 2-(cyclohexyloxy)ethyl trimethylsilyl ether (XXIX).

In recent years, trimethylsilyl ethers have been extensively employed to facilitate gas chromatographic separation of nonvolatile materials. The development[4] and widespread usage of mass spectrometers capable of making direct measurements of gas chromatographic effluents has made mass spectral investigations of trimethylsilyl ethers particularly relevant and several studies concerning the mass spectra of trimethylsilyl derivatives of a variety of natural products have recently appeared.[5] Interest in our laboratory initially focussed on the characteristic fragmentations encountered in sterol trimethylsilyl ethers.[6] During this work, it became evident that a thorough study of the electron impact promoted fragmentation of various trimethylsilyl ether types must be undertaken in order to permit more precise structural deductions. In a subsequent study[7] the fragmentation modes of certain alcohol derivatives were accurately elucidated utilizing deuterium-labeled pentanol trimethylsilyl ethers. Also discussed in that report were several electron impact induced skeletal rearrangements of which the sequential loss of a methyl radical and of formaldehyde in benzyl ether derivatives (I → a → b) is typical (Scheme I).

SCHEME I



(1) For paper CLIV, see S. J. Isser, A. M. Duffield, and C. Djerassi, *J. Org. Chem.*, **33**, 2266 (1968).
(2) Financial assistance (Grant No. AM 04257) from the National Institutes of Health is gratefully acknowledged.
(3) (a) National Science Foundation Predoctoral Fellow (1966–1967); National Institutes of Health Predoctoral Fellow (1967–1968). (b) National Institutes of Health International Postdoctoral Fellow (1965–1966) on leave from University College, Dublin.
(4) For review, see S. Ställberg-Stenhagen and E. Stenhagen in "Topics in Organic Mass Spectrometry," A. L. Burlingame, Ed., Interscience Publishers, Inc., New York, N. Y., 1968, Chapter 5.
(5) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 471–477.
(6) J. Diekman and C. Djerassi, *J. Org. Chem.*, **32**, 1005 (1967).
(7) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **32**, 3904 (1967).

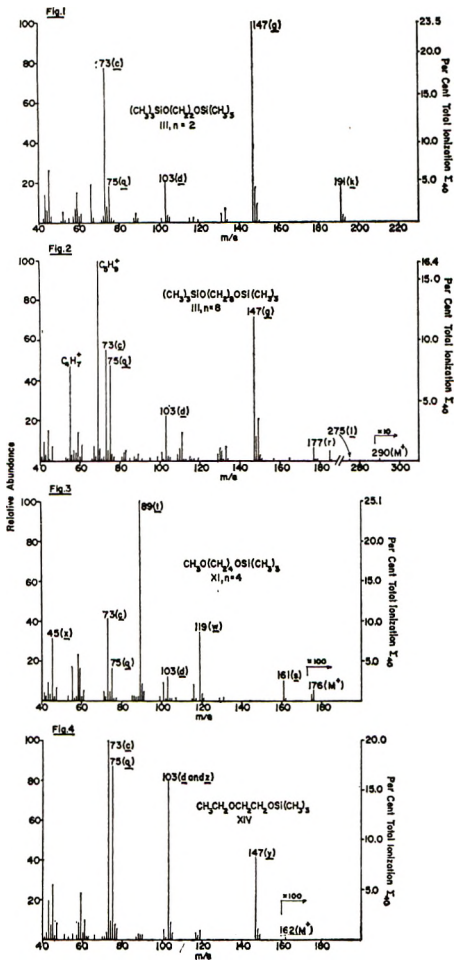


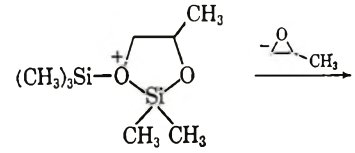
Figure 1.—Mass spectrum (CEC-103C) of ethylene glycol bistrimethylsilyl ether (III, n = 2).
Figure 2.—Mass spectrum (CEC-103C) of 1,8-octanediol bistrimethylsilyl ether (III, n = 8).
Figure 3.—Mass spectrum (CEC-103C) of 4-methoxybutyl trimethylsilyl ether (XI, n = 4).
Figure 4.—Mass spectrum (CEC-103C) of 2-ethoxyethyl trimethylsilyl ether (XIV).

Further interest in the behavior of trimethylsilyl ethers upon electron bombardment was stimulated by the mass spectrum of 1,2-propanediol bistrimethylsilyl ether (II) tabulated, without specific comment, by Sharkey, *et al.*[8] The most intense peak in this spectrum occurs at m/e 73 (c) and the α-cleavage fragments d and e are also of appreciable abundance. By contrast with the normal alkyl trimethylsilyl ethers,[7,8] the M − CH_3 peak is very weak (3.5% relative abundance).

$(CH_3)_3SiOCH_2CH(CH_3)OSi(CH_3)_3$
II

$Si(CH_3)_2$	$(CH_3)_3SiO{=}CH_2$	$CH_3CH{=}OSi(CH_3)_3$
c, m/e 73	d, m/e 103	e, m/e 117

The most interesting feature of the spectrum, however, is an abundant species (88% relative abundance) of mass 147 which must have the elemental composition $C_5H_{15}OSi_2$ and for which g seemed to us to be the most plausible representation. In view of the results presented below, we propose that the mass 147 ion (g) is formed by collapse of the cyclic oxonium ion form (f) of an M − CH_3 precursor with elimination of the elements of propylene oxide (eq 1).



f, M−CH_3

$$(CH_3)_3SiOSi(CH_3)_2 \quad (1)$$
g, m/e 147

In light of the current interest in electron impact induced skeletal rearrangements[9] and in the reported[8,10,11] mass spectra of trimethylsilyl derivatives of polyhydroxy compounds, it was decided to examine the mass spectra of the bistrimethylsilyl, phenyl trimethylsilyl, and methyl trimethylsilyl ethers of a series of polymethylene glycols together with a number of compounds of related structure. Such a study is not only pertinent for practical reasons, but is especially justified on mechanistic grounds because of interesting skeletal rearrangements.

Discussion

The mass spectra (Figures 1 and 2) of the trimethylsilyl ethers (III) of all polymethylene glycols from C_2 to C_8 show (Table I) an intense peak at m/e 147 having

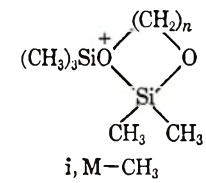
TABLE I
ABUNDANCE OF THE REARRANGEMENT PEAK g (m/e 147) IN THE MASS SPECTRA (70 eV) OF THE POLYMETHYLENE GLYCOL BISTRIMETHYLSILYL ETHERS $(CH_3)_3SiO(CH_2)_nOSi(CH_3)_3$

	CEC-103C[a]		A.E.I. MS-9[a]	
n	% Σ_{40}	% of base peak	% Σ_{40}	% of base peak
2	27.9	100	31.1	100
3	15.3	100	30.5	100
4	23.4	100	33.0	100
5	10.1	72	21.7	100
6	14.9	100	13.1	84
7	12.6	71	15.3	67
8	11.8	72	12.2	53

[a] Discussion of this rearrangement peak (g) in the text of this paper is based upon data obtained from spectra recorded on the CEC-103C mass spectrometer; the A.E.I. MS-9 data are included for comparison.

the elemental composition $C_5H_{15}OSi_2$.[12] It is difficult to envisage any reasonable structure for this species other than g. In every case an abundant meta-

$(CH_3)_3SiO(CH_2)_nOSi(CH_3)_3$ $(CH_3)_3SiO(CH_2)_n\overset{+}{O}Si(CH_3)_2$
III, n = 2–8 h, M−CH_3



i, M−CH_3

(8) A. G. Sharkey, R. A. Friedel, and S. H. Langer, *Anal. Chem.*, **29**, 770 (1957).

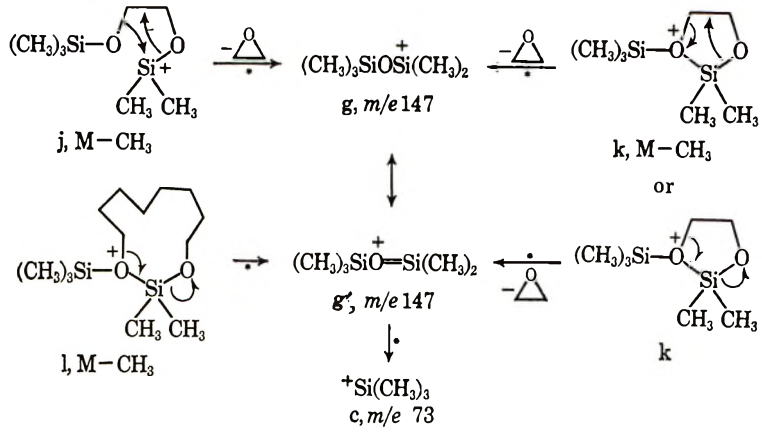
(9) For a complete review, see P. Brown and C. Djerassi, *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(10) W. Richter, M. Vecchi, W. Vetter, and W. Walther, *Helv. Chim. Acta*, **50**, 364 (1967).

(11) G. Peterson, O. Samuelson, K. Anjou, and E. Sydow, *Acta Chem. Scand.*, **21**, 1251 (1967).

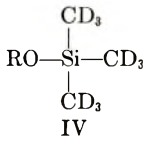
(12) The composition of all fragments discussed in this report were confirmed, when necessary, by high-resolution mass measurements.

SCHEME II



stable ion[13] is observed for the formation of g from an M − CH_3 progenitor, and it seems likely that the silicon–oxygen bond is already formed in the precursor. Intuitively, it appears more probable that the remarkably small decrease in the abundance of the *m/e* 147 species with increasing chain length (Table I) is better explained in terms of the collapse of a cyclic oxonium ion (i) rather than a 1,(n + 2) shift of the trimethylsilyloxy group in the open-chain form (h) of the M − CH_3 precursor. Thus, in the case of III (n = 2), a 1,4 shift in j seems as likely as the formation and collapse of k, but for III (n = 8) a direct 1,10 shift is improbable. This, of course, still leaves unanswered the problem of the surprising ease of formation (albeit, with equal ease of fragmentation–rearrangement) of a cyclic M − CH_3 ion such as l (Scheme II).

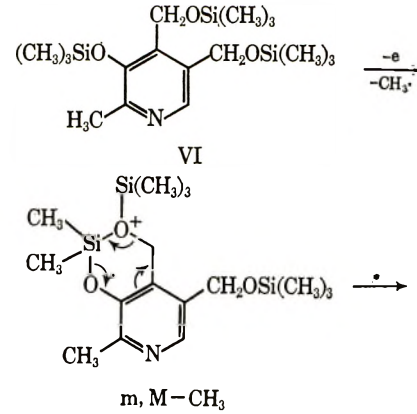
McCloskey, *et al.*,[14] have recently developed a unique method of labeling the methyl groups of trimethylsilyl ethers with deuterium atoms (IV). This process greatly facilitates the obtaining of structural information on fragment ions especially in cases where high-resolution mass measurements do not provide adequate data (e.g., the mechanistic fate of methyl hydrogens in trimethylsilyl derivatives). The utility of this labeling technique is illustrated by the mass spectra of 1,10-decanediol bistrimethylsilyl ether (V, n = 10, R = H), 1,22-docosane bistrimethylsilyl ether (V, n = 22, R = H), and their corresponding labeled analogs (R = D). These compounds also exhibit abundant *m/e* 147 peaks; and on the basis of the appropriate mass shift (*m/e* 147 → *m/e* 162) in the labeled species, McCloskey, *et al.*,[14] likewise postulate structure g for the ion of mass 147. It is interesting to note that they find no metastable ion for the formation of the mass 147 species from an M − CH_3 progenitor.



IV

V

Richter, *et al.*,[10] encountered an intense *m/e* 147 peak in the mass spectrum of the trimethylsilyl derivative of pyridoxine (VI), and they also postulate, with metastable evidence, its genesis from a cyclic oxonium ion M − CH_3 precursor (m → g) (eq 2).



A very common impurity[7] often contaminating trimethylsilyl ethers, which have been exposed to atmospheric moisture, is hexamethyldisiloxane (VII) (eq 3). Unfortunately, the base peak in the mass spectrum[15] of hexamethyldisiloxane (VII) occurs at *m/e* 147. In order to ensure that every precaution was taken to prevent the formation of this impurity, it was decided to record the mass spectrum of an equimolar mixture of the bistrimethylsilyl (III, n = 2) and bistriethylsilyl (VIII) ethers of ethylene glycol which were synthesized and stored in the same manner as were the polymethylene glycol bistrimethylsilyl ethers (III). If any impurity were formed, one would expect contamination by three compounds (VII, IX, and the mixed product X). Therefore, the mass spectrum of the equimolar mixture would be expected to exhibit, aside from the expected *m/e* 147 and *m/e* 261 (n) peaks which are found, respectively, in the mass spectra of bistrimethylsilyl (III, n = 2) and bistriethylsilyl (VIII) ether of ethylene glycol alone, peaks at *m/e* 175 (o, M − C_2H_5) and *m/e* 189 (p, M − CH_3) due to fragmentation of the presumed impurity (X) (eq 4). In fact, no peaks were encountered at *m/e* 175 or *m/e* 189, whereupon we feel confident that the *m/e* 147 peak observed in bistri-

(13) The observation of a metastable ion for a given process is indicated in the fragmentation schemes by an asterisk beside the arrow.

(14) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968). We wish to express our appreciation to Professor McCloskey for a copy of his manuscript prior to publication.

(15) V. H. Dibeler, F. L. Mohler, and R. M. Reese, *J. Chem. Phys.*, **21**, 180 (1953).

$$(C_2H_5)_3SiO(CH_2)_2OSi(C_2H_5)_3 \longrightarrow$$
VIII

$$(C_2H_5)_3SiOSi(C_2H_5)_3 \xrightarrow[-C_2H_5\cdot]{-e} (C_2H_5)_3SiO\overset{+}{S}i(C_2H_5)_2$$
IX — n, m/e 261

$$(C_2H_5)_2\overset{+}{S}iOSi(CH_3)_3 \xleftarrow[-C_2H_5\cdot]{-e} (C_2H_5)_3SiOSi(CH_3)_3 \xrightarrow[-CH_3\cdot]{-e}$$
o, m/e 175 — X

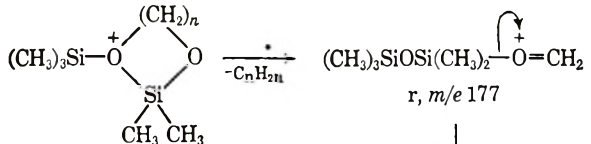
$$(C_2H_5)_3SiO\overset{+}{S}i(CH_3)_2 \quad (4)$$
p, m/e 189

methylsilyl ethers of polymethylene glycols is due entirely to rearrangement processes and not to an impurity.

The remaining features in the mass spectra of III (for typical examples, see Figures 1 and 2) are quite simple with the trimethylsilyl cation (c, m/e 73) being the only other common prominent peak. When the spectra were recorded at 12-eV ionizing energy, this m/e 73 peak disappeared whereas the m/e 147 peak (g) and the m/e 103 peak (d) undergo a slight decrease in intensity. This observation along with the appropriate metastable peaks at m/e 51.7 (calcd $73^2/103 = 51.7$) and at m/e 36.6 (calcd $73^2/147 = 36.6$) provide evidence for the genesis of c (m/e 73) from the rearrangement ion g (m/e 147) and the α-cleavage ion d (m/e 103). When $n > 5$ the elimination of trimethylsilanol to yield an M − 90 species becomes the primary fragmentation at low voltage. Hydrocarbon fragments become more abundant as the chain length increases and when $n = 5$ and 8 the base peak is due to $C_5H_9^+$ ($\Sigma_{40} = 14.0$ and 16.4, respectively). For $n = 7$, $C_4H_7^+$ is the most abundant fragment ($\Sigma_{40} = 17.7$); and the latter ion accounts for the second most intense peak ($\Sigma_{40} = 12.5$) in the spectrum when $n = 6$. In all cases the molecular ions are minute, M − CH_3 is very weak, and a peak at m/e 75 (q) is moderately strong.

$$(CH_3)_2\overset{+}{S}iOH$$
q, m/e 75

Except for the case where $n = 2$, a common feature (see Figure 1 *vs.* Figure 2) in the mass spectra of the bistrimethylsilyl ethers of polymethylene glycols is a weak (5–10% relative intensity) rearrangement peak at m/e 177 [$(C_6H_{17}O_2Si_2)$], most plausibly represented by r. This species, formed from M − CH_3 (i), offers an alternative stepwise pathway to the major rearrangement ion (g). McCloskey[14] likewise reports this rearrangement peak and substantiates its composition with the previously mentioned labeling experiments; he also finds metastable support for elimination of formaldehyde from the m/e 177 species but formulates it as r′ (eq 5).



i, n = 3–8

$$(CH_3)_2\overset{+}{S}i{=}O{-}CH_2{-}OSi(CH_3)_3 \longrightarrow (CH_3)_3SiO\overset{+}{S}i(CH_3)_2 \quad (5)$$
r′ — g, m/e 147

Three representative examples of the trimethylsilyl ethers (XI, n = 2, 4, 5) of polymethylene glycol monomethyl ethers were examined and in each case the most abundant peak in the mass spectrum (see Figure 3 and Table II) occurs at m/e 89 (C_3H_9OSi). This fragment

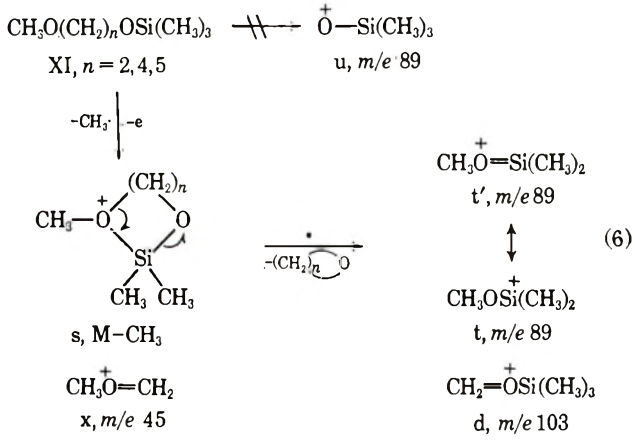
TABLE II

ABUNDANCE OF REARRANGEMENT ION FROM $RO(CH_2)_nOSi(CH_3)_3$

		$ROSi(CH_3)_2^+$			
Compound	n	R	m/e	$\%\Sigma_{40}$	% of base peak
XI	2	CH_3	89	23.0	100
XI	4	CH_3	89	25.1	100
XI	5	CH_3	89	15.8	100
XIV	2	C_2H_5	103	9.1[a]	45[a]

[a] Corrected for the contribution of α cleavage [$CH_2{=}\overset{+}{O}Si(CH_3)_3$] to m/e 103.

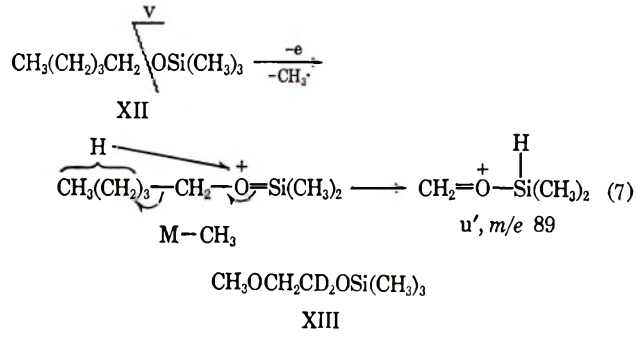
could be depicted either in terms of t or u but a strong metastable ion is observed for its formation from an M − CH_3 precursor (s). Also, in the mass spectra of numerous trimethylsilyl ethers[7] and esters[16] examined in this laboratory, the m/e 89 peak has always been found to be of low abundance (0–20% relative intensity) and therefore it is unlikely that u makes any significant contribution in this instance (eq 6). Furthermore, in



(6)

previous studies[7] where deuterium labeling was employed (*e.g.*, XII), the m/e 89 peak could never be attributed to simple cleavage of the trimethylsiloxy group (v). Rather it was shown to result from loss of a silylmethyl group followed by hydrogen transfer to the charge retaining species (u′) with concomitant olefin or cycloalkane elimination. Since a metastable peak was observed in XI (n = 2, 4, 5) for the formation of the m/e 89 species from an M − CH_3 precursor (s), the α-labeled analog XIII was synthesized in order to ascertain whether a species similar to u′ was involved. No shift in mass (m/e 89 → m/e 91) was evident, whereupon one may conclude that t is indeed the most probable formulation for the ion of mass 89 (eq 7).

(16) J. B. Thomson, J. Diekman, and C. Djerassi, to be submitted for publication.



XII

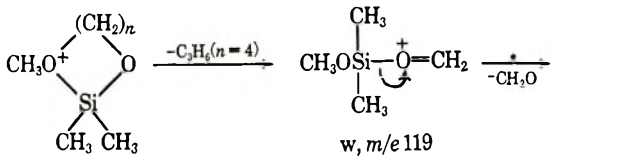
M − CH_3 u′, *m/e* 89 (7)

$CH_3OCH_2CD_2OSi(CH_3)_3$

XIII

As in the case of the bistrimethylsilyl ethers (III), the formation of the rearrangement ion t is not greatly affected (see Table II) by ring size (in s or an equivalent transition state). In the mechanism shown above (s → t) it is assumed that the oxygen atom attached to the methyl group is retained, by analogy with the phenoxy series (see below), where evidence from isotope labeling is available.

In addition one may note that the molecular ions are very weak, M − CH_3 is moderately abundant (Σ_{40} = 7.8) when n = 2 and weak (Σ_{40} = 2.5 and 0.8, respectively) when n = 4 or 5. In all three compounds, the trimethylsilyl cation (c, Σ_{40} = 10–18) and the α-cleavage fragment (x, Σ_{40} = 8–10) are prominent with the alternative α-cleavage ion (d, Σ_{40} = 3–5) being less abundant (see, for instance, Figure 3). When n = 4 and 5 a species of mass 119 (Σ_{40} = 8–9) appears for which structure w is proposed. In a manner analogous to the fragmentation pattern (i → r → g) observed in the case of polymethylene glycol bistrimethylsilyl ethers (III, n = 3–8), it is felt that w is generated from an M − CH_3 precursor (s); and observation of a metastable peak at *m/e* 66.7 (calcd $89^2/119$ = 66.6) supports the postulated elimination of formaldehyde from this species (w) to yield t (*m/e* 89) (eq 8).



s, M−CH_3 w, *m/e* 119

$CH_3OSi(CH_3)_2$ (8)

t, *m/e* 89

The two most intense peaks in the spectrum (Figure 4) of 2-ethoxyethyl trimethylsilyl ether (XIV) are at *m/e* 73 (c, Σ_{40} = 20.0) and *m/e* 75 (q, Σ_{40} = 17.0); the M − CH_3 (*m/e* 147) peak is moderately abundant (Σ_{40} = 8.2) The sole remaining prominent peak occurs at *m/e* 103 (Σ_{40} = 15.8), 95% of which is due to a species of the composition $C_4H_{11}OSi$. This fragment could conceivably arise by three different fragmentation modes.

Simple α cleavage would produce species d, whereas loss of a silylmethyl group (XIV → y) followed by skeletal rearrangement and elimination of ethylene oxide from y would yield the fragment ion z. A third alternative would be fission of the ethoxyl methyl group to produce the M − CH_3 species aa which also could rearrange and eliminate ethylene oxide to yield d′ (Scheme III). Although the two ions (d and d′) are of identical structure, they derive their methylene groups from a different portion of the parent molecule.

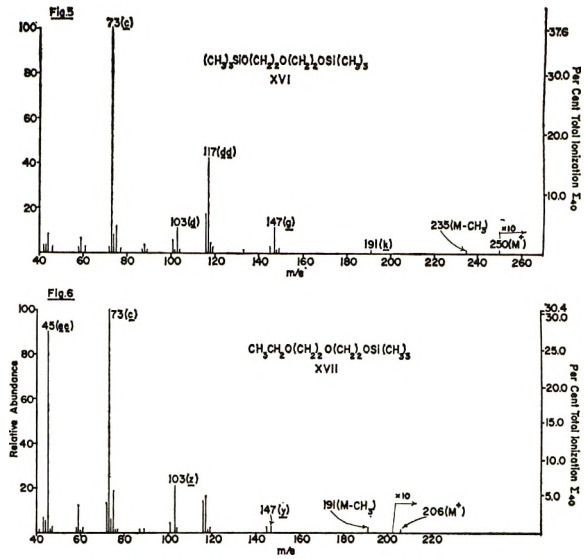
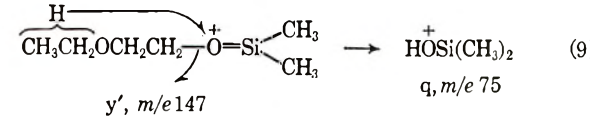


Figure 5.—Mass spectrum (Atlas CH-4) of diethylene glycol bistrimethylsilyl ether (XVI).

Figure 6.—Mass spectrum (Atlas CH-4) of carbitol trimethylsilyl ether (XVII).

A firm distinction among the three pathways was reached by synthesis of the d_5-ethoxy analog XV. In the mass spectrum of this compound, one would expect fragment d to remain at mass 103, whereas z would shift to *m/e* 108 and d′ to *m/e* 105. In actual fact, the spectrum of XV revealed that 42% of the *m/e* 103 peak results from α cleavage (d) and 58% from the rearrangement ion (z); as might be expected, species d′ does not contribute to the *m/e* 103 peak. This spectrum also indicated that, in the formation of the dimethylsilanol ion (q, *m/e* 75), 71% of the hydrogen transfer occurs from the ethoxy group (y′ → q) (eq 9).

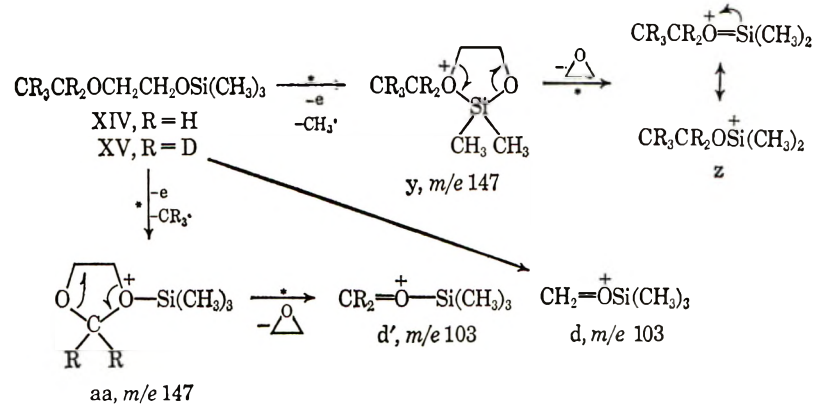


y′, *m/e* 147 q, *m/e* 75 (9)

With the intention of obtaining some information on the relative ease of rearrangement through a five- and eight-membered-ring form of an M − CH_3 precursor, the mass spectra of diethylene glycol bistrimethylsilyl ether (XVI, see Figure 5) and carbitol trimethylsilyl ether (XVII, see Figure 6) were examined, since these compounds may yield either a five- or eight-membered-ring oxonium ion (bb or cc, respectively) by ejection of a methyl radical. The latter (cc) could then decompose directly to the rearrangement ion (g or z), while the former (bb) could yield g or z in a two-step process by way of k (M − CH_3 from III, n = 2) or y (M − CH_3 from XIV). Unfortunately the rearrangement peaks in the spectra of both XVI and XVII (see Figures 5 and 6, respectively) are quite weak, *viz.* 0.4 and 0.9% Σ_{40} for the first rearrangement ion (k and y, respectively) and 4.1 and 6.4% Σ_{40} for the second rearrangement ion (g and z, respectively). In neither case is a metastable ion observed[17] for the direct formation of g or z from M − CH_3 (cc) but strong metastable ions are present for the two-step

(17) Metastable ions were recorded using an Atlas CH-4 mass spectrometer in conjunction with the logarithmic transfer recorder described by R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, *Anal. Chem.*, **37**, 776 (1965).

SCHEME III



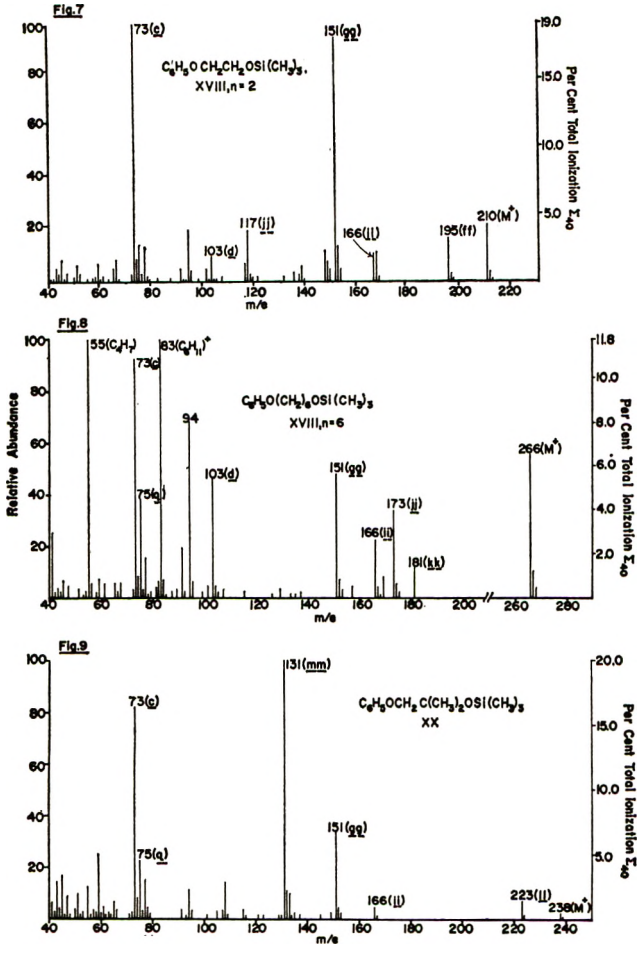


Figure 7.—Mass spectrum (AEI-MS-9) of 2-phenoxyethyl trimethylsilyl ether (XVIII, n = 2).

Figure 8.—Mass spectrum (AEI-MS-9) of 6-phenoxyhexyl trimethylsilyl ether (XVIII, n = 6).

Figure 9.—Mass spectrum (CEC-103C) of 2-phenoxy-1,1-dimethylethyl trimethylsilyl ether (XX).

rearrangement (*via* bb) (Scheme IV). When the ionization potential is reduced, the ion yield of the first rearrangement ion increases to a much greater extent (from 0.4% at 70 eV to 2.0% at 15 eV for k and from 0.9% at 70 eV to 3.0% at 15 eV for y) than does the yield of the second rearrangement fragment (from 4.1% 70 eV to 7.9% at 15 eV for g and from 6.4% at 70 eV to 7.0% at 15 eV for z). One may conclude, therefore, that in accord with expectation, a five-membered ring is favored over an eight-membered counterpart.

The base peak in the 70-eV spectra of both XVI and XVII (see Figures 5 and 6, respectively) is due to the trimethylsilyl cation (m/e 73, Σ_{40} = 37.6 and 30.4, respectively). Only one other peak exceeds 25% relative intensity in each spectrum; m/e 117 (plausibly represented as dd, Σ_{40} = 15.8) for XVI (Figure 5) and m/e 45 (the α-cleavage ion ee, Σ_{40} = 27.4) for XVII (Figure 6).

Despite the precautions taken in ensuring that the rearrangement ion g (m/e 147) in the mass spectra of the polymethylene glycol bistrimethylsilyl ethers (III, n = 2–8) was not due to impurity, it was decided to synthesize a series of compounds in which an analogous fragmentation scheme would produce a rearrangement ion which could not have a mass of 147. To this end, the spectra of the phenoxypolymethylene trimethylsilyl ethers (XVIII, n = 2–7) were recorded (see, for example, Figures 7 and 8). A rearrangement pattern analogous to that incurred in the polymethylene glycol bistrimethylsilyl ethers (III) involves cleavage of a methyl radical from the molecular ion to yield the M − CH_3 species (ff, n = 2–7) which can be depicted as a cyclic oxonium ion (ff', n = 2–7) (Scheme V). Loss of the neutral polymethylene oxide (n = 2–7) then gives the rearranged fragment gg (m/e 151, $C_8H_{11}OSi$), which is an important peak in the 70-eV spectra (see Table III) of all phenoxypolymethylene trimethylsilyl

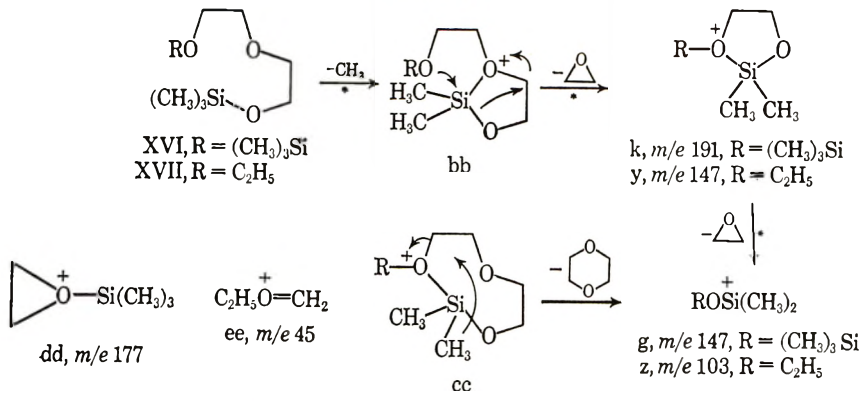
TABLE III

ABUNDANCE OF THE REARRANGEMENT PEAKS (gg) (m/e 151) AND ii (m/e 166) IN THE MASS SPECTRA OF THE PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ETHERS $C_6H_5O(CH_2)_nOSi(CH_3)_3$ (XVIII)

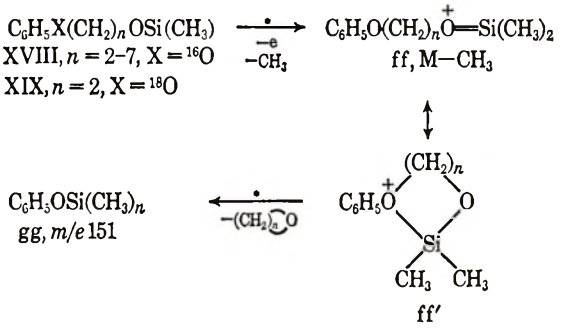
	m/e 151				m/e 166			
	70 eV		12 eV		70 eV		12 eV	
n	% Σ_{40}	% of base peak	% Σ_{40}	% of base peak	% Σ_{40}	% of base peak	% Σ_{40}	% of base peak
2	18.1	95	...	...	2.1	11	...	...
3	17.6	98	3.8	13	2.3	13	6.7	23
4	11.0	51	1.2	2	4.5	21	16.2	28
5	6.7	48	0.5	2	2.4	17	8.1	21
6	5.7	48	0.5	2	2.6	22	7.0	28
7	4.8	24	0.5	2	2.2	11	5.4	18

ethers (XVIII, n = 2–7). Like the rearrangement peak (m/e 147) in the mass spectra of III (see Table I), the m/e 151 peak decreases markedly with increasing chain length at 70 eV. As was mentioned previously, this tendency may reflect the difficulty in formation of a cyclic M − CH_3 species (ff') as chain length increases;

SCHEME IV



SCHEME V

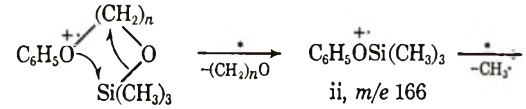


or if one assumes this process involves a 1,(n + 2) shift, the trend is to be expected.

One important labeling experiment was performed on the β-phenoxyethyl trimethylsilyl ether (XVIII, n = 2), namely, incorporation of ^{18}O into the phenoxy oxygen atom to confirm the fact that the silyl oxygen was eliminated in the rearrangement process (XVIII → gg). As expected the m/e 151 peak was shifted quantitatively to m/e 153 in the spectrum of XIX.

The molecular ion increases and the M − CH_3 ion decreases in abundance as the polymethylene chain is lengthened. It was felt that the daughter–parent relationship between the m/e 151 ion (gg) and the M − CH_3 species (ff) would be indicated by observation of a decrease in per cent total ionization of m/e 151 and a corresponding increase of M − CH_3 when the spectra are recorded at 12-eV ionizing energy (see Table III). In actual fact, at 12 eV the rearrangement species still decrease (Σ_{40} = 3.8 when n = 2 and 0.5 when n = 7) in abundance with increasing chain length but the expected large increase in the abundance of the M − CH_3 precursor was not observed. This anomaly suggested the possibility of other more favorable fragmentation modes for generation of the rearrangement peak and subsequent analysis of the metastable ions provided the clue to alternative formulations.

The observation in all spectra of a metastable peak at m/e 137.3 (calcd $151^2/166$ = 137.4) suggested the possible genesis of the mass 151 rearrangement ion by fission of a methyl radical from a species of mass 166 (ii, $C_9H_{14}OSi$); although relatively weak at 70 eV (see Table III), this peak appears in the spectra of all phenoxypolymethylene trimethylsilyl ethers (XVIII). This odd-electron species (ii) results from rearrangement of the molecular ion (hh) with elimination of the central portion of the molecule—a transition (hh → ii) which is also supported by the appropriate metastable peaks. It appears (see Table III) that at 70 eV this 1,(n + 2) shift reaches a peak when a 1,6 relationship is encountered, and surprisingly does not decrease significantly with increasing chain length (n = 5, 6, 7 are about equal). One must note, however, that at 70 eV the mass 166 species fragments further to form gg (m/e 151) and that the data with regard to amount of 1,(n + 2) shifts would be much more significant when obtained at 12 eV where further decomposition of ii would be minimized (eq 10). Indeed, at this ionizing



$C_6H_5OSi(CH_3)_2^+$ (10)
gg, m/e 151

energy, there is a definite decrease (see Table III) in the intensity of the m/e 166 peak with increasing chain length after reaching its maximum when n = 4.

Another important fragmentation to be discussed in the case of the phenoxypolymethylene trimethylsilyl ethers (XVIII, n = 2–7) involves a series of peaks (jj) for which there is no analogy in the polymethylene glycol bistrimethylsilyl (III) and the methoxypolymethylene trimethylsilyl (XI) ether series. Fission of a phenoxy radical from the molecular ion (hh) generates a fragment ion which can be formulated as a cyclic oxonium ion (jj), but quantitative statements about preferred ring size should only be based on low (12 eV) voltage spectra (see Table IV), as there is in every case (n =

TABLE IV

ABUNDANCE OF PEAK jj IN THE MASS SPECTRA OF THE PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ETHERS $C_6H_5O(CH_2)_nOSi(CH_3)_3$ (XVIII)

	70 eV			12 eV	
n	m/e	% Σ_{40}	% of base peak	% Σ_{40}	% of base peak
2	117	3.8	20	...	...
3	131	5.0	28	12.5	43
4	145	21.5	100	57.8	100
5	159	10.6	76	38.6	100
6	173	4.0	34	14.8	59
7	187	0.6	3	2.4	8

2–7), a large metastable peak corresponding to further decomposition of jj to yield the trimethylsilyl cation c (m/e 73) (eq 11). As is illustrated by the 12-eV spectra

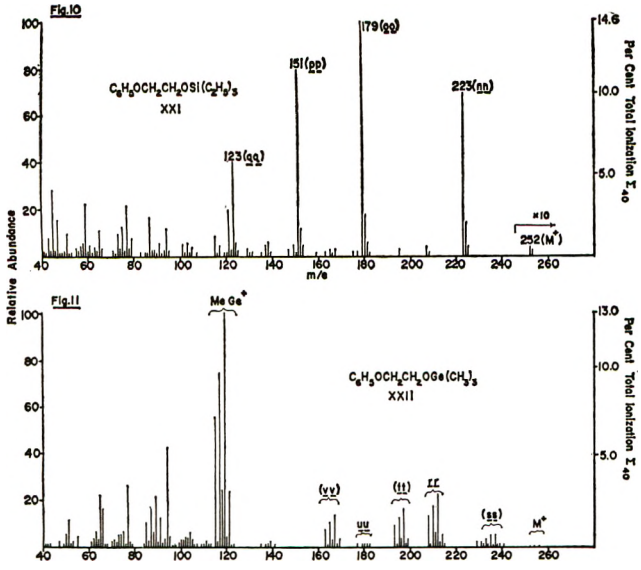
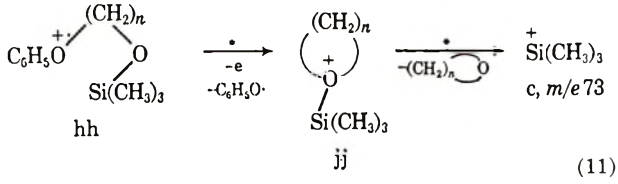


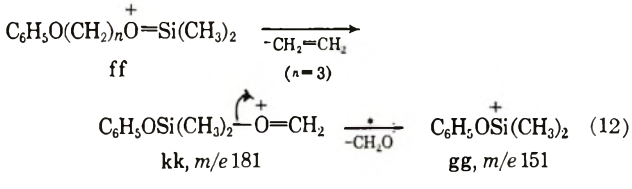
Figure 10.—Mass spectrum (CEC-103C) of 2-phenoxyethyl triethylsilyl ether (XXI).
Figure 11.—Mass spectrum (CEC-103C) of 2-phenoxyethyl trimethylgermanium oxide (XXII).

(Table IV), ring size appears to be particularly important in this fragmentation. In the case where jj exists as a five- and six-membered ring (jj, $n = 4$, and jj, $n = 5$, respectively) it produces the base peak; however, in the less favorable eight-membered structure ($n = 7$, m/e 181) the peak is insignificant (8% relative intensity).



(11)

Rearrangement of the M − CH_3 fragment (ff) to yield kk (m/e 181) and subsequent loss of formaldehyde to yield m/e 151 (gg) (eq 12) in a manner analogous to the fragmentation sequence (i → r → g) in the spectra of III (n = 3–8) occurs to a minor extent in XVIII when n = 3–7; this peak decreases with increasing chain length (Σ_{40} = 3.8 when n = 3 and 1.2 when n = 7). In all cases, except when n = 7, a metastable peak is observed at m/e 126.0 (calcd $151^2/181$ = 126.0).

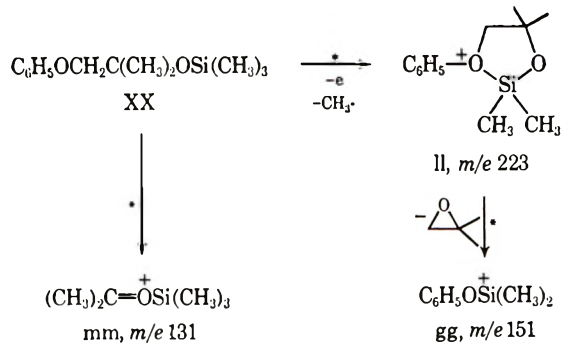


(12)

Another fragment found in the spectra of XVIII is the intense peak at m/e 73 (c, 10–20% Σ_{40}); metastable peaks indicate that jj and the α-cleavage ion d (m/e 103, Σ_{40} = 4.0 ± 1.5) are progenitors of this ion. This supports the conclusions made in a previous paper[7] disclaiming the postulated[8] formation of c (m/e 73) by direct fission of the molecular ion. Also, at 70 eV, intense hydrocarbon peaks appear at m/e 55 (C_4H_7) when n = 4, 6, and 7; at m/e 69 (C_5H_9) when n = 5; and at m/e 83 (C_6H_{11}) when n = 6. Finally, as the methylene chain length increases, there is encountered an intense peak at m/e 94 (Σ_{40} = 8–9 when $n > 4$). High-resolution mass measurements indicate an elemental composition of C_6H_6O thus suggesting that m/e 94 is generated by a hydrogen transfer process to yield a phenol-like odd-electron species.

As in the case of the benzyl trimethylsilyl ethers,[7] the presence of a branched chain causes a pronounced decrease in the amount of rearrangement species formed following electron bombardment, although the effect is not so great as in the benzyl series. In the mass spectrum (Figure 9) of 1,1-dimethyl-2-phenoxyethyl trimethylsilyl ether (XX), the M − CH_3 peak (ll, m/e 223) is weak (Σ_{40} = 1.4), the trimethylsilyl cation (c, m/e 73) is abundant (Σ_{40} = 1.4), and the rearrangement ion (gg, m/e 151) carries 6.8% of the total ion current. The base peak, m/e 131 (Σ_{40} = 16.4), is due to the α-cleavage ion (mm), which is greatly favored because of the high degree of branching at the fission site (Scheme IV).

SCHEME VI

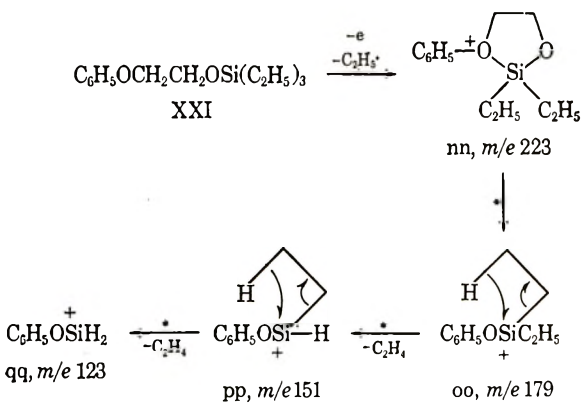


It was decided to record the spectrum of 2-phenoxyethyl triethylsilyl ether (XXI) in order to ascertain whether replacing the silylmethyl groups with the slightly bulkier silylethyl groups would inhibit the amount of skeletal rearrangement. The base peak (m/e 179) in this mass spectrum (Figure 10) is indeed associated with the rearrangement ion oo (m/e 179, Σ_{40} = 14.6) resulting from loss of ethylene oxide from the M − C_2H_5 precursor nn (m/e 223, Σ_{40} = 10.0). The two other prominent peaks (m/e 151 and m/e 123) in this spectrum (Figure 10) are generated by the hydrogen rearrangement processes which have been found[7] to be characteristic of all triethylsilyl ethers. Expulsion of two successive ethylene molecules from the rearrangement ion (oo) yields pp (m/e 151, Σ_{40} = 11.5) and qq (m/e 123, Σ_{40} = 5.8). In this particular instance, the triethylsilyl moiety certainly has no retarding effect upon the rearrangement process, as the ion oo (m/e 179) and two of its daughter ions (pp and qq) contribute 41.9% of the total ion current (Scheme VII).

It was also decided to ascertain what effect replacing the silicon atom with germanium would have upon the rearrangement process. The rearrangement persisted in the case of the trimethylgermanium oxide (XXII), whose spectrum (Figure 11) shows a series of rearrangement ions followed by successive losses of methyl radicals. No metastable ion was observed and it is not known whether tt (Σ_{40} = 5.0, total isotopic species[18]) is formed by an initial loss of ethylene oxide, through rr

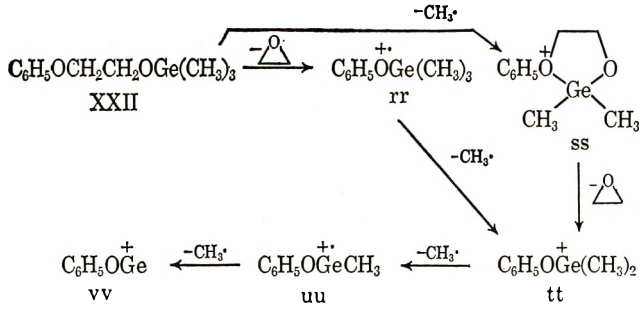
(18) The stable isotopes of germanium are Ge^{70} (20.5%), Ge^{72} (27.4%), Ge^{73} (7.7%), Ge^{74} (36.6% and Ge^{76} (7.8%).

SCHEME VII



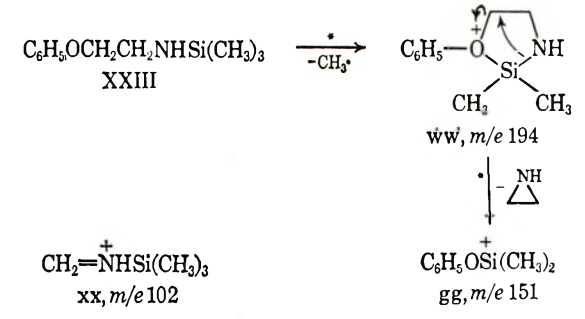
(Σ_{40} = 8.0, total isotopic species), from the molecular ion, or through a cyclic M − CH_3 intemediate ss (Σ_{40} <0.1, total isotopic species). Including the ions uu (Σ_{40} = 0.5, total isotopic species) and vv (Σ_{40} = 4.0, total isotopic species) (Scheme VIII), the total rearrangement yield is 17.5% of the total ion current. The molecular ion is extremely weak and the trimethylgermanium cation [$(CH_3)_3Ge^+$] accounts for the base peak (Σ_{40} = 36.0, total isotopic species).

SCHEME VIII



Substitution of a nitrogen atom for the oxygen atom in the case of the benzyl trimethylsilyl ethers[7] caused only a small decrease in the amount of rearrangement species. Replacement of the trimethylsilyloxy group of 2-phenoxyethyl trimethylsilyl ether (XVIII, n = 2) (Scheme IX) by a trimethylsilylamino group results

SCHEME IX



in a more pronounced decrease (Table V) in the amount of rearrangement ion (gg), but the latter still remains a prominent feature (Σ_{40} = 6.4) in the spectrum of XXIII. Two other peaks exceed the latter in intensity, namely, the trimethylsilyl cation c (m/e 73, Σ_{40} = 15.2) and the α-cleavage ion xx (m/e 102, Σ_{40} = 29.3). The molecular (Σ_{40} = 0.3) and M − CH_3 (ww, Σ_{40} = 0.9) ions are both weak.

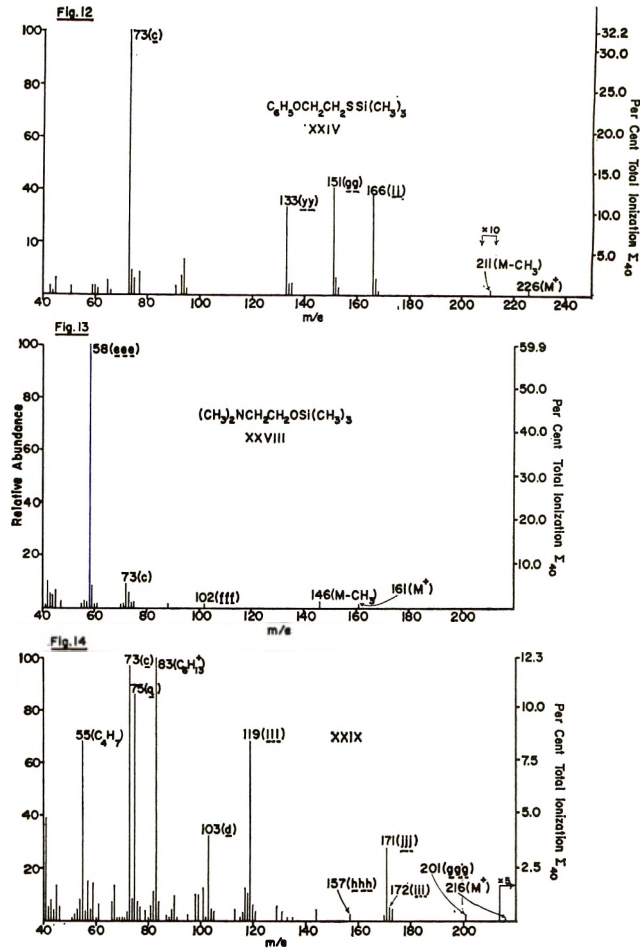


Figure 12.—Mass spectrum (AEI-MS-9) of 2-phenoxyethyl trimethylsilyl sulfide (XXIV).

Figure 13.—Mass spectrum (CEC-103C) of 2-N,N-dimethyl aminoethyl trimethylsilyl ether (XXVIII).

Figure 14.—Mass spectrum (AEI-MS-9) of 2-(cyclohexyloxy)-ethyl trimethylsilyl ether [XXIX, $C_6H_{11}OCH_2CH_2OSi(CH_3)_3$].

TABLE V

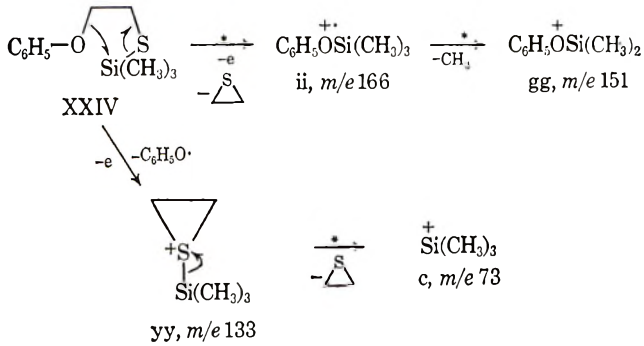
ABUNDANCE OF REARRANGEMENT ION IN THE MASS SPECTRA (70 eV) OF $C_6H_5XCH_2CH_2YSi(CH_3)_3$

Compound	X	Y	m/e	% Σ_{40}	% of base peak
$C_6H_5OCH_2CH_2OSi(CH_3)_3$ (XVIII, n = 2)	O	O	151	18.1	95
$C_6H_5OCH_2CH_2NHSi(CH_3)_3$ (XXIII)	O	N	151	6.4	22
$C_6H_5OCH_2CH_2SSi(CH_3)_3$ (XXIV)	O	S	151	13.2	41
$C_6H_5NHCH_2CH_2OSi(CH_3)_3$ (XXV)	N	O	150	1.6	3
$C_6H_5SCH_2CH_2OSi(CH_3)_3$ (XXVI)	S	O	167	1.6	7
$C_6H_5NHCH_2CH_2NHSi(CH_3)_3$ (XXVII)	N	N	150	0	0

Unlike the benzyl trimethylsilyl sulfides[7] which exhibit very weak rearrangement peaks upon electron bombardment 2-phenoxyethyl trimethylsilyl sulfide (XXIV) shows (see Figure 12 and Table V) a very prominent rearrangement peak gg (m/e 151, Σ_{40} = 13.2).[19] There is no metastable evidence for loss of ethylene sulfide from an M − CH_3 (m/e 211, Σ_{40} = 0.05) precursor; however, a large metastable peak is found at m/e 137.4 (calcd $151^2/166$ = 137.4) corresponding to expulsion of a methyl radical from the m/e 166 fragment (ii, Σ_{40} = 12.2) (Scheme X). As in the

(19) The parent thiol exhibited a slight thermal instability; therefore, its trimethylsilyl derivatives (XXIV) was adsorbed on activated charcoal and introduced using the direct probe inlet into the TO-4 ion source (heated only by the filament current to *ca.* 70°) of the Atlas CH-4 mass spectrometer. The recorded spectrum was practically identical with Figure 12 indicating that all peaks resulted from electron bombardment and not thermally induced reactions.

SCHEME X



case of the phenoxypolymethylene trimethylsilyl ethers (XVIII), there appears to be a significant amount of rearrangement of the molecular ion with expulsion of ethylene sulfide to yield *m/e* 166 (ii) which subsequently decomposes to *m/e* 151 (gg). Thus, as in the case of the benzyl trimethylsilyl sulfides[7] there does *not* appear to be a large amount of rearrangement through an M − CH_3 intermediate to give the *m/e* 151 ion (gg). The fact that the rearrangement peak originates almost entirely by rearrangement of the molecular ion is very obvious when the spectrum is recorded at 12 eV. Here, one finds neither an *m/e* 151 nor an M − CH_3 peak, whereas *m/e* 166 becomes the most intense one (Σ_{40} = 41.2).

The base peak in the spectrum (Figure 12) of 2-phenoxyethyl trimethylsilyl sulfide (XXIV) is due to the trimethylsilyl cation c (*m/e* 73, Σ_{40} = 32.2). Both low voltage measurements and a metastable peak show that c arises by loss of ethylene sulfide from an *m/e* 133 precursor (yy, Σ_{40} = 10.6), the latter being the only other important peak remaining in the spectrum. High-resolution measurements show this fragment of mass 133 to have an elemental composition of $C_5H_{13}SSi$, thus suggesting a fragmentation sequence (XXIV → yy → c) analogous to that found in the case of the phenoxypolymethylene trimethylsilyl ethers (XVIII → jj → c).

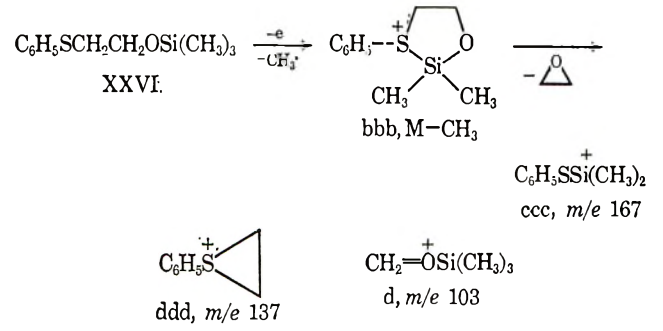
In order to assess further the effect of replacing oxygen with nitrogen and sulfur, the spectra of 2-phenylamino- (XXV) and 2-thiophenoxyethyl trimethylsilyl ether (XXVI) were recorded. Interestingly, unlike 2-phenoxyethyl trimethylsilyl amine (XXIII), a very small amount of rearrangement ion zz (*m/e* 150, Σ_{40} = 1.6) is found (see Table V) in the spectrum of XXV, which is completely dominated by the α-cleavage ion (aaa, *m/e* 106, Σ_{40} = 51.4). The molecular ion (Σ_{40} = 6.5), the M − CH_3 peak (Σ_{40} = 3.2), and the trimethylsilyl cation (Σ_{40} = 4.9) are all quite weak in this spectrum.

$C_6H_5NHCH_2CH_2OSi(CH_3)_3$ (XXV) → $C_6H_5\overset{+}{N}H{=}CH_2$, aaa, *m/e* 106

$C_6H_5NH\overset{+}{S}i(CH_3)_2$, zz, *m/e* 150

Substitution of sulfur (XXVI) for oxygen also causes a dramatic decrease in the amount of rearrangement species (see Table V); this result parallels more closely the behavior of the benzyl trimethylsilyl sulfides (Scheme XI).[7] The rearrangement ion ccc (*m/e* 167) contributes only 1.6% of the ion current. The

SCHEME XI



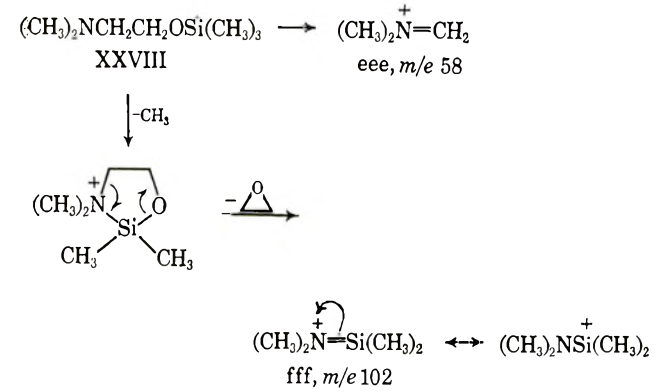
base peak in the spectrum is at *m/e* 73 (c, Σ_{40} = 22.8) and the remaining prominent species are the molecular ion (Σ_{40} = 9.1), M − CH_3 (bbb, Σ_{40} = 11.4), ddd (*m/e* 137, Σ_{40} = 7.5), and the α-cleavage fragment d (Σ_{40} = 9.3).

As might be expected (see Table V), the spectrum of N′-phenyl-N-(trimethylsilyl)ethylenediamine (XXVII) contains no rearrangement peak (zz, *m/e* 150). As in the case of XXV, the α-cleavage fragment aaa (*m/e* 106, Σ_{40} = 23.3) provides the base peak; the other α-cleavage ion (xx, *m/e* 102) is the second most intense peak (Σ_{40} = 17.5). Other abundant ions include the trimethylsilyl cation (c, Σ_{40} = 11.2) and the phenyl cation (*m/e* 77, Σ_{40} = 6.5).

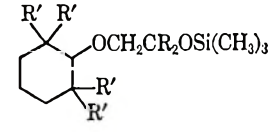
$C_6H_5NHCH_2CH_2NHSi(CH_3)_3$
XXVII

Finally, it may be noted that even in the spectrum (Figure 13) of the dimethylamino compound XXVIII, in which the α-cleavage ion (eee, *m/e* 58) carries 60% of the total ion current, the rearrangement ion (fff) is still observable (*m/e* 102, Σ_{40} = 0.6) (Scheme XII).

SCHEME XII



The last few spectra to be discussed result from an attempt to bridge the gap in structure between 2-ethoxyethyl (XIV) and 2-phenoxyethyl (XVIII, *n* = 2) trimethylsilyl ether. Consequently, the mass spectrum of 2-(cyclohexyloxy)ethyl trimethylsilyl ether (XXIX) was recovered. It is interesting to note that, although this spectrum (Figure 14) exhibits many peaks

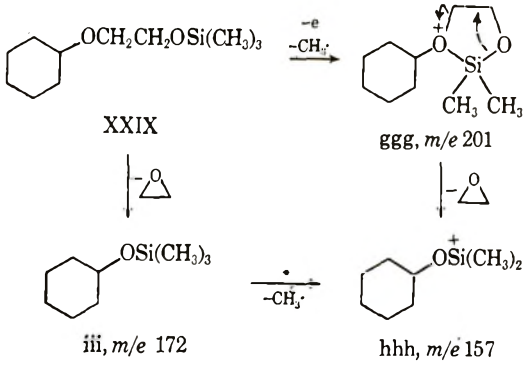


XXIX, R, R′ = H
XXX, R = D; R′ = H
XXXI, R = H; R′ = D

derived by pathways analogous to those found in the previous cases, a few of the most abundant peaks were found to be unique.

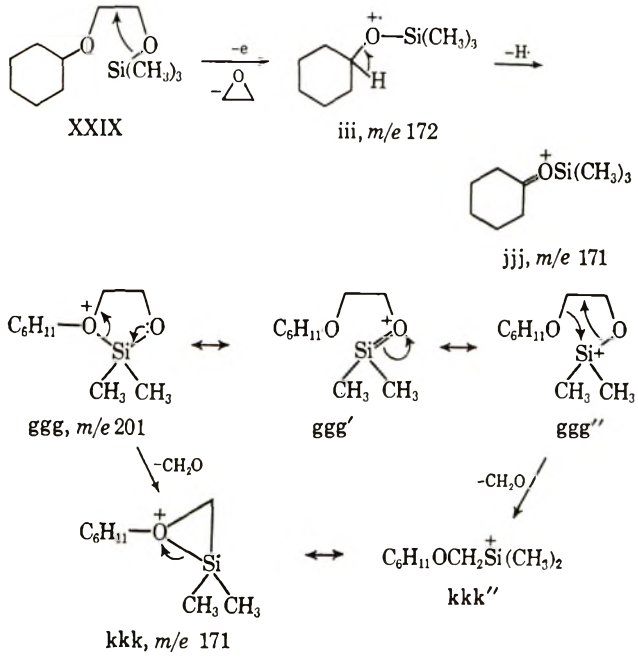
Typical of many trimethylsilyl ethers, the molecular ion (m/e 216) is weak (Σ_{40} = 0.1), the M − CH_3 peak ggg (m/e 201) is surprisingly weak (Σ_{40} = 0.2), the trimethylsilyl cation c (m/e 73) is very strong (Σ_{40} = 11.9), and the α-cleavage ion d (m/e 103, Σ_{40} = 3.9) is relatively abundant. Hydrocarbon peaks are also very intense with the cyclohexyl ion (m/e 83) accounting for the base peak (Σ_{40} = 12.3) and m/e 55 (C_4H_7) contributing 8.4% of the total ion current. It was rather surprising to find that loss of propylene oxide from the rearranged M − CH_3 species ggg (m/e 201) in the usual manner to yield a rearrangement ion hhh (m/e 157, Σ_{40} = 0.2) hardly occurs. In fact, the minute metastable peak at m/e 143.3 (calcd $157^2/172$ = 143.3) suggests that what little hhh is forming probably has the m/e 172 species (iii, Σ_{40} = 0.6) as its progenitor (Scheme XIII).

SCHEME XIII

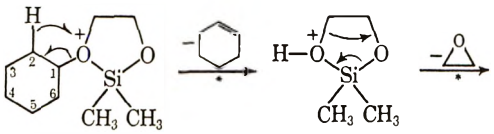


The appearance of a moderately abundant peak at m/e 171 (Σ_{40} = 3.3), which becomes one of the primary peaks (Σ_{40} = 11.6) when the spectrum is recorded at 12 eV, suggested a fragmentation mode which had not been encountered previously. High-resolution mass measurements showed this moiety to have the elemental composition $C_9H_{19}OSi$, and it was felt that one possible mode of genesis for this fragment might involve a two-step process (XXIX → iii → jjj). No metastable peaks could be located, however, either for the initial loss of the elements of ethylene oxide from the molecular ion or for subsequent expulsion of a hydrogen atom from the species of mass 172; furthermore, the m/e 171 peak increases in intensity when the spectrum is recorded at low voltage, making the loss of a hydrogen atom from the m/e 172 species an unlikely occurrence. An alternative formulation for the genesis of the mass 171 ion involves loss of formaldehyde from an M − CH_3 precursor (ggg, m/e 201). For descriptive purposes this process can be visualized as occurring either from the open-chain species ggg″ to yield kkk″ or from the alternate resonance form ggg to yield kkk (Scheme XIV). Again, there is no metastable evidence for this transition. Two labeling experiments were performed which support the occurrence of either of these fragmentation schemes. As expected, the spectrum of the α-labeled analog XXX reveals no shift of m/e 171, whereas the spectrum of the cyclohexyl-labeled analog XXXI indicates a shift in mass to m/e 175.

SCHEME XIV



The final fragmentation to be discussed involves the intense (Σ_{40} = 8.4) m/e 119 peak which completely dominates (Σ_{40} = 22.3) the 12-eV spectrum. High-resolution mass measurements indicate an elemental composition of $C_4H_{11}O_2Si$ for this species and the labeling experiments (see Table VI) indicate the possible formation of a cyclic species as well as occurrence of a hydrogen transfer process. A small metastable peak at m/e 70.5 (calcd $119^2/201$ = 70.4) suggested that the m/e 119 ion is generated by loss of cyclohexene from the M − CH_3 ion (ggg → lll, eq 13). This process obeys the



$$(CH_3)_2Si{=}\overset{+}{O}{-}H \quad (13)$$

q, m/e 75

labeling results (Table VI) in that the ethylene chain is retained (see XXX) and the cyclohexyl group is lost (see XXXI). Although the hydrogen transfer process is indicated as occurring from the C-2 position of the cyclohexyl moiety, only 53% originates from the C-2 and C-6 positions and the remainder must come from the unlabeled portion of the cyclohexyl ring.

TABLE VI

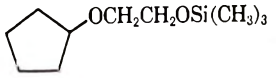
SHIFTS OF THE m/e 171, m/e 119, AND m/e 75 PEAKS IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED 2-(CYCLOHEXYLOXY)ETHYL TRIMETHYLSILYL ETHERS (XXX AND XXXI)

Compound	Isotopic composition, %	m/e 171[a]	m/e 119[a]	m/e 75[a]
XXX	100 d_2	171	121	75
XXXI	92.3 d_4, 7.7 d_3	175	119 (42%)	75 (59%)
			120 (53%)	76 (41%)

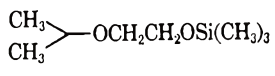
[a] Corrected for natural isotope abundance and calculated deuterium isotope composition.

The fact that the mass 119 ion becomes the most abundant one (Σ_{40} = 22.3) at 12 eV suggested the possibility of its further fragmentation at 70 eV. Indeed a metastable ion at m/e 47.2 (calcd $75^2/119$ = 47.3) indicates that lll decomposes to the dimethylsilanol ion (q) (eq 13) of mass 75 (Σ_{44} = 10.6). This process is also supported by deuterium-labeling evidence (see Table VI).

The mass spectra of the cyclopentyloxy (XXXII) and isopropyl (XXXIII) analogs were also recorded. Com-



XXXII



XXXIII

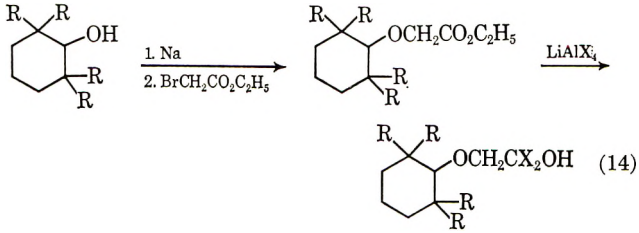
pound XXXII exhibited a spectrum exactly analogous to that of XXIX, and, although there are slight intensity variations, XXXIII behaves in a sufficiently similar fashion so as to not warrant any further discussion.

Synthesis of Labeled Compounds

The discussion of the synthesis of labeled compounds needs to include only a description of the preparation of the parent alcohols, as in practically all cases the common silylating agent, hexamethyldisilazane,[6,7,20] was utilized to convert the alcohols, amines, and mercaptans into their trimethylsilyl ether derivatives. Occasionally (XXIV and XXVII) it was necessary to employ the stronger silylating agent bis-N,O-(trimethylsilyl)acetamide.[21]

Synthesis of 1,1-d_2-2-methoxyethanol was accomplished by reducing 2-methoxyacetic acid with lithium aluminum deuteride to yield the product in high isotopic purity. Preparation of 2-d_5-ethoxyethanol involved conversion of perdeuterioethanol into d_5-ethyl bromide in a sealed-tube reaction utilizing hydrobromic acid and concentrated sulfuric acid. Subsequent reaction of the bromide with an equivalent amount of sodium metal and a threefold excess of ethylene glycol yielded the desired labeled analog.

It was necessary to synthesize two deuterium labeled analogs (XXX and XXXI) in the 2-(cyclohexyloxy)-ethyl trimethylsilyl ether series. The first compound, 1,1-d_2-2-(cyclohexyloxy)ethanol was prepared (eq 14)



(14)

by reaction of the sodium salt of cyclohexanol with 2-bromoethyl acetate to yield 2-(cyclohexyloxy)ethyl acetate; subsequent reduction with lithium aluminum deuteride (X = D) yielded the desired compound (R = H, X = D). Utilizing this same scheme but replacing lithium aluminum deuteride (X = D) with lithium aluminum hydride (X = H) and cyclohexanol (R = H) with 2,2,6,6-d_4-cyclohexanol (R = D) yielded the second analog 2′,2′,6′,6′-d_4-2-(cyclohexyloxy)ethanol (eq 12, R = D, X = H).

The final labeled compound to be discussed is the oxygen-18 analog of 2-phenoxyethanol (XXXIV). Reaction of the sodium salt of ^{18}O-enriched phenol with chlorohydrin yielded the desired product.

Experimental Section[22]

Trimethylsilyl Ethers and Amines.[7,8,20]—A mixture of 1.0 mmol of the appropriate alcohol or amine and 0.5 mmol of hexamethyldisilazane[23] (1.0 mmol in the case of bistrimethylsilyl ethers) was heated under reflux with 1 drop of trimethylchlorosilane[23] until evolution of ammonia ceased (1–4 hr for primary and secondary alcohols, 3–5 hr for primary diols, and 12–20 hr for tertiary alcohols and for the amines). The trimethylsilyl derivatives were isolated from the reaction mixture by preparative gas–liquid partition chromatography; Table VII indicates

TABLE VII

RETENTION TIMES OF TRIMETHYLSILYL DERIVATIVES

Compound	Column temperature, °C	Retention time, min.
$(CH_3)_3SiOCH_2CH_2OSi(CH_3)_3$ (III, n = 2)	125	1.3
$(CH_3)_3SiO(CH_2)_3OSi(CH_3)_3$ (III, n = 3)	125	1.8
$(CH_3)_3SiO(CH_2)_4OSi(CH_3)_3$ (III, n = 4)	145	1.9
$(CH_3)_3SiO(CH_2)_5OSi(CH_3)_3$ (III, n = 5)	145	3.0
$(CH_3)_3SiO(CH_2)_6OSi(CH_3)_3$ (III, n = 6)	160	1.8
$(CH_3)_3SiO(CH_2)_7OSi(CH_3)_3$ (III, n = 7)	155	2.7
$(CH_3)_3SiO(CH_2)_8OSi(CH_3)_3$ (III, n = 8)	155	4.2
$(C_2H_5)_3SiO(CH_2)_2OSi(C_2H_5)_3$ (VIII)	140	11.1
$CH_3OCH_2CH_2OSi(CH_3)_3$ (XI, n = 2)	100	1.0
$CH_3O(CH_2)_4OSi(CH_3)_3$ (XI, n = 4)	110	2.5
$CH_3O(CH_2)_5OSi(CH_3)_3$ (XI, n = 5)	110	3.6
$C_2H_5OCH_2CH_2OSi(CH_3)_3$ (XIV)	100	1.5
$(CH_3)_3SiOCH_2CH_2OCH_2CH_2OSi(CH_3)_3$ (XVI)	155	1.4
$C_2H_5OCH_2CH_2OCH_2CH_2OSi(CH_3)_3$ (XVII)	135	2.0
$C_6H_5O(CH_2)_2OSi(CH_3)_3$ (XVIII, n = 2)	176	11.6
$C_6H_5O(CH_2)_3OSi(CH_3)_3$ (XVIII, n = 3)	200	3.7
$C_6H_5O(CH_2)_4OSi(CH_3)_3$ (XVIII, n = 4)	190	2.4
$C_6H_5O(CH_2)_5OSi(CH_3)_3$ (XVIII, n = 5)[a]	160	4.8
$C_6H_5O(CH_2)_6OSi(CH_3)_3$ (XVIII, n = 6)[a]	165	4.9
$C_6H_5O(CH_2)_7OSi(CH_3)_3$ (XVIII, n = 7)[a]	173	5.3
$C_6H_5OCH_2C(CH_3)_2OSi(CH_3)_3$ (XX)	140	3.5
$C_6H_5OCH_2CH_2OSi(C_2H_5)_3$ (XXI)	180	3.7
$C_6H_5OCH_2CH_2OGe(CH_3)_3$ (XXII)	155	1.8
$C_6H_5OCH_2CH_2NHSi(CH_3)_3$ (XXIII)	145	3.7
$C_6H_5OCH_2CH_2SSi(CH_3)_3$ (XXIV)	190	5.1
$C_6H_5NHCH_2CH_2OSi(CH_3)_3$ (XXV)	180	3.0
$C_6H_5SCH_2CH_2OSi(CH_3)_3$ (XXVI)	212	1.6
$C_6H_5NHCH_2CH_2NHSi(CH_3)_3$ (XXVII)	165	5.1
$(CH_3)_2NCH_2CH_2OSi(CH_3)_3$ (XXVIII)	95	1.5
$C_6H_{11}OCH_2CH_2OSi(CH_3)_3$ (XXIX)	110	14.0
$C_5H_{11}OCH_2CH_2OSi(CH_3)_3$ (XXXII)	85	12.0
$C_3H_7OCH_2CH_2OSi(CH_3)_3$ (XXXIII)	50	7.1

[a] Separation was done on 1% SE-30 on Chromosorb W with a He flow rate of 100 cc/min.

(20) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

(21) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

(22) Melting points (uncorrected) were determined on the Kofler block and infrared absorption spectra were measured with a Perkin-Elmer Model 137 Infracord spectrophotometer. The 70-eV mass spectra recorded on the CEC Model 21-103C instrument were obtained by Mr. N. S. Garcia using a 200° heated, all-glass inlet system. In addition, the spectra of some of the compounds were measured by Dr. A. M. Duffield on an Atlas CH-4 mass spectrometer with an ion-source temperature of 190°. High-resolution measurements and also low-resolution spectra of many of the compounds were carried out by Mr. R. G. Ross using an A.E.I. MS-9 instrument equipped with a 200° heated inlet system. All of the trimethylsilyl derivatives were prepared on a small scale and purified by gas chromatography on a 6 ft × 0.75 in. stainless-steel column packed with 10% GE SF-96 on Chromosorb W with a He flow rate of 150 cc/min.

(23) Hexamethyldisilazane, trimethylchlorosilane, triethylchlorosilane, and bis(trimethylsilyl)acetamide were purchased from Pierce Chemical Co., Rockford, Ill.

the retention time and column temperature for each derivative. In most cases the yields of the colorless liquids were essentially quantitative. The accurate molecular weight of each compound was determined by mass spectrometry in order to assure identity of the product.

2-Phenoxyethyl Trimethylsilyl Sulfide (XXIV).—A mixture of 3 ml of acetonitrile, 308 mg of 2-phenoxyethyl mercaptan, and 450 mg of bis(trimethylsilyl)acetamide[23] was heated under reflux for 20 hr and the trimethylsilyl derivative was isolated by preparative gas–liquid partition chromatography (see Table VII). The infrared spectrum indicated typical trimethylsilyl absorptions: λ_{max} 8.0, 11.8, and 13.3 μ (Me_3Si).

Anal. Calcd for $C_{11}H_{18}OSSi$: mol wt, 226. Found: mol wt (mass spectrometry), 226.

N'-Phenyl-N-(trimethylsilyl)ethylenediamine (XXVII).—Utilizing 272 mg of N-phenylethylenediamine (Aldrich Chemical Co.) a procedure identical with that employed in the case of 2-phenoxyethyl trimethylsilyl sulfide (XXIV) yielded the desired trimethylsilyl derivative (XXVII).

Anal. Calcd for $C_{11}H_{20}N_2Si$: mol wt, 208. Found: mol wt (mass spectrometry), 208.

Ethylene Glycol Bistriethylsilyl Ether (VIII).—To 124 mg of ethylene glycol in 10 ml of dry benzene was added 100 mg of sodium metal. The mixture was heated gently under reflux for 24 hr, cooled, and a solution of 610 mg of triethylchlorosilane[23] in 5 ml of dry benzene was added. The mixture was again gently heated under reflux for 24 hr, cooled, and filtered, and the benzene was removed by means of a rotary evaporator. Isolation by means of gas–liquid partition chromatography (see Table VII) gave VIII in 73% yield. The infrared spectrum exhibited characteristic absorptions at λ_{max} 8.1, 11.8, 13.4, and 9.2 μ (SiO).

Anal. Calcd for $C_{14}H_{34}O_2Si_2$: mol wt, 290. Found: mol wt (mass spectrometry), 290.

2-Phenoxyethyl Triethylsilyl Ether (XXI).—Employing 273 mg of 2-phenoxyethanol, 50 mg of sodium metal, and 300 mg of triethylchlorosilane, a procedure identical with that utilized in the synthesis of VIII yielded 2-phenoxyethyl triethylsilyl ether (XXI).

Anal. Calcd for $C_{14}H_{24}O_2Si$: mol wt, 252. Found: mol wt (mass spectrometry), 252.

2-Phenoxyethyltrimethylgermanium Oxide (XXII).—A mixture of 138 mg of 2-phenoxyethanol and 25 mg of sodium metal in 5 ml of anhydrous benzene was stirred under reflux for 24 hr and cooled. Slowly, 200 mg of trimethylgermanium bromide (prepared by the method of Satgé[24]) in 5 ml of dry benzene was added and the mixture was heated under reflux for an additional 20 hr. After cooling, filtering, and removing the benzene on a rotary evaporator, the product was isolated by preparative gas–liquid partition chromatography (see Table VII) in approximately 50% yield.

Anal. Calcd for $C_{11}H_{18}O_2Ge$: mol wt, 256.[25] Found: mol wt (mass spectrometry), 256.

1,1-d_2-2-Methoxyethanol.—To a well-stirred suspension of 400 mg of lithium aluminum deuteride in 20 ml of anhydrous ether at 0° was added dropwise 450 mg of 2-methoxyacetic acid (Eastman Organic Chemicals, Rochester, N. Y.) in 15 ml of anhydrous ether. After complete addition the mixture was heated under reflux for 3 hr and the excess lithium aluminum deuteride decomposed by the dropwise addition (at 10°) of a saturated sodium sulfate solution. The mixture was filtered, dried over anhydrous magnesium sulfate, and again filtered, and the ether was stripped on a rotary evaporator yielding 350 mg of 1,1-d_2-2-methoxyethanol whose mass spectrum showed the isotopic composition to be 98% d_2 and 2% d_1.

d_5-2-Ethoxyethanol.—A mixture of 1 ml of perdeuterioethanol (d_6),[26] 3 ml of 48% hydrobromic acid, and 1 ml of concentrated sulfuric acid was placed in a sealed tube and heated on a steam bath for 20 hr. The tube was cooled in an ice bath and opened; the mixture was washed twice with water. Pure d_5-ethyl bromide (1.5 g) was distilled at reduced (aspirator) pressure from the water through Indicating Drierite into a vessel cooled to −40° using a short-path distillation apparatus.

In a dry nitrogen atmosphere was placed 2.43 g of ethylene glycol and 305 mg of finely divided sodium metal; the mixture was stirred and gently heated. After the reaction of the sodium and ethylene glycol was completed, the labeled ethyl bromide was slowly added, and, following the initial vigorous reaction, the mixture was heated under reflux for 2 hr, cooled, filtered, and distilled at 90° (200 mm) yielding 940 mg of d_5-2-ethoxyethanol whose mass spectrum revealed the following isotopic composition: 98% d_5 and 2% d_0.

3-Phenoxypropan-1-ol.—Reduction of 1 g of 3-phenoxypropionic acid with 1 g of lithium aluminum hydride utilizing the same procedure used in the reduction of 2-methoxyacetic acid yielded 750 mg of a colorless liquid after purification by preparative gas–liquid partition chromatography (10% GE SF-96 on Chromosorb W with a He flow rate of 100 cc/min at 200°). The infrared spectrum showed absorptions characteristic of 3-phenoxypropan-1-ol at λ_{max} 3.0, 8.0, 9.4, 13.2, and 14.4 μ.

Anal.[27] Calcd for $C_{12}H_{20}O_2Si$: mol wt, 224. Found: mol wt (mass spectrometry), 224.

4-Phenoxybutan-1-ol.—Reduction of 5.4 g of 4-phenoxybutyric acid with 1.7 g of lithium aluminum hydride was accomplished by the procedures discussed previously except that the mixture was heated under reflux for 12 instead of 2 hr. The product (4.6 g) exhibited infrared absorptions at λ_{max} 3.05, 8.05, 9.5, 13.2, and 14.4 μ (lit.[28] 3.15, 8.1, 9.6, 13.2, and 14.4 μ).

Anal.[27] Calcd for $C_{13}H_{22}O_2Si$: mol wt, 238. Found: mol wt (mass spectrometry), 238.

5-Phenoxypentan-1-ol.—A mixture of 3 g of 4-phenoxybutan-1-ol (see above), 3 ml of concentrated sulfuric acid, and 9 ml of 48% hydrobromic acid was heated under reflux for 24 hr. After cooling and washing twice with water, the mixture was extracted three times with ether and the ethereal extracts were dried over anhydrous magnesium sulfate. The solution was filtered, the ether removed on a rotary evaporator, and 2.8 g of 4-phenoxybutyl bromide collected by distillation at 133–135° and 10 mm (lit.[29] 151–155° and 16 mm). Utilizing the procedure and apparatus described in previous work,[7] 2.0 g of 4-phenoxybutyl bromide was converted into its Grignard reagent with 404 mg of magnesium. Subsequent carbonation with anhydrous carbon dioxide[7] yielded a solid material whose infrared spectrum was characteristic of 5-phenoxyvaleric acid: λ_{max}^{Nujol} 3.3 (broad), 5.8, 8.0, 9.6, 13.3, and 14.4 μ. Reduction of 5-phenoxyvaleric acid with 475 mg of lithium aluminum hydride according to previously described procedures yielded 5-phenoxypentan-1-ol as indicated by its infrared spectrum: λ_{max} 3.0, 8.0, 9.6, 13.3, and 14.4 μ.

Anal.[27] Calcd for $C_{14}H_{24}O_2Si$: mol wt, 252. Found: mol wt (mass spectrometry), 252.

6-Phenoxyhexan-1-ol.—Using procedures described above 624 mg of 6-phenoxyhexanoic acid (K & K Laboratories, Hollywood, Calif.) was reduced with 114 mg of lithium aluminum hydride to yield 6-phenoxyhexan-1-ol whose infrared spectrum exhibited absorptions at λ_{max} 3.0, 8.05, 9.7, 13.2, and 14.4 μ.

Anal.[27] Calcd for $C_{15}H_{26}O_2Si$: mol wt, 266. Found: mol wt (mass spectrometry), 266.

7-Phenoxyheptan-1-ol.—Applying a synthetic sequence identical with that used in the synthesis of 5-phenoxypentan-1-ol, 1.7 g of 6-phenoxyhexan-1-ol was converted into 1.8 g of 6-phenoxyhexyl bromide. Formation of the corresponding Grignard reagent and subsequent carbonation yielded a solid material which melted at 53–55° without recrystallization (lit.[30] mp 55°). The infrared spectrum verified the identity of the compound as 7-phenoxyheptanoic acid: λ_{max}^{Nujol} 3.3 (broad), 5.8, 8.0, 9.6, 13.3, and 14.4 μ. Reduction of this acid with lithium aluminum hydride yielded 7-phenoxyheptan-1-ol which melted at 32–35° (lit.[31] mp 34°) and exhibited infrared absorptions at λ_{max} 3.0, 8.05, 9.6, 13.2, and 14.5 μ.

Anal.[27] Calcd for $C_{16}H_{28}O_2Si$: mol wt, 280. Found: mol wt (mass spectrometry), 280.

2-^{18}O-Phenoxyethanol.—To a solution of 46 mg of sodium metal in 1 ml of absolute ethanol was added slowly 186 mg of ^{18}O-phenol[32] (10% enriched) followed by the addition of 160 mg of

(24) J. Satgé, *Ann. Chim.*, **6**, 519 (1961).

(25) The calculated molecular weight assumes the mass of the germanium atom to be 74, the mass of its most abundant isotope (see ref 18).

(26) Perdeuterioethanol was purchased from Stohler Isotope Chemicals, Azusa, Calif.

(27) Mass spectral analysis was performed on the trimethylsilyl ether rather than on the parent compound.

(28) E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

(29) R. F. Brown and G. H. Schmid, *ibid.*, **27**, 1289 (1962).

(30) E. Dobrowolska and Z. Eckstein, *Prvem. Chem.*, **42**, 556 (1963).

(31) E. R. Littmann and C. S. Marvel, *J. Amer. Chem. Soc.*, **52**, 287 (1930).

(32) Oxygen-18 enriched phenol was purchased from Yeda Research and Development Co., Rehovoth, Israel.

chlorohydrin in 0.5 ml of absolute ethanol. The mixture was heated under reflux for 18 hr and, after removal of the ethanol by distillation on a steam bath, the residue was diluted with water and extracted with three 10-ml portions of ether; the combined ethereal extracts were washed three times with 5 ml of 10% aqueous potassium hydroxide. After washing with water, drying over anhydrous magnesium sulfate, and evaporating the solvent, the pale yellow oil was purified by preparative gas–liquid partition chromatography (10% GE SF-96 on Chromosorb W with a He flow rate of 100 cc/min at 210°) to yield 40 mg of ^{18}O-phenoxyethanol identical in all respects with the unlabeled compound.

2-Phenoxy-1,1-dimethylethanol.—To a stirred solution of methylmagnesium iodide, prepared from 960 mg of magnesium and 5.68 g of methyl iodide, in 50 ml of anhydrous ether was added, over a period of 1 hr, 1.66 g of the methyl ester of 2-phenoxyacetic acid. The mixture was heated under reflux for 7 hr, cooled, and treated with aqueous ammonium chloride followed by the addition of dilute sulfuric acid until the solution became clear. The ethereal layer was separated, washed with water and aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. After filtration and removal of the ether on a rotary evaporator, preparative gas–liquid partition chromatography yielded 2-phenoxy-1,1-dimethylethanol as indicated by its infrared spectrum: λ_{max} 2.95, 8.0, 9.5, 13.2, and 14.4 μ.

Anal.[27] Calcd for $C_{13}H_{22}O_2Si$: mol wt, 238. Found: mol wt (mass spectrometry), 238.

2-Phenoxyethylamine.—Utilizing previously discussed procedures, 1 g of 2-phenoxyacetamide was reduced with 1 g of lithium aluminum hydride to yield 2-phenoxyethylamine as indicated by infrared absorptions at λ_{max} 2.95, 3.1, 8.05, 13.2, and 14.4 μ.

Anal.[27] Calcd for $C_{11}H_{19}NOSi$: mol wt, 209. Found: mol wt (mass spectrometry), 209.

2-Phenoxyethyl Mercaptan.—Utilizing previously discussed procedures, 2-phenoxyethanol was converted into 2-phenoxyethyl bromide which was subsequently converted into a pale yellow solid upon reaction with potassium ethyl xanthate according to Djerassi, *et al.*[33] After three recrystallizations from hexane, a colorless solid was obtained, mp 50–52°, and was shown to be homogeneous by analytical thin layer chromatography performed on silica gel G. The infrared spectrum indicated characteristic absorptions at λ_{max}^{Nujol} 8.0, 8.3, 9.4, 13.2, and 14.4 μ.

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 54.55; H, 5.82; S, 26.44; mol wt, 242. Found: C, 54.32; H, 5.77; S, 26.76; mol wt (mass spectrometry), 242.

Reduction of 2-phenoxyethylethyl xanthate was accomplished according to the procedure of Djerassi, *et al.*,[33] with the following variations. The initial addition to lithium aluminum hydride was performed at 0° instead of room temperature, and the resulting mixture was not refluxed for 4 hr,[33] but instead stirred at room temperature for 24 hr. After decomposition of the excess lithium aluminum hydride, the product was isolated by threefold extraction with ether, drying over anhydrous magnesium sulfate, filtration, and removing the ether on a rotary evaporator. Distillation yielded 2-phenoxyethyl mercaptan, bp 105–108° and 7 mm (lit.[34] bp 108–109° and 8 mm) which decomposed at high temperature to yield a mixture of phenol and three unidentified compounds. Infrared absorptions were observed at λ_{max} 3.9 (weak), 8.0, 13.3, and 14.4 μ.

Anal. Calcd for $C_8H_{10}OS$: mol wt, 154. Found: mol wt (mass spectrometry), 154.

(33) C. Djerassi, M. Gorman, F. X. Markley, and E. B. Oldenburg, *J. Amer. Chem. Soc.*, **77**, 568 (1955).

(34) E. N. Prilezhakva, N. P. Petukhava, and M. F. Shostakovski, *Dokl. Akad. Nauk SSR*, **154**, 160 (1964).

2-Thiophenoxyethanol.—According to previously described procedures, 2-thiophenoxyacetic acid was reduced with lithium aluminum hydride to yield 2-thiophenoxyethanol: λ_{max} 3.0, 9.5, 13.5, and 14.5 μ.

Anal.[27] Calcd for $C_{11}H_{18}OSSi$: mol wt, 226. Found: mol wt (mass spectrometry), 226.

2-(Cyclohexyloxy)ethanol.—In a moisture-free atmosphere 240 mg of sodium metal was added to 1.1 g of cyclohexanol in 8 ml of dry ether, and the mixture stirred for 12 hr at room temperature. To the resulting yellow suspension was added 1.2 g of ethyl bromoacetate in 12 ml of dry ether and the solution again stirred for 12 hr. After filtration, the ethereal solution was immediately reduced with 520 mg of lithium aluminum hydride in the normal manner to produce 2-(cyclohexyloxy)ethanol after purification by preparative gas–liquid partition chromatography (15% Carbowax on Chromosorb W with a He flow rate of 80 cc/min at 195°). The infrared spectrum indicated characteristic absorptions at λ_{max} 2.95, 8.95, and 9.4 μ.

Anal.[27] Calcd for $C_{11}H_{24}O_2Si$: mol wt, 216. Found: mol wt (mass spectrometry), 216.

1,1-d_2-2-(Cyclohexyloxy)ethanol.—Utilizing the identical procedure employed in the synthesis of 2-(cyclohexyloxy)ethanol, except that lithium aluminum hydride was replaced by lithium aluminum deuteride, 1,1-d_2-(cyclohexyloxy)ethanol was prepared. Its mass spectrum indicated an isotopic composition of 100% d_2.

2′,2′,6′,6′-d_4-(Cyclohexyloxy)ethanol.—Conditions identical with those employed in the synthesis of 2-(cyclohexyloxy)-ethanol were utilized to synthesize this labeled analog except cyclohexanol was replaced by 2,2,6,6-d_4-cyclohexanol, synthesized by the method of Seibl and Gaümann.[35] The mass spectrum of 2′,2′,6′,6′-d_4-2-(cyclohexyloxy)ethanol indicated an isotopic composition of 92% d_4 and 8% d_3.

2-(Cyclopentyloxy)ethanol and 2-Isopropylethanol.—These analogs were prepared according to the procedure used in the synthesis of 2-(cyclohexyloxy)ethanol except that cyclohexanol was replaced by cyclopentanol and isopropyl alcohol, respectively.

Registry No.—III (n = 2), 7381-30-8; III (n = 8), 16654-42-5; VIII, 13175-68-3; XI (n = 4), 16654-44-7; XIV, 16654-45-8; XVI, 16654-74-3; XVII, 16654-46-9; XVIII (n = 2), 16654-47-0; 3-phenoxypropan-1-ol, 6180-61-6; XVIII (n = 3), 16654-49-2; 2-phenoxyethyl ethyl xanthate, 16654-50-5; XVIII (n = 4), 16654-51-6; 5-phenoxypentan-1-ol, 16654-52-7; XVIII (n = 5), 16654-53-8; 6-phenoxyhexan-1-ol, 16654-54-9; XVIII (n = 6), 16654-55-0; 7-phenoxyheptan-1-ol, 16654-56-1; XVIII (n = 7), 16654-57-2; 2-phenoxy-1,1-dimethylethanol, 13524-74-8; XX, 16654-59-4; XXI, 16654-60-7; XXII, 16654-61-8; XXIV, 16654-62-9; XXVII, 16654-63-0; XXVIII, 16654-64-1; XXIX, 16654-65-2; XXX, 16654-66-3; XXXI, 16654-67-4; 2-phenoxyethylamine 1758-46-9; 2-phenoxyethylamine trimethylsilyl derivative, 16654-69-6; 2-thiophenoxyethanol, 699-12-7; 2-thiophenoxyethanol trimethylsilyl ether, 16654-71-0; 2-(cyclohexyloxy)ethanol, 1817-88-5; 2-(cyclohexyloxy)ethanol trimethylsilyl ether, 16654-73-2.

(35) J. Seibl and T. Gaümann, *Helv. Chim. Acta*, **46**, 2857 (1963).

On the Mechanism of 1,3-Dipolar Cycloadditions

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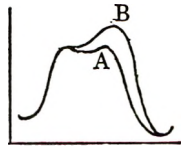
A mechanism for 1,3-dipolar cycloadditions is outlined in which, contrary to the four-center, "no-mechanism" theory, a spin-paired diradical intermediate is proposed.

The concept of 1,3-dipolar cycloadditions was first suggested in 1938 by Smith.[1] The generality of the reaction was recognized by Huisgen in a brilliant series of researches, during which many new reactions have been predicted and discovered.[2] The mechanism also has received much attention from Huisgen's group, and the picture which they have drawn in a convincing manner[3] is that of a single-step, four-center, "no-mechanism" cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent. In accord with this mechanism are the kinetics, the large negative entropy of activation (*ca.* −30 eu), the general effects of structural variation in the dipoles and dipolarophiles, and, most particularly, the strictly *cis* nature of the additions. This mechanism has received wide acceptance, and has not been questioned, to our knowledge, anywhere.

The purpose of this paper is to present an alternative mechanism for 1,3-dipolar cycloadditions. It is true that the data concerning these additions are so manifold that no single mechanism can be written today that accommodates them all, but it is nevertheless hoped to cover the vast majority of these reactions, while yet recognizing that a duality of mechanism may exist in the field as a whole.

A. Mechanism.—In place of a one-step pathway with a single transition state, we propose a two-step reaction with a discrete intermediate, a spin-paired diradical, with the first step rate determining. The stereochemical facts impose upon this mechanism the further restriction that the activation energies for *both advance and retrograde* motion along the reaction coordinate from this intermediate be very small, smaller in fact than that for rotation around a single bond. The energy profile can be sketched as path A.



It is a corollary of this mechanism that, for every successful collision between the two partners, many others will occur in which the first bond can form but the orientation is poor for the second (path B). In these cases the intermediate reverts to starting materials, leaving no memory of itself except a reduced frequency factor. Low entropies of activation are thus to be expected.

It must be noted that the idea of diradical intermediates in thermal cycloaddition reactions is not a new one. It was proposed for the Diels–Alder reaction in 1937 by Kistiakowsky, *et al.*,[4] and revived more recently by Walling and Peisach[5] and it has been widely suggested for small-ring cycloadditions.[6]

B. Stereospecificity.—The *cis* nature of the reaction means that geometrical relationships among the substituents on both the reactants are preserved in the product. As mentioned previously, this is required by the one-step theory, but fits the two-step mechanism only if the activation energy for single-bond rotation in the intermediate is greater than that for either formation of the second bond or reversion to reactants. This is not unreasonable in view of the fact that, even in ethane, the least substituted carbon–carbon single bond, this figure is 2.9 kcal,[7] and a much larger value would be anticipated for the comparatively encumbered intermediates we propose. On the other hand, the activation energy for ring closure of a properly disposed spin-paired diradical is probably much less than 2.9 kcal/mol, possibly approaching zero.[8-11] As for reversion to reactants, we do not know how to estimate a likely number, but it could well be a very small one.

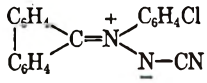
C. Dipolarophile Structure.—"The most striking phenomenon observed here is the promoting effect that conjugation exerts on the dipolarophilic activity of all multiple bonds."[12] This strongly supports the two-step theory, wherein the intermediate, be it dipolar[13] or diradical in nature, derives some stabilization through conjugation. The delocalization energy in a high-energy intermediate, and also in its transition state for formation,[14] might well be greater than that of the ground-state reactants. In a concerted cycloaddition, the situation is exactly reversed; whatever stabilization

(1) L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).
(2) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).
(3) R. Huisgen, *ibid.*, **2**, 633 (1963).
(4) J. B. Harkness, G. B. Kistiakowsky, and W. H. Mears, *J. Chem. Phys.*, **5**, 682 (1937).
(5) C. Walling and J. Peisach, *J. Amer. Chem. Soc.*, **80**, 5819 (1958).
(6) (a) E. E. Lewis and M. A. Naylor, *ibid.*, **69**, 1968 (1947); (b) E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949); (c) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 8 (1962); (d) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Amer. Chem. Soc.*, **86**, 616, 622, 628 (1964); (e) W. C. Solomon and L. A. Dee, *J. Org. Chem.*, **29**, 2790 (1964); (f) A. Cairncross and E. P. Blanchard, *J. Amer. Chem. Soc.*, **88**, 496 (1966); (g) P. S. Skell and R. C. Woodworth, *ibid.*, **78**, 4496 (1956); (h) P. Scheiner, *ibid.*, **88**, 4759 (1966).
(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 35.
(8) The dimerizations of both methyl[9] and *t*-butoxy[10] radicals have activation energies of approximately zero.
(9) R. Gomer and G. B. Kistiakowsky, *J. Chem. Phys.*, **19**, 85 (1951)
(10) D. J. Carlsson, J. A. Howard, and K. U. Ingold, *J. Amer. Chem. Soc.*, **88**, 4725 (1966).
(11) It is often alleged that an intermediate whose further transformation requires zero activation energy can be no more than an imaginary creature; under such circumstances, the two-step mechanism becomes identical with the one-step by this criterion. This notion is false, however, for even with such an intermediate the distinction made between the two mechanisms regarding the extent to which formation of the *second bond* has proceeded in the transition state is entirely preserved. Thus predictions based on the two theories remain divergent.
(12) See ref 3, p 638.
(13) W. I. Awad, S. M. A. R. Omran, and F. Nagieb, *Tetrahedron*, **19**, 1591 (1963).
(14) C. Walling in "Free Radicals in Solutions," John Wiley and Sons, Inc., New York, N. Y., 1957, p 124.

energy the dipolarophile possesses ought to diminish steadily along the reaction coordinate as the π bond is consumed.

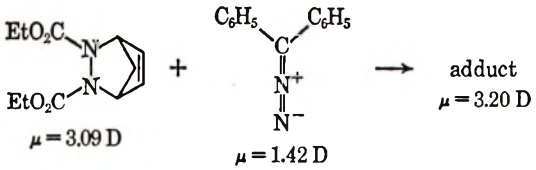
This question has been dealt with[12,15,16] by what can only be described as an important departure from the concerted cycloaddition theory: the formation of the two new bonds, though still simultaneous, is no longer held to be synchronous.

D. Solvent Effects.—Over a wide range of polarities, the rates of 1,3-dipolar cycloadditions show a remarkably small solvent dependence.[16-23] This fact is not consistent with a one-step mechanism, in which the dipolarity of the starting compound must be partially discharged in the transition state. Such a mechanism requires an inverse relation of rate to solvent polarity, the magnitude depending on the amount of charge dispersal; yet even for 1,3 dipoles of unusually high polarity the solvent effect is small. For the addition of I (μ = 6.7) to dimethylacetylenedicarboxylate,[17] for example, the rate diminishes by a factor of only 6 as the solvent is changed from benzene to dimethylformamide. For less polar 1,3 dipoles the factor is smaller, approximating 1 in many cases.



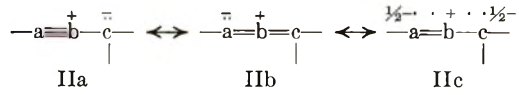
I

It is possible to reconcile with theory[24] the small solvent dependence of many examples, such as the one just cited, by postulating that the transition state is merely an orientation complex in which covalent bonding has hardly begun; a considerable part of the free energy of activation is accounted for by entropy changes. A proposal close to this postulate has been made for some[25] (but not all[16]) cases. There is a conflict, however, with a theory of orientational effects in which covalently bound resonance forms figure prominently.[15] Moreover, there are other examples whose transition states' dipole moments would be too low in any event. For instance, in the following reaction, the transition state must have a dipole moment of 4.6 D in order to have zero solvent dependence.[17] Its moment



was estimated at 4.4 D, in good agreement with the required value. However, the *vector* sum of the two dipoles in the orientation complex is only *ca.* 3.4 D, a good deal lower. Likewise, for the addition of phenyl azide (μ = 1.55[26]) to norbornene (μ = 0.40[27]), whose rate is also independent of solvent polarity,[18] theory requires a dipole moment of 2.16 D for the transition state of a concerted pathway, but the orientation complex would be only in the neighborhood of 1.6 D. Other cases could be cited also.[20]

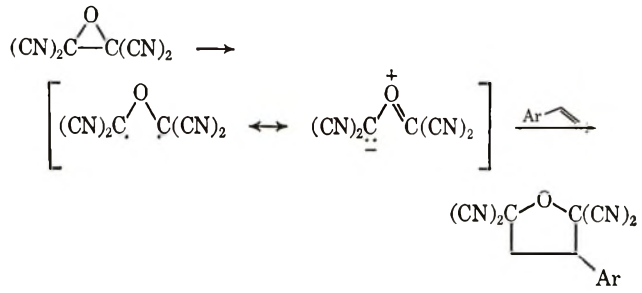
In a two-step mechanism, on the other hand, in which only one bond is partially formed in the transition state, this species might reasonably be expected to have approximately the same polarity as the orientation complex of the components. Consider the three principal canonical forms of a typical 1,3 dipole, II. These are all octet structures which have the same number of



IIa IIb IIc

bonding electrons. All other forms, such as sextet structures, have fewer bonding electrons and can be discounted. Form c is drawn according to Linnett's method[28] and is quantum-mechanically equivalent to a ⟷ b. Since the dipole moments of most 1,3 dipoles are small compared with the theoretical values for full charge separation,[17] the expression c may usually be accepted as the principal representation of II. The diradical attributes of II are thus made apparent, and if the blend of polar and diradical qualities in the transition state leading to the diradical intermediate is about the same as that in II, solvent effects on the rate would be expected to be small.[29]

In the cycloaddition of tetracyanoethylene oxide to *para*-substituted styrenes, in which the TCNEO must first be activated to a 1,3 dipole, the small dependence of rate on either solvent or the nature of the *para* substituent led Linn[19] to propose a diradical structure for activated TCNEO.



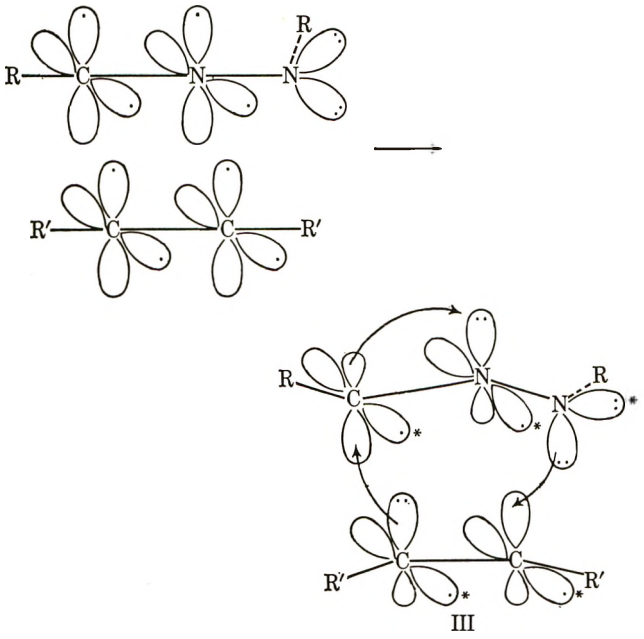
E. Acetylenic Dipolarophiles.—A number of 1,3 dipoles react with acetylenes to produce aromatic systems directly, *e.g.*, nitrile imines, nitrile oxides, and azides. In a concerted reaction, a portion of this aromatic stabilization should exist in the transition state. With these dipoles, then, greatly enhanced reactivity is expected for acetylenic dipolarophiles over their ethylenic counterparts in a concerted cycloaddition; yet, in comparing the reaction rates of diphenyl(nitrile imine), benzonitrile oxide, and phenyl azide with the two pairs styrene–phenylacetylene and

(15) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).
(16) R. Huisgen, G. Szeimines, and L. Möbius, *ibid.*, **100**, 2494 (1967).
(17) See ref 3, p 635.
(18) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Amer. Chem. Soc.*, **87**, 306 (1965).
(19) W. J. Linn, *ibid.*, **87**, 3665 (1965).
(20) R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).
(21) A. S. Bailey and J. E. White, *J. Chem. Soc., Sect. B*, 819 (1966).
(22) P. D. Kadaba, *Tetrahedron*, **22**, 2453 (1966).
(23) A. Ledwith and D. Parry, *J. Chem. Soc., Sect. C*, 1408 (1966).
(24) S. Glasstone, K. J. Laidler, and H. Eyring in "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p 419.
(25) See ref 3, p 645.
(26) L. G. Wesson, "Tables of Electric Dipole Moments," Technology Press, Cambridge, Mass., 1948.
(27) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).
(28) J. W. Linnett, "The Electronic Structure of Molecules," Methuen and Co., London, 1964. See, for example, the structures for O_3, p 63, and N_2O, p 67.
(29) Orientational phenomena and energetics can also be explained in terms of forms like IIc. This aspect of the mechanism will be reserved for a future publication.

acrylic–propiolic esters, no such differences in reactivity are found.[15,16,30]

This question has been treated in terms of hypothetical orbital changes during reaction.[15,25] The thesis is that orbital symmetry theory[31,32] requires an acetylenic dipolarophile to approach a 1,3 dipole, such as diphenyl (nitrile imine), from above or below. The transition state is puckered and cannot profit from the aromatic resonance of the product. The resemblance of the transition state to the orientation complex (whose new σ bonds are still quite long), rather than the product, has also been stressed.[25]

However, we believe that a cycloaddition leading to an aromatic product, if it were to occur concertedly, would not be required to eschew the arrangement III, in which the five reacting atoms are coplanar. The



III

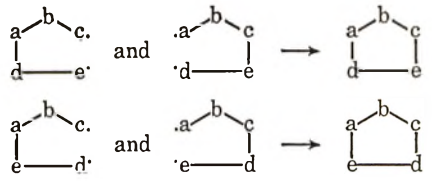
orbitals marked with asterisks constitute the developing aromatic π cloud; they are no less parallel in III than they are in the product. The implication is not intended that electrons are localized in the orbitals as shown, or that they must move according to the arrows. They are depicted for counting purposes only. Calculations show that III does not violate the Woodward–Hoffmann theory.[33] Therefore, rate accelerations are expected with a four-center mechanism.

The normal reactivities of acetylenic dipolarophiles present no difficulty for a two-step mechanism because the appearance of the aromatic system is substantially delayed until after the rate-determining step.

F. Orientation.—Unsymmetrical dipolarophiles can add to unsymmetrical 1,3 dipoles in two directions, of which one only is usually found. An understanding of this problem requires consideration of both steric and electronic factors as well as the principle of maximum gain in σ-bond energy.[34] In addition, other forces not yet recognized may play a role.

Despite this complexity, many cases are known in which the variables seem well enough understood for predictions to be made. It is our contention that *the electronic factors, when the others are controlled, should direct the course of a concerted cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole.* For a two-step cycloaddition with a dipolar intermediate[13] the prediction is the same.

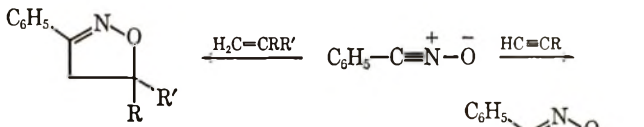
If the course of the cycloaddition passes through a diradical intermediate, however, the expected product sometimes has the opposite orientation from the one that would be formed through the other mechanisms. The method of prediction is to pick the best looking of the four possible diradical intermediates (taking into account steric, kinetic and σ-bond energy factors).



The chief difficulty is that the factors governing radical formation and stability are so poorly understood today that few secure predictions can be made. A further complication is created by the possibility that electrostatically bound prereaction complexes may sometimes influence orientation even of a fundamentally nonpolar reaction.

For these reasons, emphasis in the following section will be placed primarily on contradictions to concerted (and polar two-step) mechanisms. Diradical intermediates are drawn, not on the basis of predictions, but of orientational patterns whose principles of organization can be understood in terms of these intermediates.

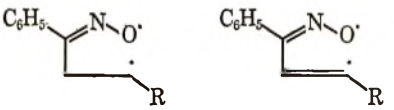
Benzonitrile N-oxide combines with all monosubstituted ethylenes or acetylenes predominantly in the same direction, whether the substituent be alkyl or aryl, electron attracting or electron donating.[35]



R = H; R′ = C_6H_5,[36] COOEt,[37] CN, OAc,[38] CH_3, *n*-alkyl[39]
R = R′ = CH_3,[39] OEt[40]

R = C_6H_5, OCH_3, OEt[40]

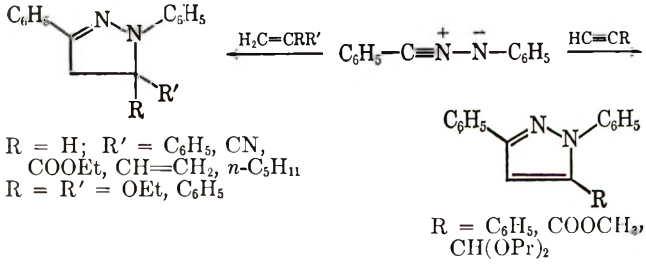
For one or the other group of substituents, this orientation must be wrong for a concerted cycloaddition. Both groups, however, would stabilize a diradical intermediate[41] if these structures were the preferred ones.



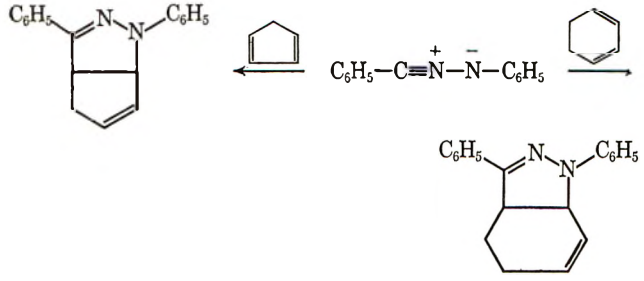
(30) See ref 3, p 639.
(31) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).
(32) K. Fukui, *Bull. Chem. Soc. Jap.*, **39**, 498 (1966).
(33) We are indebted to Dr. P. I. Pollak of these laboratories for the calculations.
(34) See ref 3, p 641.
(35) See ref 3, p 642.
(36) P. Grünanger, *Gazz.*, **84**, 359 (1954).
(37) See ref 2, p 574.
(38) G. Stagno d'Alcontres and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 741 (1950).
(39) G. Stagno d'Alcontres, *ibid.*, **82**, 627 (1952).
(40) P. Grünanger and M. R. Langella, *ibid.*, **89**, 1784 (1959).
(41) In accord with this idea is the report by A. Dondoni, *Tetrahedron Lett.*, 2397 (1967), that in the addition of C_6H_5CNO to *p*-$X(C_6H_4)C{\equiv}CH$, with X = NO_2, Cl, H, Me, and OMe, all substituents accelerate relative to H.

The explanation given[35] for this phenomenon was that steric factors outweighed electronic ones; yet even with HCNO, where steric factors are at a minimum for nitrile oxides, essentially no change in orientation is seen.[42-44]

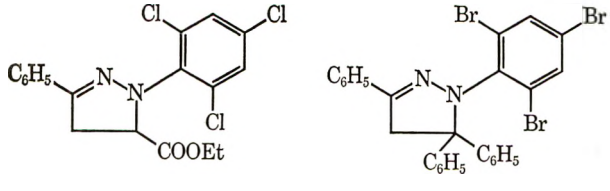
Furthermore, the same situation obtains with diphenyl(nitrile imine), a 1,3 dipole with analogous electronic structure but which now bears phenyl groups on



both ends.[45,46] Even with cyclopentadiene and 1,3-cyclohexadiene, dipolarophiles which are sterically almost symmetrical, the rule is not relaxed.[45] The steric explanation is still defended,[15,47] however, based on the

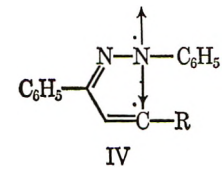


hypothesis that the phenyl group on the carbon atom in the 1,3 dipole, which is sp hybridized in the ground state, will suffer greater interference from the dipolarophile than will the phenyl group on the outer nitrogen atom, but the transition state for a concerted cycloaddition is sterically impossible unless the 1,3 dipole, linear in the ground state, undergoes considerable rehybridization so that it can bend. When this is done, according to our view (*vide supra*) the steric influence of the two phenyl groups is approximately equalized. Furthermore, it was impossible to reverse the direction of addition by placing bulky substituents on the N-phenyl group and the C_1 of the dipolarophile, as shown by the following adducts.[46-48] "The strictness with



which the same orientation rule is followed is really remarkable and casts doubt on a purely steric interpretation." [47]

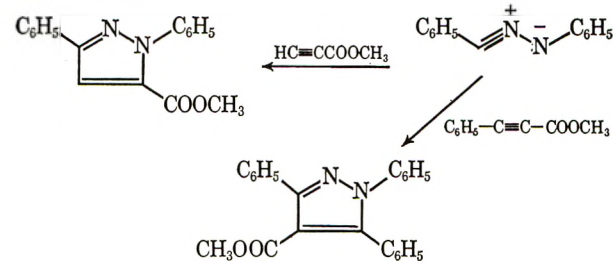
However, "the unidirectional addition to monosubstituted ethylenes and acetylenes can (admittedly) be understood in terms of the intermediate IV." We



IV

agree with this statement but Huisgen rejects it[47] on the following grounds.

Diphenyl(nitrile imine) adds to propiolic and phenylpropiolic esters in the opposite direction (diphenyldiazomethane behaves similarly). This is said to reflect



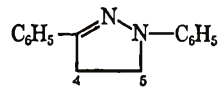
steric control, with phenyl bulkier than carbethoxy, and to disprove control through diradical stability because carbethoxy is more activating than phenyl. The statement is supported by the relative rate constants for addition of a variety of 1,3 dipoles onto styrene *vs.* acrylic ester; the latter is more reactive in all cases by factors ranging from 7 to 500.[12]

This argument is not convincing, however, because it assumes that the two activating groups, conjugated with each other through the same multiple bond, behave exactly as they do in separate molecules, and do not interact with each other; yet the phenyl group, normally electron attracting, undoubtedly is electron releasing toward carbethoxy in cinnamic[49] and phenylpropiolic esters. Furthermore, reversal of orientation of exactly this type is a known characteristic of radical addition; *i.e.*, carbethoxy, which normally determines the direction of radical addition in acrylic and crotonic esters, yields control to phenyl in cinnamic esters;[50,51] yet cinnamic ester is strongly deactivated relative to styrene,[52] while acrylic ester is not.[53,54]

The whole question of relative dipolarophile reactivities is shrouded with uncertainty, as shown not only by the wide range of factors previously mentioned, but also the even wider range in other comparisons, for which no rational interpretation yet exists. For example, the list of relative reactivities of ethyl acrylate *vs.* norbornene toward four varied 1,3 dipoles[30] ranges from 0.052 to 244!

(42) A. Quilico and G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, **79**, 654, 703 (1949).
(43) G. Stagno d'Alcontres and G. Fenech, *ibid.*, **82**, 175 (1952).
(44) R. Huisgen and M. Christl, *Angew. Chem. Intern. Ed. Engl.*, **6**, 456 (1967).
(45) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
(46) J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, and V. Weberndorfer, *Chem. Ber.*, **100**, 1593 (1967).
(47) See ref 3, p 643.
(48) R. Huisgen, R. Sustmann, and G. Wallbillich, *Chem. Ber.*, **100**, 1786 (1967).
(49) F. G. Bordwell and K. Rohde, *J. Amer. Chem. Soc.*, **70**, 1191 (1948).
(50) C. F. Koelsch and V. Boekelheide, *ibid.*, **66**, 412 (1944).
(51) M. S. Kharasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).
(52) Toward addition of ·CCl_3, the rate ratio of ethyl cinnamate to styrene is 0.008.[51]
(53) Toward addition of a variety of radicals, the rate ratio of methyl acrylate to styrene varies from 0.18 to 1.9.[54]
(54) See ref 14, p 123.

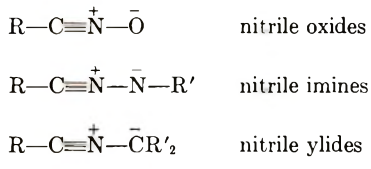
A recent attempt has been made to put the concerted mechanism on a more quantitative basis.[15] In the addition of a large variety of dipolarophiles to diphenyl(nitrile imine), the tendency of each of the substituents methyl, isopropyl, carbalkoxy, and phenyl to occupy either the 4 or 5 position in the product was divided into a steric and an electronic component. These factors were different for each substituent but constant throughout the series for mono- and disubstituted ethylenes. In keeping with the concerted mechanism, it was found that the electronic factor



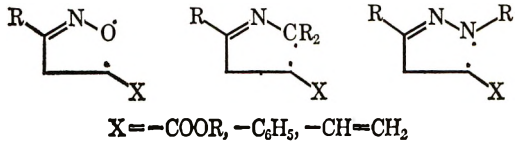
for each substituent was about the same in both positions, but not the steric factor, which was generally *ca.* 0.01 for the 4 position and unity (*i.e.*, no effect at all) in the 5 position.

In addition to what has been said earlier about the steric phenomena, it may be pointed out that the consistency of this method rests upon the assumption, which we deem unlikely, that alkyl groups exert no electronic effect in the transition state, but a steric one only. Moreover, it is difficult to see why, in a concerted cycloaddition, the 4 but not the 5 position should be so hindered (*cf.* III), although there is no problem with a two-step mechanism (*vide infra*). As for the electronic aspect, not all substituents have a constant factor for both positions, and not all disubstituted ethylenes fit the additivity rule. The explanations have stressed the nonsynchronous nature of the reaction, but this (in addition to the point raised in section D) does not account for the constancy of the electronic factor for $-COOMe$ in both acrylic and fumaric esters, or for the abnormally low rate for methyl 3-dimethylaminoacrylate. Space limitations preclude further discussion of this very interesting paper, whose study is recommended.

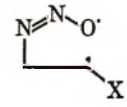
The 1,3 dipoles discussed above are two of the three members of a class of dipoles which can be imagined as having been built upon the nitrile group (see below).



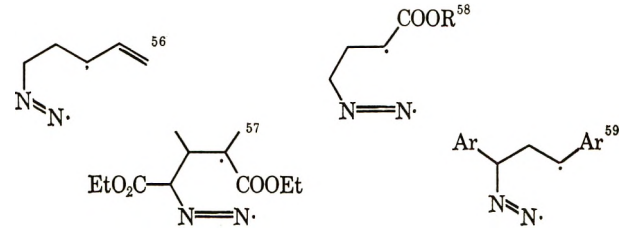
This group as a whole shows a strong unidirectional pattern of orientations which, in our opinion, is not polar in origin, and yet is clearly electronic in nature rather than steric. When consideration is limited to dipolarophiles whose sites of favored radical addition can be "safely" predicted, such as acrylic esters, styrene, 1,3-butadiene, etc., the predicted best diradical intermediates look very much alike. Within this framework, of course, steric effects are still to be anticipated; *cf.* diphenyl(nitrile imine).



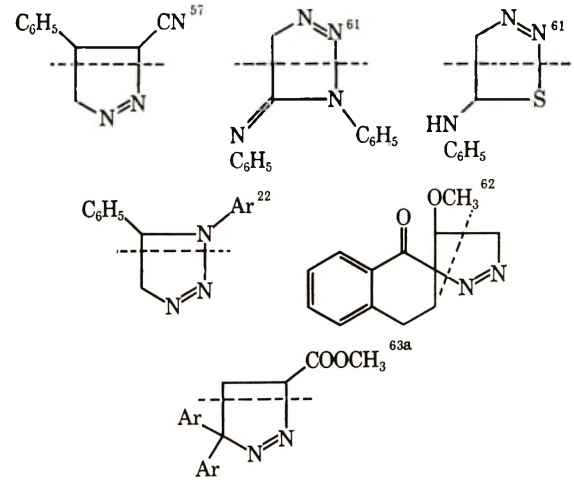
The group of 1,3 dipoles built similarly upon the nitrogen molecule consists of nitrous oxide, diazoalkanes, and alkyl and aryl azides. The first dipole fits the best diradical rule, although data are sparse.[55]



Diazoalkanes, however, add in the opposite sense, although it remains true that the predicted best diradical is always of the same type (that shown below).

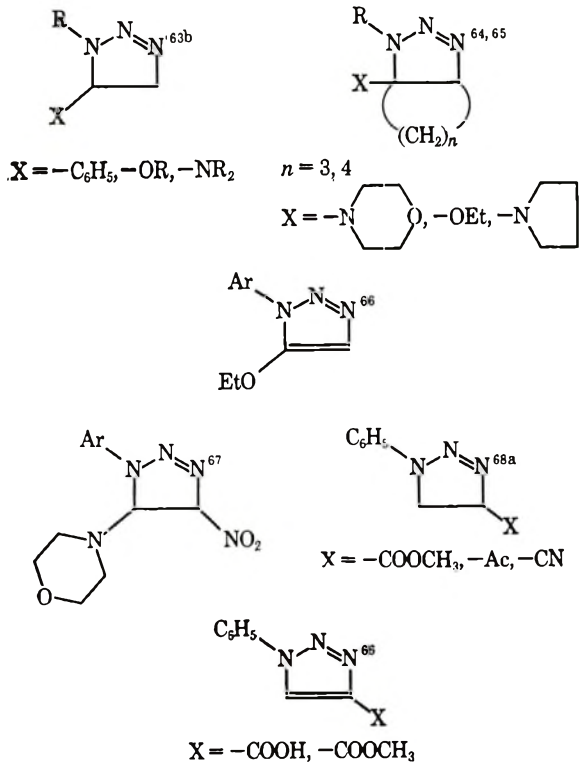


It should be noted that in some of these cases, as well as in the adducts shown below, the orientation is contrary to that predicted by our interpretation of the one-step mechanism because diazoalkanes are polarized with the outer nitrogen negative.[60]



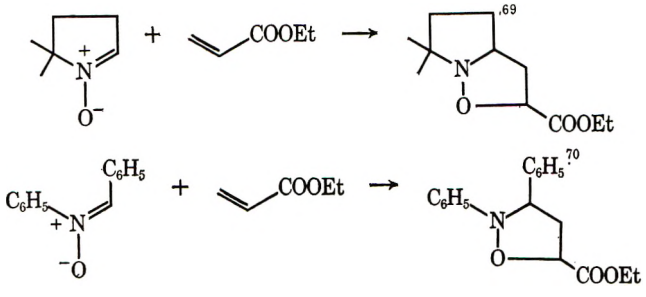
The addition of azides, however, cannot be fitted to a best diradical rule. With dipolarophiles containing electron-releasing substituents they add predominantly in one direction, which is reversed when the substituents are electron attracting.

(55) See ref 2, p 580.
(56) E. Müller and O. Roser, *J. Prakt. Chem.*, **133**, 291 (1932).
(57) K. v. Auwers and O. Ungemach, *Ber.*, **66**, 1198, 1205 (1933).
(58) See ref 2, p 576.
(59) C. G. Overberger, N. Weinshenker, and J-P. Anselme, *J. Amer. Chem. Soc.*, **87**, 4119 (1965).
(60) See ref 2, p 575.
(61) See ref 2, p 577.
(62) D. Nasipuri and K. K. Biswas, *Tetrahedron Lett.*, 2963 (1966).
(63) (a) W. M. Jones, P. O. Sanderfer, and D. G. Baarda, *J. Org. Chem.*, **32**, 1367 (1967); (b) see ref 2, p 579.

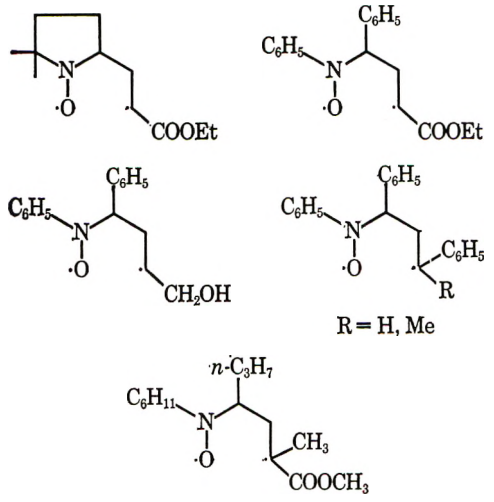


In all these cases, the orientations are not those predicted for concerted cycloadditions because azides are polarized with the outer nitrogen negative.[68b]

Nitrones are another class of 1,3 dipoles whose direction of addition is frequently incorrect for polar and one-step pathways.



Moreover, a strong pattern of "favored diradical" intermediates is again discernible.[70,71]



It is true that a steric explanation could also account for orientation with nitrones, but in most of these examples the expected steric effect seems to us rather small.

In the preceding discussion, stress has been placed on the unidirectional nature of addition of many classes of 1,3 dipoles to olefins whose activating groups can all stabilize radicals but not always the proper type of charge. Attention must therefore now be drawn to azomethine imines, a class that does not add unidirectionally. The orientation among their adducts cannot easily be rationalized by the diradical mechanism,[72] and we must admit the likelihood of a concerted or two-step polar pathway. Another peculiarity of azomethine imines, however, is that their cycloadditions are frequently reversible, and perhaps the products that have been isolated are not always the first ones formed; this difficulty has cropped up in the nitrone series.[69]

G. Conclusion.—The extensive and rapid development of the field of 1,3-dipolar cycloadditions, for which Professor Huisgen's group is almost entirely responsible, has been accompanied, in our opinion, by insufficient debate on the part of other chemists as to the details of mechanism; yet even tiny differences among possible reaction pathways can be of great importance because they affect our picture of the nature of chemical binding, a matter of vital interest to chemists. The intent of this paper, therefore, is not to settle controversy but to arouse discussion.

(64) R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965).
(65) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965).
(66) R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *ibid.*, **98**, 4014 (1965).
(67) S. Maiorana, D. Pocar, and P. Dalla Croce, *Tetrahedron Lett.*, 6043 (1966).
(68) (a) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966); (b) see ref 2, p 578.
(69) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4963 (1963).
(70) See ref 2, p 588.
(71) M. Iwamura and N. Inamoto [*Bull. Chem. Soc. Jap.*, **40**, 702, 703 (1967)] report that nitrones undergo 1,3 addition of two free radicals, with the first most probably adding to carbon.
(72) See ref 2, p 583.

On the Mechanism of 1,3-Dipolar Cycloadditions. A Reply

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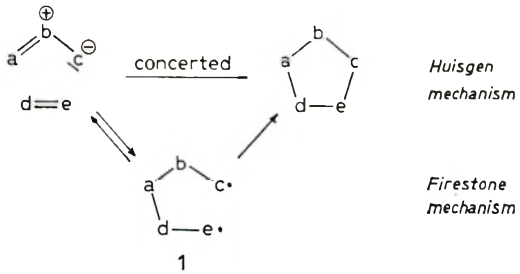
Received December 27, 1967

The arguments for a diradical intermediate proposed in the preceding paper are refuted. The available evidence speaks for a concerted addition. The "two-planes" orientation complex of 1,3 dipole and dipolarophile is experimentally well founded and with its (4 + 2) π electrons allows a concerted thermal addition. Activation parameters, *cis* stereospecificity, and solvent dependence are in accord with this mechanism. Substituent effects and orientation phenomena are discussed.

Criticism and reply contribute to clarification. Dr. Firestone's valuable comments are welcomed because they present an opportunity to discuss some widespread significant misinterpretations. It will be up to the reader to decide whether the concept of a single-step concerted 1,3-dipolar cycloaddition[1] will be hardened in criticisms *fire* to *stone* or will crumble into dust.

Terminology.—Doering and Roth's[2] description of a "no-mechanism" reaction has wittily stressed the impossibility of obtaining *direct* mechanistic proof. In the meantime, the processes with cyclic electron shifts have grown into a rather large class of reactions, which are no less understood than many other single-step processes. Thus the pessimism which is implied in the term "no-mechanism" reaction seems no longer justified, especially since the principle of conservation of orbital symmetry[3] provides a fruitful theoretical basis for such processes.

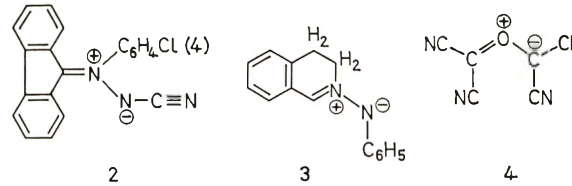
***cis* Stereospecificity.**—The greatest obstacle for the assumption of a diradical intermediate is the stereospecificity observed in the cycloadditions of the 1,3 dipole with *cis–trans* isomeric dipolarophiles. 1,3-Dipolar cycloaddition shares this characteristic as well as others with the Diels–Alder reaction. Firestone overcomes this obstacle by the ingenious, but improbable hypothesis that in the diradical **1** the energy barrier for rotation around single bonds is greater than the activation energy for ring closure or for reversion of **1** to the reactants. Thus, all diradicals **1** which are not formed in the correct conformation for ring closure will return to starting materials.



1

Reversion includes a change of hybridization at a and d and, concomitantly, a deep-seated alteration of molecular geometry. The bond ad of **1** must undergo considerable stretching before the retrograde process can profit from the incipient formation of the π bonds. A low activation barrier for reversion is contrary to our chemical intuition, but also is not reconcilable with known facts. Montgomery, Schueller, and Bartlett[4] observed a high degree of stereoequilibration in the cycloaddition of 1,1-dichloro-2,2-difluoroethylene to the geometrical isomers of 2,4-hexadiene. In the spin-paired diradical involved (it appears to be the 1,4 analog of **1**), the rotation competes well with the ring closure. Even open-chain 1,4 zwitterions, such as the one formed from 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*-propenyl propyl ether, do not fully retain configuration during ring closure[5] despite electrostatic attraction.

Firestone's hypothesis becomes the more artificial and the less tenable, since the strength of the bond ad in the intermediate **1** may vary. By linking the whole set of 1,3 dipoles with the dipolarophiles, the bond ad can be made up of nearly every combination of C, N, and O. A single example of a *cis*-stereospecific addition would not be a convincing mechanistic argument. However, stereospecificity is regarded a more weighty criterion for concertedness, if no exception is found in several dozen cases with a large variety of 1,3 dipoles. A scrupulous search for a mutual admixture of adducts has disclosed stereospecificity for cycloadditions of the following 1,3 dipoles: diphenylnitrilimine,[6,7] benzonitrile N-oxide,[8,9] diazomethane,[10,11] 4-nitrophenyl azide,[12] an azomethine ylide of the 1-pyrroline series,[13] the azomethine imines **2**[14] and **3**,[15,16] 3.4-dihydroisoquinoline N-oxide,[17] and the carbonyl ylide **4**.[18]

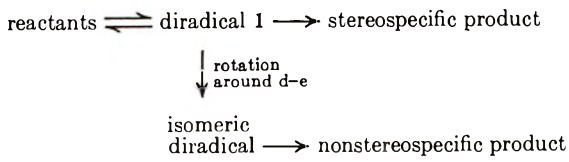


2 3 4

In Scheme I, implied by Firestone's mechanism, the reversion of **1** to reactants must be at least 30 times

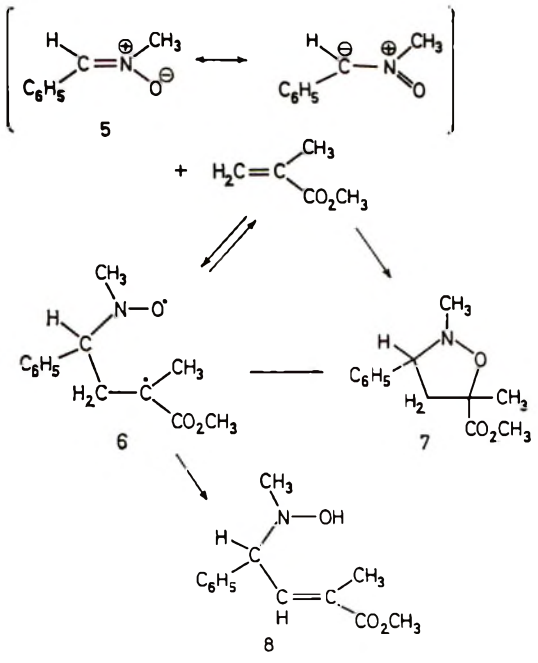
(1) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 633 (1963).
(2) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).
(3) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395, 2046, 2511, 4388, 4389 (1965).
(4) L. K. Montgomery, K. Schueller, and P. D. Bartlett, *ibid.*, **86**, 622 (1964).
(5) S. Proskow, H. E. Simmons, and T. L. Cairns, *ibid.*, **88**, 5254 (1966).
(6) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
(7) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, and V. Weberndörfer, *Chem. Ber.*, **100**, 1580 (1967).
(8) A. Quilico, G. Stagno d'Alcontres, and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 479 (1950).
(9) M. Christl, Diploma Thesis, University of München, 1966.
(10) K. v. Auwers and E. Cauer, *Ann.*, **470**, 284 (1929).
(11) P. Eberhard, Diploma Thesis, University of München, 1967.
(12) R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).
(13) R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tetrahedron Lett.*, 481 (1964).
(14) A. Eckell, Ph.D. Thesis, University of München, 1962; see ref 1, p 636.
(15) R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960); see ref 16, p 583.
(16) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).
(17) R. Huisgen, H. Seidl, R. Grashey, and H. Hauck, *Chem. Ber.*, in press; see ref 1, p 637.
(18) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965).

SCHEME I



faster than rotation around d-e to account for the observed stereospecificity ($\leqslant 3\%$ of isomeric adduct). Thus, $\Delta G^{\pm}$ of the retrograde process 1 → reactants is at least 2.1 kcal smaller than the rotation barrier which is probably not greater than 3.4 kcal. The activation energy of the reversion process must therefore be smaller than 1.3 kcal/mol!

Energetics of Firestone's Diradical Intermediate.—The spin-paired diradical intermediate 1 contains one σ bond more, but two π bonds less than the reactants. Furthermore, the resonance energy, which stems from the π delocalization of the 1,3 dipole, has to be sacrificed and the stabilization energy of the diradical is gained. On comparing the energy balance for the formation of 1 with experimental values of activation enthalpies, one becomes aware of a discrepancy which precludes the possible occurrence of 1. Regrettably, some of the thermochemical data are unknown so that we must depend on "sound guesses."



The addition of N-methyl-C-phenylnitrone (5) to methyl methacrylate in toluene shows the following Eyring parameters: $\Delta H^{\pm} = 15.7$ kcal/mol, $\Delta S^{\pm} = -32$ eu.[19] For the formation of 6 we calculate a net loss of 54 kcal/mol in bond energy; the activation energy has to be larger (Table I).

Furthermore, O radicals are notorious for their hydrogen affinity. The diradical 6 (were it formed) should produce the unsaturated hydroxylamine 8 *via* intramolecular disproportionation;[20] this conversion is expected to be exothermic by ≈55 kcal/mol. A side product of type 8 has never been isolated in cycloadditions of nitrones, nor has any other 1,3-dipole + dipolarophile system produced an analogous product. Also hydrogen transfer from the solvent to intermediate 1 has not been observed.

(19) Ph.D. Thesis, H. Seidl, University of München, 1964; see ref 1, p 637.

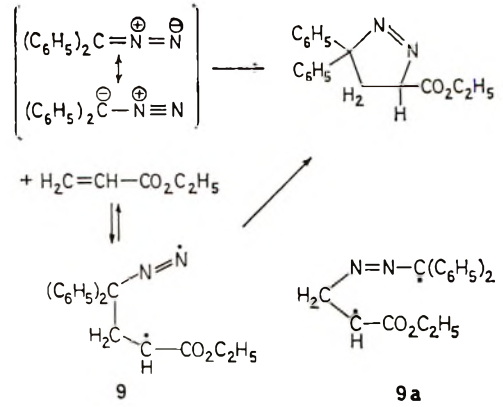
(20) For an example, see C. G. Overberger and J. G. Lombardino, *J. Amer. Chem. Soc.*, **80**, 2317 (1958).

TABLE I

Loss	
C=C → C—C	65 kcal/mol
C=N → C—N[a]	68
C_6H_5C= conjugation energy	4
Nitrone resonance[b]	20
$CH_3O_2C(CH_2)C$= conjugation	4
	161 kcal/mol
Gain	
C—C	83
Resonance energy of the diradical 6[c]	24
	107 kcal/mol

[a] A. F. Bedford, P. B. Edmondson, and C. T. Mortimer [*J. Chem. Soc.*, 2927 (1962)] found 74.7 kcal/mol for C—N and 142.6 for C=N. The more suitable data for C—N$^+$ and C=N$^+$ are not known. [b] From pK_a values, a resonance energy of the allyl anion of 9 kcal is derived: D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 19. The resonance energy of the carboxylate anion is 36 kcal: L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, 1960. The resonance energy of the nitrone should lie in between. [c] Partial use of data given by C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 50.

For the addition of diphenyldiazomethane to ethyl acrylate in dimethylformamide, $\Delta H^{\pm} = 8.0$ kcal/mol and $\Delta S^{\pm} = -43$ eu were measured.[21] Diazomethane adds even faster by a factor of 10^2.[22] An analogous crude calculation reveals that the diradical 9 possesses ≈65 kcal/mol less bond energy than the reactants. The other addition direction (which was not observed) should furnish the better diradical 9a.



Why does the diradical 9, according to Firestone, revert to reactants instead of losing nitrogen? If the decarboxylation of the acetoxy radical is exothermic by 20 kcal/mol,[23] should not the tendency to cleave the C—N bond to form a diphenylmethyl radical + N_2 be still higher? In fact, the known reactions of diazoalkanes with triphenylmethyl,[24,25] trichloromethyl,[26,27]

(21) R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).

(22) Experiments of D. Jung, München, 1963.

(23) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).

(24) W. Schlenk and C. Bornhardt, *Ann.*, **394**, 183 (1912).

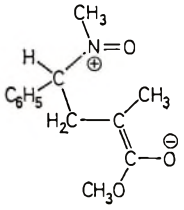
(25) D. B. Denney and N. F. Newman, *J. Amer. Chem. Soc.*, **89**, 4692 (1967).

(26) W. H. Urry and J. R. Eiszner, *ibid.*, **74**, 5822 (1952).

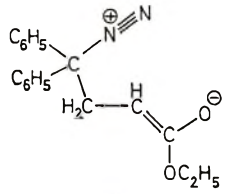
(27) W. H. Urry and J. W. Witt, *ibid.*, **76**, 2594 (1954).

or nitric oxide[28,29] are acompanied by immediate loss of nitrogen.

We see a better alternative to the concerted pathway of 1,3-dipolar cycloaddition in the formation of a zwitterionic intermediate; **10** and **11** would correspond with **6** and **9**. The zwitterions contain the same number of bonds as the reactants. We have discussed their possible intermediacy in detail elsewhere;[1] recently, such zwitterionic intermediates in the addition of organic azides were abandoned on the basis of hard experimental facts.[30]



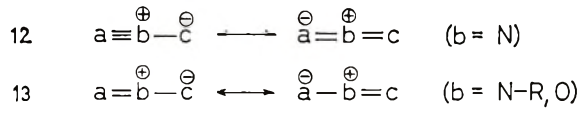
10



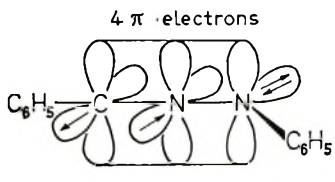
11

Electronic Structure of the 1,3 Dipole.—*A 1,3 dipole is a compound abc which undergoes 1,3 cycloadditions and is described by zwitterionic octet structures.*

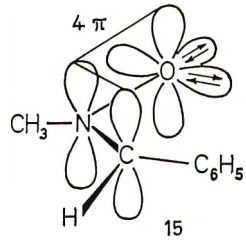
The author does not understand the significance of Firestone's formula IIc for the 1,3 dipole. In the corresponding text a "blend of dipolar and radical qualities" and "diradical attributes of II" are mentioned. A diradical is by definition a structure with two electrons which do not form a bond. According to classical resonance theory,[31] diradical resonance contributions can be neglected, because they contain one bond less than the zwitterionic octet formulae **12** and **13** of the 1,3 dipole.



The author is convinced that MO theory affords a superior description. All 1,3 dipoles contain four π electrons in three parallel p orbitals. As in the isoelectronic allyl anion, the four electrons occupy pairwise the two lowest molecular orbitals. Formulae **14** (diphenylnitrilimine) and **15** (N-methyl-C-phenylnitrone) illustrate this for one dipole of each class (with and without a double bond in the 1,3 sextet structure).[16] As pointed out below, this allyl anion structure is responsible for the ability of the 1,3 dipole to undergo cycloadditions.[32,33]



14

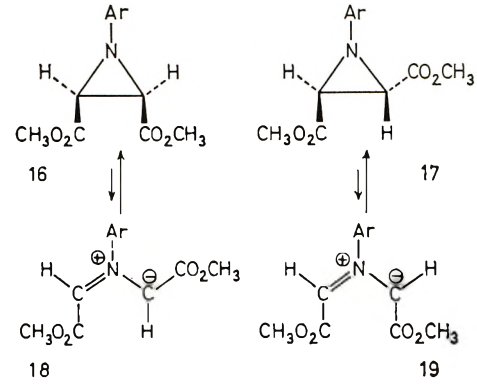


15

The molecular orbital description of the 1,3 dipole leaves no room for a "spin-paired diradical structure." Only by promoting one electron into the next higher molecular orbital—higher in energy by $2\sqrt{2}\beta$ [34]—is a state reached where the two electrons do not form a bond. However, this excited singlet state has not much to do with the ground state which enters into cycloaddition reactions.

Firestone mentioned, in this connection, that Linn[35] proposed a diradical structure for "activated" tetracyanoethylene oxide which undergoes cycloadditions; these, incidentally, obey all the criteria of 1,3-dipolar cycloadditions. Linn described the species as a zwitterion–biradical hybrid which is open to the same objections expressed above. Linn regarded a 1,3-dipolar ion as untenable, because the structure should be symmetrical; he overlooked the fact that resonance of the type **13**—two identical canonical structures—offers perfect symmetry.

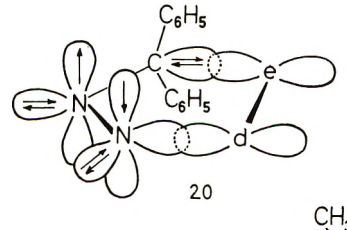
Linn's intermediate is the carbonyl ylide **4**. This follows from the close analogy with the thermal opening of the aziridine ring in **16** and **17** which gives stereospecifically the *cis–trans* isomeric azomethine ylides **18** and **19**.[36,37] The conrotation established here is in accord with the Woodward–Hoffmann prediction[3] for the isoelectronic system cyclopropyl anion → allyl anion.



16 17

18 19

Electronic Pathway of 1,3-Dipolar Cycloaddition.—On the first glance at the general scheme, one is tempted to assume that all five centers of 1,3 dipole and dipolarophile form a planar transition state. This mistake is repeated by Firestone in section E.



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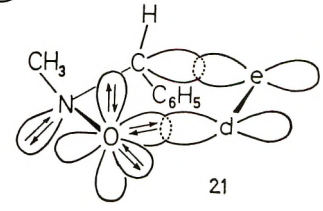


21

(28) L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.*, **94**, 290 (1961).

(29) O. L. Chapman and D. C. Heckert, *Chem. Commun.*, 242 (1966).

(30) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967).

(31) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p 15.

(32) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).

(33) See ref 1, p 644.

(34) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 40.

(35) W. J. Linn, *J. Amer. Chem. Soc.*, **87**, 3665 (1965).

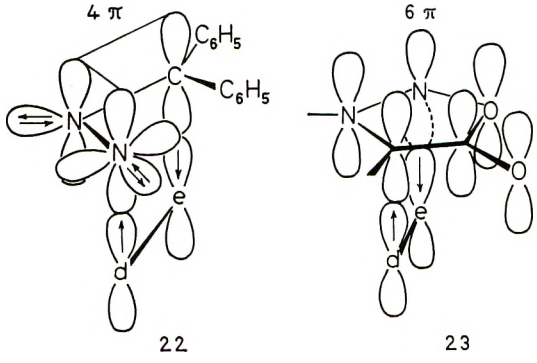
(36) R. Huisgen, W. Scheer, and H. Huber, *ibid.*, **89**, 1753 (1967).

(37) R. Huisgen, *Helv. Chim. Acta*, **50**, 2421 (1967).

A closer inspection reveals paradoxical consequences. The linear nitrilium and diazonium betaines must bend to make contact with the orbitals of the dipolarophile. The direction of bending in diphenyldiazomethane, shown in **20**, destroys the diazoalkane resonance. This kind of bending alone probably needs more energy than the $\Delta H^{\pm} = 8.0$ kcal/mol found for the whole activation process.

The nitrone **5** as an azomethine oxide is bent in the ground state. However, to reach the planar transition state **21**, twisting around the C—N bond must occur, so that the nitrone resonance is lost.

In contrast to Firestone's opinion, the Woodward–Hoffmann rules[3] cannot be applied to the transition states **20** and **21** for the cycloadditions.[38] The electrons involved on the side of the 1,3 dipole are not arranged in a proper molecular orbital. The four electrons are not even π bonded but occupy two lone-pair orbitals. Furthermore, in **21** the conjugation is damaged. A concerted cycloaddition through a low-energy transition state is inconceivable.

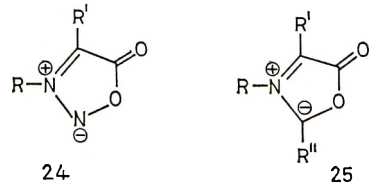


22 **23**

Formula **22** depicts the orientation complex preceding the transition state for the addition of diphenyldiazomethane to a dipolarophile de, according to our theory, first published in 1963.[33] Here, the bending of the linear 1,3 dipole *within* the horizontal plane preserves the allyl anion orbital which makes contact with the π bond of the dipolarophile. The gradual rehybridization from p to sp^3 and sp^2 orbitals, which occurs during the reaction, is accompanied by an uplifting of the middle diazoalkane nitrogen until it reaches the 1-pyrazoline plane in the product.

The "two-planes" orientation complex **22** indicates that (4 + 2) π electrons are involved in the cycloaddition process exactly as in the Diels–Alder reaction. The symmetry considerations[39] with the correlation diagrams reveal that the concerted thermal cycloaddition is allowed.[32]

We proposed the orientation complex **22** before Woodward and Hoffmann[3] published the rules for conservation of orbital symmetry. This proposal was supported by our experimental finding that sydnones **24** and mesoionic oxazolones **25** react as 1,3 dipoles



24 **25**

(38) Professor R. Hoffmann, Cornell University, personal communication.

(39) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **87**, 2045 (1965).

with alkenes and alkynes.[40,41] These cycloadditions showed all the typical features of the 1,3-dipolar type: moderate activation enthalpies, high negative activation entropies, small solvent dependence, the usual activity scale of dipolarophiles.[42]

Sydnone **24** and ψ-oxazolones **25** are planar aromatic structures. Since they exhibit azomethine imine or azomethine ylide reactivity, respectively, only an orientation complex like **23** is possible.[43] To avoid a highly improbable dichotomy of mechanistic pathways, we postulated that *all* 1,3-dipolar cycloadditions follow the pattern shown in **22** and **23**. It is quite satisfying that the "two-planes" model strengthens the close relation to Diels–Alder addition in the application of the Woodward–Hoffmann rules.

If this model for the steric course is accepted, Firestone's arguments concerning relative rates of addition to acetylenic and olefinic dipolarophiles become irrelevant. The reader is referred to our earlier discussion.[44]

Solvent Effects on Rates.—Our kinetic studies disclose that 1,3-dipolar cycloadditions are only moderately influenced by solvent polarity;[1] spreads of rate constants by a factor of no less than $^1/_6$ and no more than 10 with increasing polarity of the solvent were found.[14,30] Firestone's intuitive criticism stems from the false expectation that the disappearance of the 1,3 dipole should bring about a strong inverse dependence on solvent polarity.

However, the term 1,3 dipole should not be misunderstood to imply a high dipole moment. The charge compensation by resonance of type **12** or **13** is often quite extensive as shown by $\mu = 1.42$ D for diphenyldiazomethane or 1.56 D for phenyl azide. Furthermore, if one sums the resonance structures of **12** and **13**, the anionic charge is distributed on either side of the positive center, giving a "tripole."[45] Such "tripoles" seem to be poorly solvated. On the other hand, the dipole moments of cycloadducts often approach the ones of the corresponding 1,3 dipoles or even exceed them.

We regard the magnitude of solvent effects as entirely adequate for the concerted pathway of 1,3-dipolar cycloaddition. With the supposition of zero solvent dependence on rate, one can calculate the dipole moment of the transition state from those of the two reactants on the basis of Kirkwood's theory.[46] We have compared such values with dipole moments of the adducts. Successful estimates of solvent influences on rates were based on the model of a continuous transition from reactants to adduct (one-step process).[1,47]

Even additions of those 1,3 dipoles whose dipole moment exceeds 5 D are slowed down only moderately with increasing solvent polarity. How far has bond

(40) R. Huisgen, R. Grashey, H. Gotthardt, and R. Schmidt, *Angew. Chem. Intern. Ed. Engl.*, **1**, 48 (1962).

(41) R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, **1**, 49 (1962).

(42) R. Huisgen, The Chemical Society, Special Publication No. 21, The Chemical Society, London, 1967, p 51.

(43) For the sake of clarity, lone pair orbitals of the N and O atoms of the sydnone ring in formula **23** have been omitted.

(44) See ref 1, pp 639 and 645.

(45) In a correcter terminology it would be a quadrupole.

(46) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934). This theory has been developed into a correlation between rate constants of bimolecular reactions and dielectric constants of solvents by S. Glasstone, K. L. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p 419.

(47) R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).

formation progressed in the transition state? If the orientation complex (like 22 and 23) is formed, the major part of the "entropy price" is paid. Our guess, that the formation of the two new σ bonds has reached some 20 or 30%, should not be taken too literally. Nevertheless, 1,3 dipoles with large moments should still possess much of their polarity in the transition state.

In our opinion, the low solvent dependence is much less compatible with the formation of Firestone's diradical intermediate in the rate-determining step. According to recognized principles, the transition state should be close to the structure of a high-energy intermediate. In cases of more polar 1,3 dipoles, one should anticipate a sharper drop of rate constant with increasing solvent polarity.

Conjugation and the Activity of the Dipolarophile.—Conjugation with *electron-attracting* or *electron-releasing* substituents increases the dipolarophilic activity of a multiple bond. If one plots the electron density of an olefinic double bond *vs.* cycloaddition rates, U-shaped curves are obtained which are different for various 1,3 dipoles.

We have explained this phenomenon by two effects which might well be interrelated:[1,32] (1) conjugation increases the polarizability of the π bond of the dipolarophile; (2) concerted formation of the two new σ bonds is not necessarily synchronous, *i.e.*, a precise "marching-in-step." Unequal progress of bond formation in the transition state leads to partial charges, which can be stabilized by substituents.

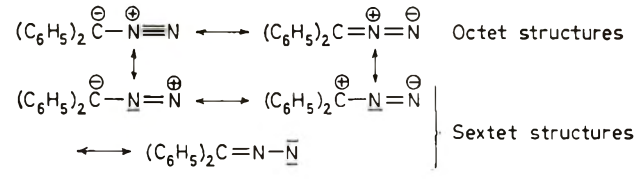
Firestone regards effect 2 as "an important departure from the concerted cycloaddition theory." We cannot agree. The idea of unequal bond formation and breaking has become a fruitful rationale in the interpretation of many mechanisms. Is it necessary to remind the reader of the spectrum of solvolysis reactions which varies in the amount of bonding by the nucleophile in the transition state? Has not the same principle been very successful in classifying E2 reactions?[48,49] There is no theoretical reason to renounce this principle in the treatment of cycloadditions.

Rate increase by conjugation is one of many characteristics which strengthens the close mechanistic relationship between 1,3-dipolar cycloaddition and the Diels–Alder reaction. A careful weighing of all mechanistic criteria recently led Sauer[50] to favor strongly the concerted mechanism for the latter reaction.[51]

Orientation Phenomena.—The largest section of Firestone's paper deals with orientation. These phenomena constituted the starting point and the central argument of the diradical hypothesis. We join Firestone in the opinion that the addition reactions of azomethine imines do not fit the diradical theory, and the orientations followed by organic azides do not conform to a best diradical rule. In our eyes, diazoalkanes also preferably show orientations which are not in harmony with the best diradical. By supplementing the examples above with unpublished data or reactions not considered by Firestone, one approaches a statistical 50:50 of orientations consonant and dissonant with the diradical hypothesis; only two orientations are possible.

Some 1,3-dipolar cycloadditions are reversible. The suspicion raised by Firestone that separation of kinetic and thermodynamic control has not always been achieved is undeserved. We investigated this point carefully. The orientation phenomena which we published in our some 70 papers in the field are *kinetically* determined.

Instead of expanding grossly the list of discrepancies between observed orientations and the ones predicted for the diradical intermediate, we wish to emphasize a major point. Firestone's assumption that many orientations are in conflict with the concerted mechanism is the result of a misconception. The widespread contention that the electrophilic end of the dipolarophile should link with the negative end of the 1,3 dipole is built on sand. The formal negative charge of the 1,3 dipole is distributed on either side of the onium center as illustrated by diphenyldiazomethane. In the sextet structures, the formal charges are interchangeable. (Normally we avoid the use of sextet structures in formulation, because they are often misinterpreted as "reaction formulae.") What is the nucleophilic end of diphenyldiazomethane? The direction of the small dipole moment indicates that the outer nitrogen bears a larger part of the negative charge. However, a carbanion is more nucleophilic than an anionic nitrogen.[52]



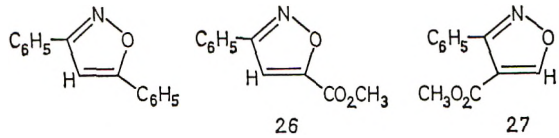
As we have pointed out repeatedly,[1,53] *it is not meaningful to assign an electrophilic and a nucleophilic end to a 1,3 dipole.* Otherwise, it would be possible to define a direction of the cyclic electron shift in the addition process—clockwise or counterclockwise. Does the fact that the two ends of ozone are identical decrease its 1,3-dipolar activity? A consideration of the MO description of concerted additions reveals that it is only meaningful to attribute a certain electron density to the incipient σ bonds in the transition state.

The orientation phenomena in 1,3-dipolar as well as Diels–Alder addition offer perhaps the biggest *unsolved* problem in the field. We have discussed the possible interplay of steric and electronic factors, but we never pretended to have a full understanding. Rate and orientation phenomena in aromatic and aliphatic substitutions have been studied for decades; one knows a lot, but consistency is still lacking. Systematic exploration of substituent effects in concerted cycloaddition is still in its infancy. Thus, the detailed discussion may be limited to a few examples which prove the concertedness of the cycloaddition in question.

1. Many additions which were described earlier as unidirectional turned out to give mixtures. Firestone

(48) C. K. Ingold, *Proc. Chem. Soc.*, 265 (1962).
(49) J. F. Bunnett, *Angew. Chem.*, **74**, 731 (1962).
(50) J. Sauer, *Angew. Chem. Intern. Ed. Engl.*, **6**, 16 (1967).
(51) Compare R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., London, 1964, p 739.
(52) In the discussion of diazoalkane and azide additions, Firestone does not distinguish properly between nucleophilicity and the amount of negative charge.
(53) R. Huisgen, *Bull. Soc. Chim. Fr.*, 3431 (1965).

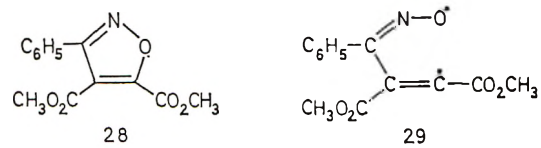
uses benzonitrile N-oxide additions as witness no. 1 for the diradical concept. This nitrile oxide combines with methyl propiolate to give a 72:28 mixture of the isoxazoles **26** and **27**,[54] hardly compatible with a diradical intermediate. Why should the relative addition



26 27

k_2(rel.) ≡ 1.0 7.0 2.7

constant, measured by competition experiments,[55] be larger for dimethyl acetylenedicarboxylate (formation of **28**) than for methyl propiolate? The second methoxycarbonyl group cannot contribute much to the



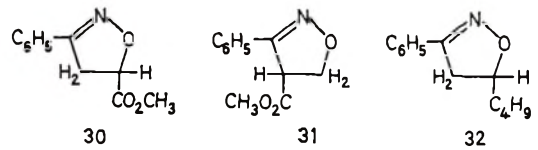
28 29

k_2(rel.) 27

stability of **29**. The acceleration by conjugating substituents at *either* side of the acetylenic bond leaves no doubt that *both centers* participate in the rate-determining step.

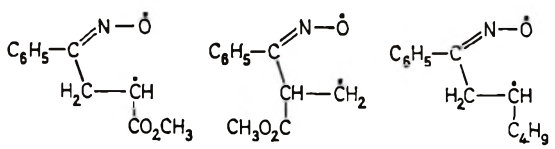
The same effect appears in the cycloadditions of the azomethine imine **2** (chlorobenzene, 80°)[56] or N-methyl-C-phenylnitrone **5** (toluene, 85°),[19] where dimethyl acetylenedicarboxylate adds 11 times or 29 times faster, respectively, than methyl propiolate. Using C-methyl-N-phenylsydnone (**24**) the following values for 10^5k_2 were found: 1-tetradecyne, 6.0; methyl propiolate, 823; dimethyl acetylenedicarboxylate, 2580 (*p*-cymene, 140°).[57]

2. Benzonitrile N-oxide adds to methyl acrylate to give the methyl 5-carboxylate **30** and the 4-carboxylate **31** in 96 and 4% yield.[9] That corresponds to $\Delta\Delta G^{\pm}$ = 1.9 kcal/mol for the two directions; the energy difference between the corresponding diradicals **33** and **34** should amount to well above 12 kcal/mol. The better



30 31 32

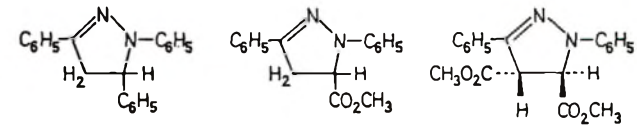
k_2(rel.) 27 1.1 ≡ 1.0



33 34 35

stabilization of **35** compared with that of **34** does not show up in the rate factors.

3. The *quantitative* evaluation of substituent effects is more advanced for cycloadditions of diphenylnitrilimine. The following sequence discloses the increasing dipolarophilic activity in the series 1-alkene, methyl acrylate, dimethyl fumarate.[32] Substituents at either



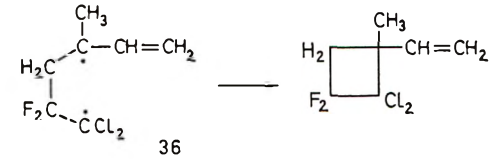
k_2(rel.) ≡ 1 343 2 050

end of the ethylene system contribute additively to the activation energy of the cycloaddition as demonstrated for many dipolarophiles.[32] Our numerical separation of substituent effects into steric and electronic factors contains some arbitrariness, as Firestone mentions. However, the net effects satisfy the additivity principle within certain limits.

One anticipates that the rate constant of a concerted addition to a substituted ethylene will be the product of k_2 (ethylene) and all substituent factors, but how should the Firestone diradical from diphenylnitrilimine and dimethyl fumarate profit from the second methoxycarbonyl, located at a saturated center?

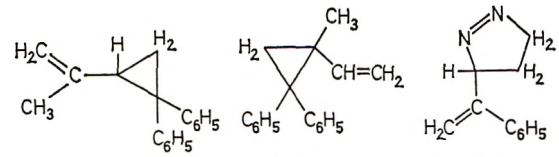
4. Also the dienophilic activity of ethylene in Diels–Alder reactions is increased by substitution at either carbon atom. Rate constants for cyclopentadiene additions to cyanoethylenes[58] at 20° spread over an impressive range ($10^5k_2 \cdot mol^{-1}$ sec^{-1}): $H_2C{=}CHCN$ (1.0); $NCCH{=}CHCN$ (81); $H_2C{=}C(CN)_2$ (45,500); $NCCH{=}C(CN)_2$ (~500,000); $(NC)_2C{=}C(CN)_2$ (~43,000,000).

5. The methylated double bond of isoprene adds 1,1-dichloro-2,2-difluoroethylene 5.5 times faster than the 3,4 double bond.[59] The diradical **36** is stabilized by the methyl group as well as the vinyl residue.



36

In contrast, isoprene combines with diphenyldiazomethane at 20° preferentially at the *unmethylated* double bond. The pyrazolines suffer nitrogen loss and the cyclopropanes **37** and **38** were obtained in an 88:12 ratio.[60]



37 38 39

The phenyl group in 2-phenylbutadiene should stabilize an intermediate radical even better. However, diphenyldiazomethane and diazomethane add solely to the *unsubstituted* double bond; in the latter case, the 1-pyrazoline **39** was isolated.[60]

The transition state of polycentric additions is very sensitive to *steric* effects. The least substituted dipolarophilic multiple bond is normally preferred. Thus,

(54) R. Sustmann, Ph.D. Thesis, University of München, 1965.
(55) M. Christi, W. Mack, and K. Bast, München, unpublished experiments.
(56) Measurements by M. V. George and A. S. Kende, München, 1962.
(57) R. Huisgen and H. Gotthardt, *Chem. Ber.*, **101**, 1059 (1968).
(58) J. Sauer, H. Wiest, and A. Mielert, *ibid.*, **97**, 3183 (1964).
(59) P. D. Bartlett and L. K. Montgomery, *J. Amer. Chem. Soc.*, **86**, 628 (1964).
(60) Unpublished experiments by A. Ohta, München, 1966.

2-substituted butadienes offer a sensitive probe to distinguish between a diradical intermediate and a concerted pathway. Encumbrance of the dipolarophilic center and diradical stabilization lead to opposite predictions for the activity of substituted *vs.* unsubstituted double bonds.

Other 1,3 dipoles show analogous phenomena. Diphenylnitrilimine adds to the less encumbered double bond of isoprene 4.0 times faster than to the one bearing the methyl group.[61]

Historical Note.—The cycloadditions of aliphatic diazo compounds were discovered[62] in 1888, and those of organic azides[63] in 1893. In a very valuable paper, published in 1938, Smith[64] collected the available data on 1,3 additions without differentiating between additions of bases H–B and cycloadditions. The special driving force for the cyclic reaction path stemming from a fundamentally dissimilar mechanism was not recognized. In 1938 (as in 1900) only cycloadditions of diazoalkanes and azides were known.

That Staudinger's nitrenes[65] and nitrones were considered in this paper[64] as formally derived from ketenes and allenes did not contribute to a clear classification of dipolar reagents. Perhaps for this reason, Smith's review did not attract much attention as shown by the small number of papers on the subject published between 1938 and 1958.

(61) Experiments by W. Fliege, München, 1967.
(62) E. Buchner, *Ber. Deut. Chem. Ges.*, **21**, 2637 (1888).
(63) A. Michael, *J. Prakt. Chem.*, [2] **48**, 94 (1893).
(64) L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).
(65) Staudinger's nitrenes had another structure. Cycloadditions of azomethine ylids *alias* nitrenes were first described by R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

We have reported elsewhere the train of thought which led to the general concept of 1,3-dipolar cycloaddition in 1958;[66] the original mechanistic consideration concerned the addition of diazoalkanes to angle-strained double bonds.

Another generalization recently revealed a synthetic principle which makes accessible a large number of six-membered heterocycles.[67] The term *1,4-dipolar cycloaddition* should not be misinterpreted; there is good experimental evidence and theoretical reason to characterize this scheme as a two-step process passing through a zwitterionic intermediate.[68] The *1,4 dipole* combines only with those dipolarophiles which display pronounced electrophilic or nucleophilic reactivity. This limits severely the range of applicable dipolarophiles.[69]

Just the opposite is observed for *1,3-dipolar cycloaddition*. Here nearly every multiple-bond system including heteroatoms can act as a dipolarophile. The result is an amazingly wide scope of this synthetic principle[16] which is far from being exhausted. It is a fascinating idea that 1,3-dipolar addition owes this wide scope to the concerted mechanism which avoids the necessity of charge separation along the reaction pathway.

The position that 1,3-dipolar cycloadditions, at least those studied so far, do *not* conform to one general mechanism is unfounded.

(66) R. Huisgen, *Proc. Chem. Soc.*, 357 (1961).
(67) R. Huisgen and K. Herbig, *Ann.*, **688**, 98 (1965).
(68) R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967).
(69) A brief review on 1,4-dipolar cycloaddition will be published in the Proceedings of the First International Congress of Heterocyclic Chemistry, Interscience Publishers, Inc., New York, N. Y., 1968.

Photochemistry of Cyclic Mercaptoles[1]

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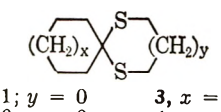
Received October 11, 1967

The photochemistry of the mercaptoles 1–4 has been investigated. The major pathway for reaction of the ethylene mercaptoles 1 and 2 involved elimination of the elements of ethylene sulfide to form the corresponding cyclic thione which was isolated as the dimer in the case of 1. The thione or its dimer underwent secondary photochemical reactions to form the corresponding disulfide, sulfide, and mercaptan. The major pathway for reaction of the propylene mercaptoles, **3** and **4**, involved over-all isomerization of one of the geminal sulfur atoms to an adjacent carbon atom; the ratio of *cis/trans* product in each case was approximately 8:1.

The ultraviolet spectra of mercaptals and mercaptoles show an absorption band in the region of 235–250 mμ ($\epsilon \sim 250$–850) which has been attributed to an excited state involving sulfur–sulfur interaction.[4,5] In view of this excited-state interaction, the photochemistry of mercaptoles has been investigated to determine the nature of products from excitation at this long-wavelength absorption band. The compounds selected for study were the ethylene and propylene mercaptoles **1**–**4**. Mercaptole **1** was studied under a variety of conditions to determine those which gave optimum yield of the major products; these conditions were then applied to mercaptoles **2**–**4**.



1, $x = 1; y = 0$ **3**, $x = 1; y = 1$
2, $x = 0; y = 0$ **4**, $x = 0; y = 1$

The photolysis of 1,4-dithiaspiro[4.5]decane (**1**) under various conditions yielded the product mixtures listed in Table I. Runs 5–7 were analyzed only for the major product (**7**). A thin film of brown polymer coated the walls of the reaction vessel when the Hanovia high-pressure Hg lamp was used; no such polymer formation was observed with the low-pressure Hg lamps. Cyclohexane, *n*-hexane, and Freon-113 were satisfactory solvents. The formation of a similar product mixture in these three solvents indicates that no significant amount of products arises from reaction with solvent. No reaction was observed in anhydrous methanol.

(1) Supported by National Science Foundation Grant No. GP-5761.
(2) National Institutes of Health Predoctoral Fellow.
(3) Alfred P. Sloan Fellow, 1963–1967.
(4) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 84 (1949).
(5) S. Oae, W. Tagaki, and A. Ohno, *Tetrahedron*, **20**, 437 (1964).

SCHEME I

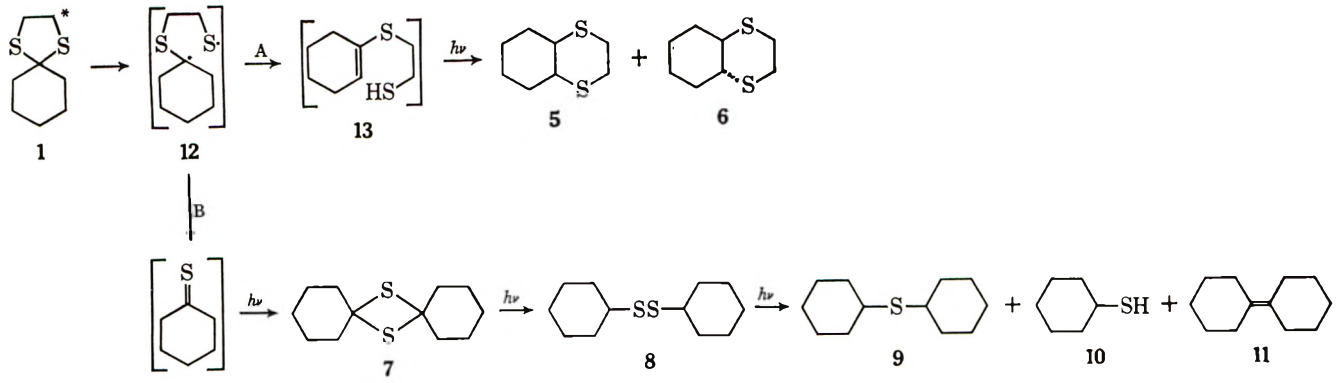


TABLE I

PRODUCTS FROM PHOTOLYSIS OF 1

Reaction no.	Light source[a]	Solvent	Concn, *M*	Time, hr	Products, % yield 5	6	7	8	9	10	11	Unreacted 1
1	A	Cyclohexane	0.112	94.5	<1	1	9	11	4	2	2	66
2	B	Cyclohexane	0.16	9	<1	<1	14	2	2	1	1	76
3	B	*n*-Hexane	0.12	8	<1	<1	23	3	1	<1	<1	68
4	B	Freon-113	0.12	12	1	2	13	<1	2	1	<1	75
5	A	Cyclohexane	0.08	5			5					
6	A	Cyclohexane	0.034	10			4					
7	A	Methanol	0.20	16			0					

[a] A means a Hanovia type A, 550-W lamp; B means Rayonet photochemical reactor, 2537-Å, low-pressure Hg vapor lamps.

The major product was 7,14-dithiadispiro[5.1,5.1]-tetradecane (**7**) and it was the first product detected when the reaction was followed by gas chromatography. The yield of **7** reached its maximum value at 8–12 hr; continued photolysis slowly decreased the yield of **7** but increased the yield of **8**–**11**. Since this behavior indicates **7** was undergoing further photochemical reaction, the photolysis of **7** was investigated. After a period of 8 hr, **7** was converted in 8.5% yield into the disulfide **8**. Photolysis of this disulfide (**8**) produced **9** (1%), **10** (2%), **11** (1%), and **7** (2%). The remainder of the reaction mixture was unreacted disulfide. These results are in agreement with the previously reported photochemical studies of disulfides.[6-8]

It appears that photo-excited mercaptole **1** fragments to the diradical **12** which undergoes further reaction by either one of two pathways (Scheme I, A or B). Evidence for the intermediacy of **12** rests on the esr spectrum[9] obtained during photolysis of pure **1** at liquid nitrogen temperatures. The spectrum shows an unsymmetrical pattern with five distinct *g* values: three are indicative of the primary sulfur radical[10] (2.0261, 2.0056, 1.9968) and the remaining (2.0168, 1.9831) may be due to the tertiary carbon radical adjacent to sulfur. Although no evidence exists for the intermediacy of **13**, it would appear to be a reasonable intermediate in the formation of the dithians **5** and **6**, particularly in view of the ratio of *cis/trans* isomers obtained in the photolysis of mercaptoles **3** and **4** as described later. Intermediate **13** could arise from **12** through intramolecular hydrogen atom abstraction by the primary sulfur radical. The possibility of a concerted migration of the sulfur atom or hydrogen atom can not be excluded by the data available.

The formation of **7** undoubtedly proceeds through initial formation of cyclohexanethione. Solutions of **1** immediately turn pink on irradiation; cyclohexane thione is deep red in color, λ_{max} 495 mμ (ϵ 10).[7,11] Products **8**–**11** arise from **7** as described earlier. The formation of **7** in the photolysis of the disulfide **8** undoubtedly proceeds through formation of cyclohexanethione. Rosengren[8] has shown that **8** is converted into cyclohexanethione on photolysis in a rigid glass at 77°K.

The conditions selected for photolysis of **2**–**4** were cyclohexane solvent and the Rayonet 2537-Å low-pressure Hg vapor lamp source. The results are listed in Table II.

The photochemistry of 1,4-dithiaspiro[4.4]nonane, **2**, appeared to be essentially the same as **1**. The presence of dithians **14** and **15** was indicated by comparison of the mass spectra of samples collected by gas chromatography with authentic samples. The small quantities available from the photochemical reaction, however, were not pure and could not be separated from the contaminating materials.

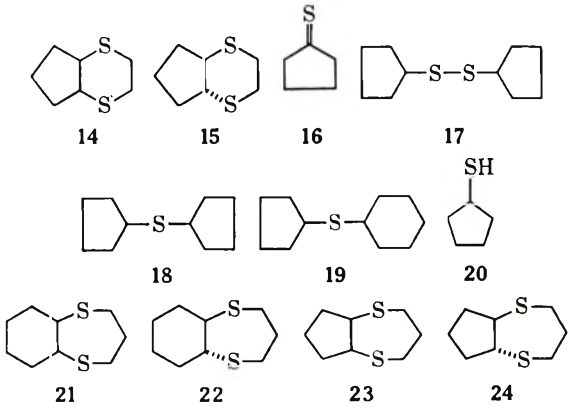
The predominant reaction involves elimination of the elements of ethylene sulfide with formation of cyclopentanethione (**16**). Although the dimer of thione **16** has been isolated from other photochemical reactions,[12] there was no evidence for its formation in this reaction. Either the dimer undergoes photochemical reaction as rapidly as it is formed or the excited thione reacts to form **17**–**19** in preference to dimerization. The major product in this reaction, **19**, arises from reaction of thione **16** with solvent. Although **17** could arise from

(6) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).
(7) K. Rosengren, *Acta Chem. Scand.*, **16**, 1401 (1962).
(8) K. Rosengren, *ibid.*, **16**, 2284 (1962).
(9) We wish to thank Professor K. Bowers of this department for measuring the spectrum.
(10) J. J. Windle, A. K. Wiersema, and A. L. Tappel, *J. Chem. Phys.*, **41**, 1996 (1964).
(11) M. J. Janssen, *Rec. Trav. Chim. Pays-Bas*, **79**, 464 (1960).
(12) M. C. Panek and G. A. Berchtold, unpublished work from these laboratories.

TABLE II

PRODUCTS FROM PHOTOLYSIS OF 2–4

Mercaptole	Concn, M	Time, hr	Products (% yield)							Unreacted starting material (%)
2	0.121	18	**14** (<3)	**15** (<1)	**16** (4)	**17** (5)	**18** (3)	**19** (14)	**20** (1)	**2** (64)
3	0.182	42.5	**21** (40)	**22** (6)						**3** (12)
4	0.113	8	**23** (39)	**24** (5)						**4** (55)



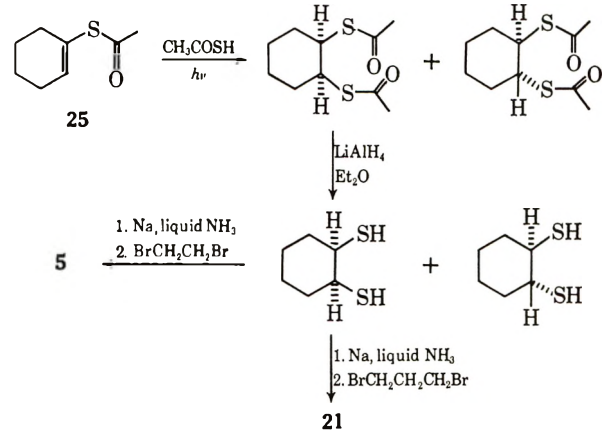
the thione dimer, it is probably formed from dimerization of the cyclopentane thiyl radical.

1,5-Dithiaspiro[5.5]undecane, **3**, undergoes photochemical reaction to the two isomers, **21** and **22**, listed in Table II. These two products and unreacted mercaptole **3** account for 58% of the starting material. There are at least 13 other components in the reaction mixture, all of which are formed only in minor yield. The rate of formation of **21** and **22** leveled off after approximately 8 hr. In a similar fashion, the photolysis of 1,5-dithiaspiro[5.4]decane, **4**, showed little change after 8 hr and produced **23** and **24** as the major products with only slight traces of minor products.

Thus, it appears that the major pathway for reaction of the diradical, initially formed from the propylene mercaptoles, involves hydrogen atom abstraction by the primary thiyl radical to form the 3-mercaptopropylthiocycloalkene which then undergoes cyclization. The ratio of *cis/trans* isomers from mercaptoles **3** and **4** are essentially that which one would expect from radical addition of mercaptan to the substituted olefinic system.[13]

The structures of all photochemical products except **7** and **16** were established by comparison with authentic samples. The structure of **7** was unambiguous from the spectral data and analysis. The structure of thione **16** was assigned on the basis of its visible spectrum, λ_{max}^{EtOH} 495 mμ, and its gas chromatographic retention time. It rapidly polymerized on standing. The synthesis of all authentic samples was straightforward (see Experimental Section) except for the *cis* isomers **5**, **14**, **21**, and **23**. The authentic samples of **5** and **21** were prepared as follows. Pyrolysis of the diacetate of 1,1-cyclohexanedithiol produced 1-cyclohexene thiolacetate (**25**) which was converted into an 85:15 mixture of *cis*- and *trans*-1,2-cyclohexane bisthiolacetates by the light-catalyzed addition of thiolacetic acid. Reduction of the mixture with lithium aluminum hydride gave a similar mixture of *cis*- and *trans*-1,2-cyclohexanedithiols in quantitative yield which were separated by distillation. Cyclization of the bis sodium salt of the *cis* isomer with 1,2-dibromoethane and with 1,3-dibromopropane produced **5** and **21**, respectively (Scheme II).

SCHEME II



The authentic samples of **14** and **23** were prepared in a similar fashion from 1-cyclopentene thiolacetate except that the *cis–trans* isomers were separated by distillation as the diacetates and the pure *cis*-1,2-cyclopentane bisthiolacetate was reduced to the *cis*-dithiol.

Experimental Section[14]

Photolysis of 1,4-Dithiaspiro[4.5]decane (1). A.—A solution of 11.15 g (0.064 mol) of **1**[15] [λ_{max}^{EtOH} 242 mμ (ε 316)] in 350 ml of reagent grade cyclohexane[16] was irradiated for a period of 9 hr in a Rayonet photochemical reactor[17] using lamps with a maximum output at 2537 Å. A stream of oxygen-free, dry nitrogen was passed through the solution during the photolysis and then through a Dry Ice–acetone trap followed by a solution of bromine in carbon tetrachloride. After 30 min the solution had turned from colorless to bright pink; after 4 hr the solution had become and remained pale orange. At no time was any insoluble polymeric material noted. The crude photolysis solution was concentrated *in vacuo* to yield 9.94 g of an orange liquid. The mixture was analyzed by gas chromatography; the temperature was programmed from 100–230° at a rate of 2°/min. Comparison with authentic samples showed the mixture to consist of the components listed with reaction no. 2 of Table I. The Dry Ice–acetone trap contained only solvent and a trace of white polymeric material. The bromine in CCl_4 solution contained 1,2-dibromoethane corresponding to an 18% yield of ethylene as determined by integrating the nmr spectrum of a known volume of

(13) N. A. LeBel and A. DeBoer, *J. Amer. Chem. Soc.*, **89**, 2784 (1967), and references cited therein.

(14) All melting points are corrected, and all boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 237 or 337 recording spectrophotometer. The ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. The nmr spectra were recorded on a Varian A-60 nmr spectrometer, and chemical-shift data are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Mass spectra were recorded on a Consolidated Electrodynamics Model 21-130 mass spectrometer with an ionizing potential of 68 V and are recorded in percentages relative to the most intense peak as 100%. Elemental analyses were performed by Scandinavian Microanalytical Laboratory or Galbraith Laboratories, Inc. Gas chromatograms were recorded on an F & M Model 810 gas chromatograph and were calibrated with bicyclohexyl as an internal standard; the column used was an 8-ft 20% SE-30 on Chr P, 80–100 mesh.

(15) H. Fuhrer and H. Günthard, *Helv. Chim. Acta*, **45**, 2036 (1962).

(16) Passed through Merck acid-washed alumina prior to use.

(17) Southern New England Ultraviolet Co., Middletown, Conn., Model RPR 100: 35 W; reactor barrel, 10 in. (diameter) by 15 in. (depth).

solution containing a known amount of *p*-dichlorobenzene as a reference standard.

The structure of **7** was established from the following data: mp 128–129° (lit.[18] 132–133°); $\nu_{max}^{CCl_4}$ 2955, 2945, 2930, 2855, 2845, 1450, 1435, 1425, 1270, 1255, 1245, and 1195 cm^{-1}; λ_{max}^{EtOH} 285 mμ (ε 34); mass spectrum, *m/e* 228 (11%), 185 (2%), 114 (100%), 109 (4%), 81 (87%), and 71 (39%).

Anal. Calcd for $C_{12}H_{20}S_2$: C, 63.09; H, 8.82; S, 28.07. Found: C, 63.19; H, 8.81; S, 28.09.

B.—A solution of 10 g (0.056 mol) of **1** in 500 ml of cyclohexane[16] was irradiated with a 550-W Hanovia, type A, mercury arc lamp contained in a water-cooled quartz immersion well. The solution was swept continuously with a stream of oxygen-free, dry nitrogen. The nitrogen stream was passed through a Dry Ice–acetone trap and then through a solution of bromine in CCl_4. The irradiation was continued for a period of 94.5 hr; it was necessary to clean the immersion well of a thin brown polymeric film 11 times during the course of the photolysis. At the end of the photolysis the clear golden yellow solution was concentrated *in vacuo* to yield 9.80 g of orange-brown liquid which was analyzed by gas chromatography as described in A. The results are listed with reaction 1 in Table I.

The other photolyses of **1** listed in Table I were carried out as described in part A or B depending on the light source used.

Photolysis of 2, 3, and 4.—The photolysis of **2**[19] [λ_{max}^{EtOH} 245 mμ (ε 274)], **3**[20] [λ_{max}^{EtOH} 247.5 mμ (ε 833)], and **4** [$\lambda_{max}^{isooctane}$ 251 mμ (ε 732)] was carried out as described in section A for the photolysis of **1**. The conditions and the product analyses are listed in Table II.

1,5-Dithiaspiro[5.4]decane (4).—To a refluxing solution of 77.7 g (0.924 mol) of cyclopentanone in 300 ml of benzene containing 0.5 g of *p*-toluenesulfonic acid was added, dropwise with stirring, 100 g (0.924 mol) of 1,3-propanedithiol. The water formed in the reaction was removed as the benzene azeotrope by a Dean–Stark trap. The brownish solution was washed with three 25-ml portions of 10% aqueous sodium hydroxide and three 250-ml portions of water. The organic layer was dried (Na_2SO_4), the benzene was removed *in vacuo*, and the resulting yellow liquid was distilled to yield 132 g (82%) of clear, colorless liquid: bp 86–87° (0.05 mm); $\nu_{max}^{CCl_4}$ 2955, 2910, 2880, 1450, 1430, 1310, 1280, 1245, 1185, 1170, 1120, 1040, 1005, 950, 910, 870, and 680 cm^{-1}; $\lambda_{max}^{isooctane}$ 251 mμ (ε 732); nmr (CCl_4), δ 2.92 (triplet with fine splitting, 4 H) and 2.0 ppm (multiplet, 10 H); mass spectrum, *m/e* 174 (29%), 145 (18%), 141 (8%), 113 (7%), 100 (63%), 71 (32%), 67 (100%), 45 (42%), and 41 (65%).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.10; H, 8.09; S, 36.80. Found: C, 55.30; H, 8.10; S, 36.85.

Photolysis of 7, 14-Dithiadispiro[5.1,5.1]tetradecane (7).—A solution of 400 mg (0.0031 mol) of **7** in 20 ml of *n*-hexane was irradiated for a period of 12 hr as described in section A for the photolysis of **1**. The brown solution was concentrated *in vacuo*, dissolved in the minimum amount of methylene chloride and the resulting solution was analyzed by gas chromatography. The only material present other than starting material in a 1% yield was dicyclohexyl disulfide (absolute yield 8%).

Photolysis of Dicyclohexyl Disulfide (8).—A solution of 6.5 g (0.028 mol) of **8** in 350 ml of cyclohexane[16] was irradiated for 12 hr as described in section A for the photolysis of **1**. The solvent was removed *in vacuo*, and the residue was analyzed by gas chromatography. The products present were **7** (2%), **9** (1%), **10** (2%), and **11** (1%).

Dicyclohexyl disulfide (8) was prepared in 57% yield as previously reported,[21] bp 100° (0.05 mm).

Dicyclopentyl disulfide (17) was prepared in 54% yield as previously reported,[22] bp 69° (0.05 mm).

Dicyclopentyl sulfide (18) was prepared in 30% yield as previously reported,[22] bp 164° (21 mm).

Cyclohexyl cyclopentyl sulfide (19) was prepared in 84% yield as previously reported,[22] bp 136–137° (13 mm).

Cyclopentyl mercaptan (20) was prepared in 50% yield as previously reported,[22] bp 130°.

***trans*-1,2-Cyclohexanedithiol** was prepared in 80% yield from *trans*-cyclohexane-1,2-dithiol trithiocarbonate[23] as previously reported,[24] bp 94–98° (9 mm).

trans-**2,5-Dithiabicyclo[4.4.0]decane (6).**—Sodium metal (0.70 g) was added to 2 g (0.0134 mol) of *trans*-1,2-cyclohexanedithiol in 50 ml of liquid NH_3. To this blue solution was added 2.63 g (0.014 mol) of 1,2-dibromoethane, the blue color being discharged immediately. The NH_3 was evaporated after standing for 2 hr, the residue was treated with ether and water, and the layers were separated. The ethereal layer was washed with water, with 6 *N* HCl, and again with water. It was dried ($MgSO_4$) and concentrated *in vacuo* to give 2 g (86%) of a white crystalline solid, mp 72–74°. Chromatography on alumina and sublimation *in vacuo* at room temperature gave 1.04 g (45%) of product: mp 76–77°; $\nu_{max}^{CCl_4}$ 2940, 2915, 2860, 1450, 1420, 1335, 1295, 1280 and 1110 cm^{-1}; λ_{max}^{EtOH} shoulder at 230 mμ (ε 200); nmr (CCl_4), δ 1.50 (multiplet, 8 H) and 2.93 ppm (multiplet, 6 H); mass spectrum, *m/e* 174 (56%), 146 (10%), 131 (13%), 114 (60%), 105 (23%), 81 (100%), 67 (22%), 61 (37%), 59 (46%), 45 (47%), and 41 (30%).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.09; S, 36.78. Found: C, 54.91; H, 8.26; S, 36.90.

trans-**2,6-Dithiabicyclo[5.4.0]undecane (22).**—This compound was prepared from 2.20 g (0.015 mol) of *trans*-1,2-cyclohexanedithiol and 4.60 g (0.0156 mol) of 1,3-diiodopropane except that pentane was used in place of ether as the organic solvent. The pentane layer was dried (Na_2SO_4) and concentrated *in vacuo* to give 1.01 g of white crystalline material which was chromatographed on alumina (hexane solvent) to give 507 mg (17%) of product: mp 57–58°; $\nu_{max}^{CCl_4}$ 2950, 2930, 2915, 2870, 2860, 1460, 1430, 1320, 1280, 1220, 1200, 1120, 1055, 995, and 880 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ε 309); nmr (CCl_4), δ 2.90 (multiplet, 6 H) and 1.59 ppm (multiplet, 10 H); mass spectrum, *m/e* 188 (52%), 146 (6%), 119 (11%), 114 (34%), 106 (100%), 81 (55%), 73 (35%), 45 (50%), and 41 (67%).

Anal. Calcd for $C_9H_{16}S_2$: C, 57.39; H, 8.56; S, 34.05. Found: C, 57.11; H, 8.56; S, 34.26.

***trans*-1,2-Cyclopentanedithiol.**—To a slurry of 2.6 g (0.068 mol) of $LiAlH_4$ in 50 ml of dry ether was added, dropwise with stirring, under an atmosphere of N_2, 7.4 g (0.042 mol) of *trans*-1,2-cyclopentanedithiol trithiocarbonate[23] in 150 ml of dry dimethoxyethane. The mixture was stirred overnight at room temperature, the excess $LiAlH_4$ was decomposed with water, and the mixture was acidified with 10% HCl. The organic layer was separated and the aqueous layer was extracted with 75 ml of pentane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was distilled to give 3.13 g (55%) of product: bp 97–98°(21 mm); $\nu_{max}^{CCl_4}$ 2985, 2885, 2570, 1475, 1460, 1330, and 1235 cm^{-1}; nmr, δ 1.93 (broad multiplet, 8 H), 1.78 (singlet, 1 H), and 1.72 ppm (singlet, 1 H).

Anal. Calcd for $C_5H_{10}S_2$: C, 44.73; H, 7.50; S, 47.76. Found: C, 44.63; H, 7.52; S, 47.95.

trans-**2,5-Dithiabicyclo[4.3.0]nonane (15).**—To a solution of 1.0 g of *trans*-1,2-cyclopentanedithiol in 50 ml of liquid NH_3 is added 0.50 g (0.0218 g-atom) of Na. After hydrogen ceases to evolve, the blue solution is treated with 1.90 g (0.0102 mol) of 1,2-dibromoethane. The blue color disappears and a white precipitate forms. The NH_3 was evaporated after 2 hr and the residue was dissolved in H_2O and hexane. The hexane layer was separated, dried ($MgSO_4$), filtered, and evaporated. The resulting colorless liquid was chromatographed on 50 g of Merck acid-washed alumina (elution with hexane), and the major fraction was distilled to give 0.26 g (21%) of **15** which solidified and was sublimed at 25° (0.05 mm): mp 45–46°; bp 67° (0.3 mm); ν_{max}^{KBr} 2960, 2950, 2920, 2900, 2880, 2860, 1450, 1410, 1325, 1305, 1295, 1255, 1220, 1160, 1060, 940, 925, 880, 870, 825, and 680 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 225 mμ (ε 280); nmr (CCl_4), δ 2.4–3.3 (multiplet, 6 H) and 0.9–2.3 ppm (multiplet, 6 H); mass spectrum, *m/e* 160 (66%), 132 (16%), 113 (7%), 100 (78%), 67 (100%), 45 (63%), and 41 (31%).

Anal. Calcd for $C_7H_{12}S_2$: C, 52.45; H, 7.54; S, 40.01. Found: C, 52.87; H, 7.70; S, 39.64.

trans-**2,6-Dithiabicyclo[5.3.0]decane (24).**—In a 100-ml, round-bottomed, three-necked flask equipped with stirrer, gas inlet tube, Dry Ice condenser, and rubber septum was placed 1.15 g (0.05 g-atom) of sodium metal and 0.04 g of $FeCl_3$. Liquid NH_3 (75 ml) was condensed in the flask. After 30 min all of the blue color had disappeared and a slate gray precipitate of $NaNH_2$ was present. To this stirred suspension was added dropwise

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(21) K. Rosengren, *Acta Chem. Scand.*, **16**, 1401 (1962).
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(23) C. C. J. Culvenor, W. Davies, and K. H. Pansacker, *J. Chem. Soc.*, 1050 (1946).
(24) S. M. Igbal and L. N. Owen, *ibid.*, 1030 (1960).

3.1 g (0.023 mol) of *trans*-1,2-cyclopentanedithiol, followed by 10 g (0.034 mol) of 1,3-diiodopropane. The reaction vessel was kept at room temperature until the NH_3 evaporated. The mixture was treated with water and extracted with pentane. The pentane extract was washed with 10% HCl and water, dried, and concentrated *in vacuo*. Distillation of the residue gave 1.54 g (25%) of product: $\nu_{max}^{CCl_4}$ 2975, 2935, 2880, 1465, 1425, 1315, 1270, 1230, 1080, 1070, 855, and 730 cm^{-1}; nmr (CCl_4), δ 3.10 (multiplet, 6 H) and 2.00 ppm (multiplet, 8 H); mass spectrum, *m/e* 174 (21%), 141 (24%), 100 (23%), 81 (21%), 79 (21%), 67 (100%), 55 (25%), 45 (36%), and 41 (77%).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.10; H, 8.09; S, 36.80. Found: C, 54.93; H, 8.04; S, 37.01.

1-Cyclohexene Thiolacetate (25).—To a solution of 76 g (0.52 mol) of 1,1-cyclohexanedithiol[25] in 700 ml of pyridine at 0° was added 84 g (1.07 mol) of acetyl chloride over a period of 1 hr with stirring. The pyridinium hydrochloride precipitated at once and the reaction was very exothermic. The mixture was stirred 4 hr and filtered, and the pyridine was evaporated *in vacuo*. The residue was dissolved in 500 ml of hexane and extracted with 200-ml portions of 10% HCl until the aqueous layer remains colorless. The hexane layer was washed with water, dried ($MgSO_4$), and evaporated to give 95 g (79%) of pale yellow diacetate: ν_{max}^{film} 3360, 2925, 2850, 1685, 1450, 1350, 1270, 1250, 1185, 1105, 1000, 940, 890, 875, 860, 820, and 750 cm^{-1}. This oil (95 g, 0.41 mol) was dissolved in 700 ml of hexane and passed through an 8-in. column of glass helices maintained at 500° with N_2 as the carrier gas. The rate of addition was adjusted to maintain the temperature in the tube but also to allow the effluent gases to be condensed in a trap maintained at 0°. After three-fourths of the hexane solution was pyrolyzed, the hexane in the trap was evaporated and the residue was distilled. The low-boiling fraction (product) was separated from the high-boiling starting material which was added to the remaining hexane solution. The pyrolysis was continued to completion, the hexane was removed *in vacuo*, and the residue was distilled. The low-boiling fractions were combined and redistilled to give 40.5 g (62%) of product: bp 54° (0.05 mm); ν_{max}^{film} 3375, 3020, 2930, 2870, 2850, 2825, 1700, 1450, 1430, 1350, 1260, 1135, 1125, 1050, 1015, 940, 920, 915, 830, 790, and 725 cm^{-1}; λ_{max}^{hexane} 227 mμ (ϵ 4750); nmr (CCl_4), δ 6.10 (multiplet, 1 H), 2.22 (singlet, 3 H), 2.15 (multiplet, 4 H), and 1.68 ppm (multiplet, 4 H); mass spectrum, *m/e* 156 (20%), 114 (100%), 81 (95%), 71 (13%), and 43 (78%).

Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74; S, 20.52. Found: C, 61.60; H, 7.87; S, 20.46.

***cis*- and *trans*-1,2-Cyclohexane Bisthiolacetates.**—A solution of 27.7 g (0.18 mol) of **25** and 134.5 g (1.77 mol) of thiolacetic acid in a 250-ml quartz vessel was irradiated with a 500-W GE sun lamp for 48 hr. The excess thiolacetic acid was removed *in vacuo* and the residue was distilled to give 15.7 g, bp 105° (0.05 mm), of product which was shown by gas chromatography to be 84% *cis* and 16% *trans* adduct. Distillation through a 36-in. Teflon annular still gave 13.3 g (31%) but failed to effect separation of the isomers: ν_{max}^{film} 3365, 2945, 2855, 1690, 1450, 1355, 1275, 1135, 1110, 995, 955, 910, 880, 835, 755, and 705 cm^{-1}; λ_{max}^{EtOH} 233 mμ (ϵ 9000).

Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.69; H, 6.94; S, 27.60. Found: C, 51.94; H, 6.95; S, 27.39.

***cis*-1,2-Cyclohexanedithiol.**—A solution of 12.2 g (0.05 mol) of the mixture of *cis*- and *trans*-1,2-cyclohexane bisthioacetates in 100 ml ether was added with stirring over a period of 1 hr to a solution of 4.0 g (0.11 mol) of $LiAlH_4$ in 500 ml of ether. The mixture was stirred an additional 30 min, and the excess $LiAlH_4$ was destroyed by addition of water. The precipitate was dissolved by addition of HCl, and the ether layer was separated, washed with water, dried, and evaporated to give 7.6 g of crude dithiols. Gas chromatography analysis indicated the mixture to be 84% *cis* and 16% *trans*-dithiol (preparation of pure *trans* isomer reported above). Distillation through a 36-in. Teflon annular still gave 3.5 g of pure *cis* isomer: bp 107–108° (8 mm); ν_{max}^{film} 2950, 2900, 2860, 2555, 1450, 1350, 1330, 1290, 1275, 1225, 1190, 1080, 1000, 930, 880, 825, 805, 740, 715, and 675 cm^{-1}; nmr ($CDCl_3$), δ 3.25 (multiplet, 2 H), 2.50–1.0 (multiplet, 8 H), and 1.86 ppm (doublet, J = 7.5 Hz, 2 H).

Anal. Calcd for $C_6H_{12}S_2$: C, 48.59; H, 8.16; S, 43.25. Found: C, 48.88; H, 8.21; S, 42.89.

(25) J. Jentzsch, J. Fabian, and R. Mayer, *Chem. Ber.*, **95**, 1764 (1962).

***cis*-2,5-Dithiabicyclo[4.4.0]decane (5).**—This compound was prepared from 1.0 g (0.0068 mol) of *cis*-1,2-cyclohexanedithiol, 0.4 g (0.018 g-atom) of sodium metal, and 1.4 g (0.0075 mol) of 1,2-dibromoethane in 50 ml of NH_3 as described for the preparation of **6** except that hexane was used as the organic solvent instead of ether. Chromatography on 50 g of Merck acid-washed alumina (hexane solvent) and sublimation at 25° (0.2 mm) gave 0.5 g (43%) of **5**: mp 61–62°; ν_{max}^{KBr} 2940, 2850, 1440, 1405, 1285, 1270, 990, 924, 910, 875, 850, 825, 740, 690, and 680 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ϵ 440); nmr ($CDCl_3$), δ 3.10 (multiplet, 2 H), 2.80 (multiplet, 4 H), and 1.15–2.60 ppm (multiplet, 8 H); mass spectrum, *m/e* 174 (43%), 131 (3%), 113 (30%), 105 (9%), 92 (20%), 81 (100%), 67 (14%), 61 (10%), 45 (32%), and 41 (24%).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.09; S, 36.79. Found: C, 55.26; H, 8.20; S, 36.20.

***cis*-2,6-Dithiabicyclo[5.4.0]undecane (21).**—This compound was prepared from 2.0 g (0.014 mol) of *cis*-1,2-cyclohexanedithiol, 0.77 g (0.034 g-atom) of sodium metal, and 2.9 g (0.014 mol) of 1,3-dibromopropane in 50 ml of NH_3 as described for the preparation of **5**. The product was obtained as white crystals in a yield of 0.94 g (37%): mp 44–45°; ν_{max}^{KBr} 2935, 2855, 1445, 1410, 1305, 1285, 1275, 1220, 1200, 1180, 1000, 905, 880, 855, 835, 735, and 680 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ϵ 490); nmr ($CDCl_3$), δ 2.4–3.4 (multiplet, 6 H) and 1.2–2.4 ppm (multiplet, 10 H); mass spectrum, *m/e* 188 (25%), 106 (100%), 81 (16%), 73 (12%), 45 (25%), and 41 (32%).

Anal. Calcd for $C_9H_{16}S_2$: C, 57.39; H, 8.56; S, 34.05. Found: C, 57.71; H, 8.64; S, 33.80.

1-Cyclopentene Thiolacetate.—This compound was prepared from 110 g of 1,1-cyclopentanedithiol[25] by the same procedure used to prepare **25**. The crude diacetate, 126 g (71%), slowly decomposed on standing. The yield of product was 41 g (53%): bp 42° (0.05 mm); ν_{max}^{film} 3400, 3060, 2970, 2905, 2850, 1710, 1470, 1445, 1360, 1320, 1295, 1240, 1210, 1140, 1110, 1060, 1040, 1020, 950, 900, and 810 cm^{-1}; λ_{max}^{EtOH} 238 mμ (ϵ 4320), 224 mμ (ϵ 5040); nmr ($CDCl_3$), δ 6.00 (multiplet, 1 H), 2.45 (multiplet, 4 H), 2.22 (singlet, 3 H), and 1.98 ppm (multiplet, 2 H); mass spectrum, *m/e* 142 (14%), 100 (38%), 71 (16%), 67 (77%), 43 (100%), and 41 (40%).

Anal. Calcd for $C_7H_{10}OS$: C, 59.12; H, 7.08; S, 22.55. Found: C, 59.56; H, 7.21; S, 22.01.

***cis*-1,2-Cyclopentane Bisthiolacetate.**—A solution of 36.5 g (0.275 mol) of 1-cyclopentene thiolacetate and 56 g (0.735 mol) of freshly distilled thiolacetic acid was stirred for 10 hr and then irradiated 40 min with a 500-W GE sun lamp. The excess thiolacetic acid was evaporated *in vacuo* and the residue was distilled to give 44 g, bp 95° (0.05 mm), of product which was shown by gas chromatography to be 79% *cis* and 21% *trans* isomer. Distillation through a 36-in. Teflon annular still gave 13 g (22%) of pure *cis* isomer: bp (0.05 mm) 95°; ν_{max}^{film} 3370, 2970, 2930, 2880, 1690, 1470, 1450, 1420, 1350, 1315, 1255, 1130, 1105, 1000, 950, 880, and 810 cm^{-1}; λ_{max}^{EtOH} 234 mμ (ϵ 8660); nmr ($CDCl_3$), δ 4.08 (multiplet, 4 H), 2.30 (singlet, 6 H), and 1.75 ppm (multiplet, 6 H).

Anal. Calcd for $C_9H_{14}O_2S_2$: C, 49.51; H, 6.46; S, 29.37. Found: C, 49.52; H, 6.48; S, 29.29.

***cis*-1,2-Cyclopentanedithiol.**—This compound was prepared from 11 g (0.055 mol) of *cis*-1,2-cyclopentane bisthiolacetate and 3.0 g (0.079 mol) of $LiAlH_4$ by the same procedure used to prepare *cis*-1,2-cyclohexanedithiol. The yield was 5.76 g (86%): bp (0.3 mm) 37°; ν_{max}^{film} 2960, 2875, 2550, 1460, 1440, 1305, 1295, 1275, 1250, 1215, 1125, 1025, 1000, 940, 920, 890, 840, 790, and 740 cm^{-1}; λ_{max}^{EtOH} 219 mμ (ϵ 420); nmr ($CDCl_3$), δ 3.25 (multiplet, 2 H), 1.5–2.5 (multiplet, 6 H), and 1.80 ppm (doublet, J = 6 Hz, 2 H).

Anal. Calcd for $C_5H_{10}S_2$: C, 44.73; H, 7.51; S, 47.76. Found: C, 44.82; H, 7.47; S, 47.64.

***cis*-2,5-Dithiabicyclo[4.3.0]nonane (14).**—This compound was prepared from 2.5 g (0.0187 mol) of *cis*-1,2-cyclopentanedithiol, 0.97 g (0.042 g-atom) of sodium metal, and 3.76 g (0.020 mol) of 1,2-dibromoethane in 50 ml of NH_3 as described for the preparation of **5**. After chromatography the product was distilled to give 1.3 g (44%): bp 71° (0.25 mm); ν_{max}^{film} 2980, 2940, 2910, 2870, 2800, 1470, 1440, 1420, 1320, 1300, 1280, 1250, 1215, 1200, 1165, 1125, 1115, 1015, 995, 940, 920, 880, 850, 800, and 680 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ϵ 270); nmr ($CDCl_3$), δ 3.15 (multiplet, 2 H), 2.75 (multiplet, 4 H), and 1.90 ppm (multiplet, 6 H); mass spectrum, *m/e* 160 (45%), 99 (34%), 92 (20%), 67 (100%), and 45 (35%).

Anal. Calcd for $C_7H_{12}S_2$: C, 52.45; H, 7.54; S, 40.01. Found: C, 52.80; H, 7.64; S, 39.74.

cis-2,6-Dithiabicyclo[5.3.0]decane (**23**).—This compound was prepared from 2.5 g (0.0187 mol) of *cis*-1,2-cyclopentanedithiol, 0.92 g (0.04 g-atom) of sodium metal, and 4.0 g (0.0191 mol) of 1,3-dibromopropane in 40 ml of NH_3 as described for the preparation of **5**. After chromatography the product was distilled to give 1.67 g (51%): bp 91° (0.25 mm); ν_{max}^{film} 2970, 2920, 2860, 2800, 1465, 1445, 1410, 1330, 1310, 1265, 1240, 1215, 1140, 1070, 1050, 1020, 1000, 965, 940, 925, 910, 880, 850, 790, 735, and 680 cm^{-1}; uv end absorption only; nmr ($CDCl_3$) δ 3.10–3.50 (multiplet, 2 H), 2.30–3.05 (multiplet, 4 H), and 1.50–2.20 ppm (multiplet, 8 H); mass spectrum, *m/e* 174 (25%), 106 (100%), 73 (16%), 67 (36%), 45 (40%), and 41 (60%).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.09, S, 36.79. Found: C, 55.35; H, 8.10; S, 36.55.

Registry No.—**4**, 15077-17-5; **5**, 16214-56-5; **6**, 16291-03-5; **7**, 4410-24-6; **14**, 16214-58-7; **15**, 16214-59-8; **21**, 16214-71-4; **22**, 16214-60-1; **23**, 16214-61-2; **24**, 16214-62-3; **25**, 15786-82-0; *cis*-1,2-cyclopentanedithiol, 16214-64-5; *trans*-1,2-cyclopentanedithiol, 2126-11-6; *cis*-1,2-cyclohexene bisthiolacetate, 16214-66-7; *trans*-1,2-cyclohexane bisthiolacetate, 16214-67-8; *cis*-1,2-cyclohexanedithiol, 2242-71-9; 1-cyclopentene thiolacetate, 16214-69-0; *cis*-1,2-cyclopentane bisthiolacetate, 16214-70-3.

Multiple Multicenter Reactions of Perfluoro Ketones with Olefins

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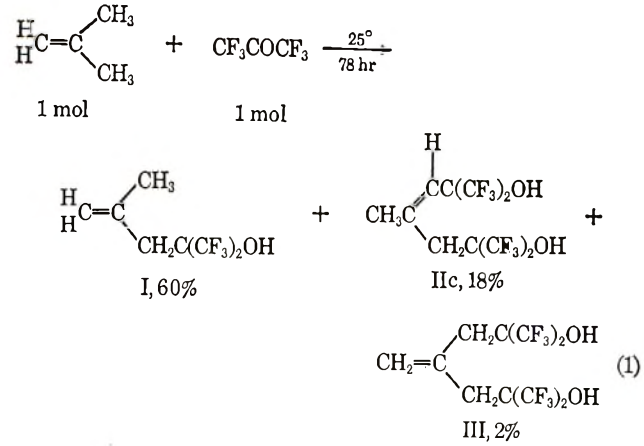
Hexafluoroacetone gives stepwise reactions with olefins [$>CHC{=}CH + CF_3COCF_3 \rightarrow -C{=}CCHC(CF_3)_2OH + CF_3COCF_3 \rightarrow HO(CF_3)_2CCC{=}CC(CF_3)_2OH$] some of which, surprisingly, occur at 25°. Products in a 2:1 ratio are general, and 2-methylpropene also gives a 3:1 product. Terminal olefins are the most reactive with 2-methyl-1-alkenes giving faster rates than 1-alkenes. Otherwise, olefin reactivity is decreased with increased alkyl substitution of their unsaturated carbon atoms. With such tri- and tetrasubstituted olefins or 1:1 products, acid-catalyzed isomerizations (product fluoro alcohols are acidic) occur prior to further reaction with hexafluoroacetone. Reactions giving 2:1 products are stereospecific owing to steric effects.

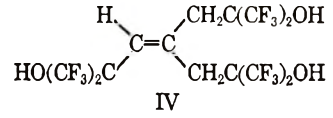
The facile reactions of perfluoro ketones with olefins are known to give 1:1 products;[1-6] and, with 2-methylpropene,[4,5] 2-phenylpropene,[5] and allene,[6] 2:1 products have been reported. The current work shows that the successive reactions occur with comparable rates, and hence 2:1 products are always formed. Indeed, these results suggest that further study of related reactions of olefins with maleic anhydride,[7,8] maleates,[8] fumarates,[8] methylene malonates,[8] pyruvates,[9] or azodicarboxylates[7] may reveal that they also yield such multiple products.

With 2-methylpropene (eq 1), this reaction is unique in its ease and extent (all yields given below are based on olefin used), and the specificity common to them is observed. All of the hexafluoroacetone was consumed (over-all yields based upon it were 100%). Hence, higher ketone/olefin ratios gave more IIc and III, and their yields approached equality at higher reaction temperatures (a ketone/olefin ratio of 2.6 at 25° for 72 hr gave 72% IIc and 8% III; a ratio of 2.0 at 180° for 72 hr gave 56% IIc and 38% III). The reaction of 1,3-dichloro-1,1,3,3-tetrafluoropropanone (2.2 molar excess) with 2-methylpropene at 120° for 72 hr gave products analogous to IIc (54%) and III (29%). To indicate the reaction specificity, no IIt, the *trans*-geometrical isomer of IIc (t or c denotes such products in which the fluorine-containing groups are *trans* or *cis* to each other), was formed in any of the above reactions.



(1)

2-Methylpropene is the only olefin studied that gave a 3:1 product. It (1 mol) with hexafluoroacetone (4.52 mol) at 209° for 150 hr gave 3% IIc, 3% III, and 91% IV. A ketone/olefin ratio of 3.1 at 200° for 60 hr gave 13% IIc, 11% III, and 76% IV.



IV

Other 2-methyl-1-alkenes give these sequential reactions with ease to give 2:1 products. However, 3:1 products were not observed since in general large groups on the terminal olefinic carbon atoms of the allylic systems [C_2H_5– in V, $CH_3(CH_2)_6CH_2$– in VII, and indeed $-C(CF_3)_2OH$ in IIc, VIc, and VIIIc] in-

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(2) H. R. Davis, Abstracts of the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept, 1961, p 25M.
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(6) H. R. Davis, U. S. Patent 3,284,516 (Nov 8, 1966).
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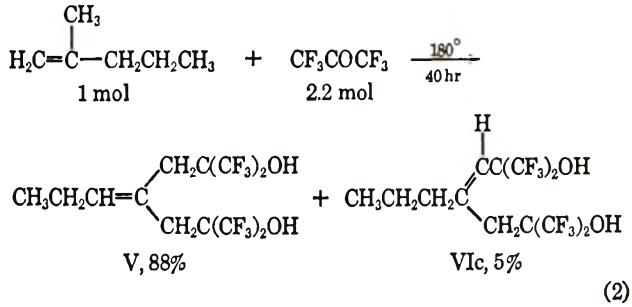
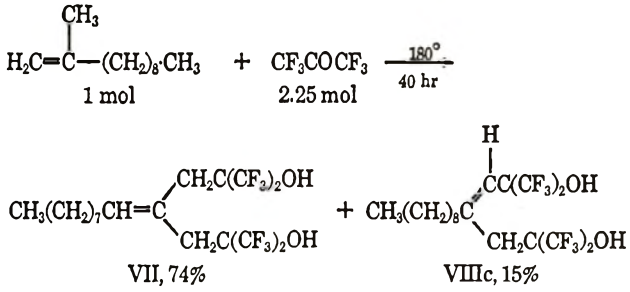
(8) R. T. Arnold and J. S. Showell, *J. Amer. Chem. Soc.*, **79**, 419 (1957).
(9) R. T. Arnold and P. Veeravagu, *ibid.*, **82**, 5411 (1960).

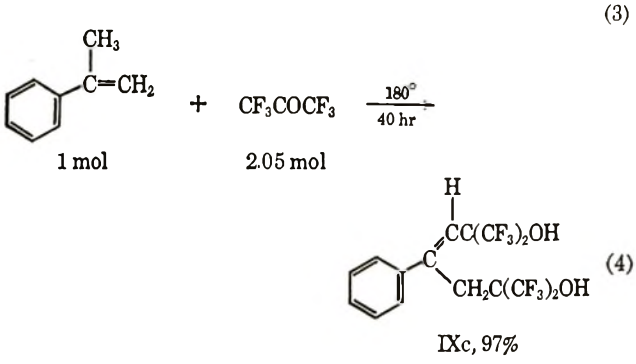
hibit this condensation reaction. Again, only the *cis* forms VIc, VIIIc, and IXc were observed (eq 2–4).



(2)

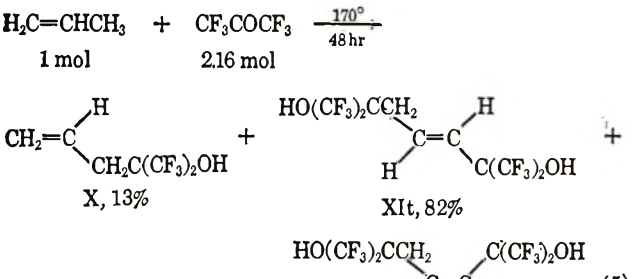


(3)

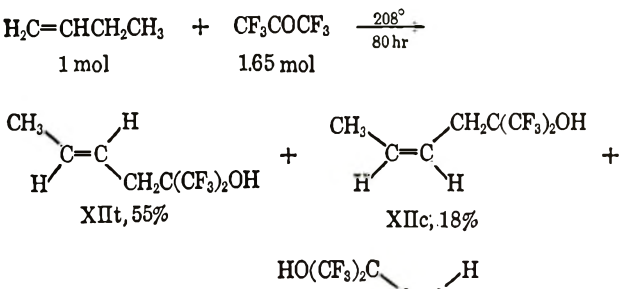


(4)

1-Alkenes, such as propene and 1-butene, are less reactive than the olefins above. Apparently, the conversions of X into XI (reaction 5; 0.33 mol of CF_3COCF_3 remained unreacted) and XII to XIII (reaction 6; 0.38 mol of CF_3COCF_3 was unused) are slower than the corresponding reactions with 2-methyl-1-alkenes. The latter reaction (XII → XIII) is also slower than the former (X → XI). Again, the reactions are selective, but here *trans* isomers are dominant. With 1-butene (1 mol) and hexafluoroacetone (0.53 mol) at 25° for 72 hr, only 40% of the latter was consumed to give XIIt (19.5%) and XIIc (1.5%). At the higher temperatures necessary to form 2:1 products (reaction 6), relatively more XIIc was found.

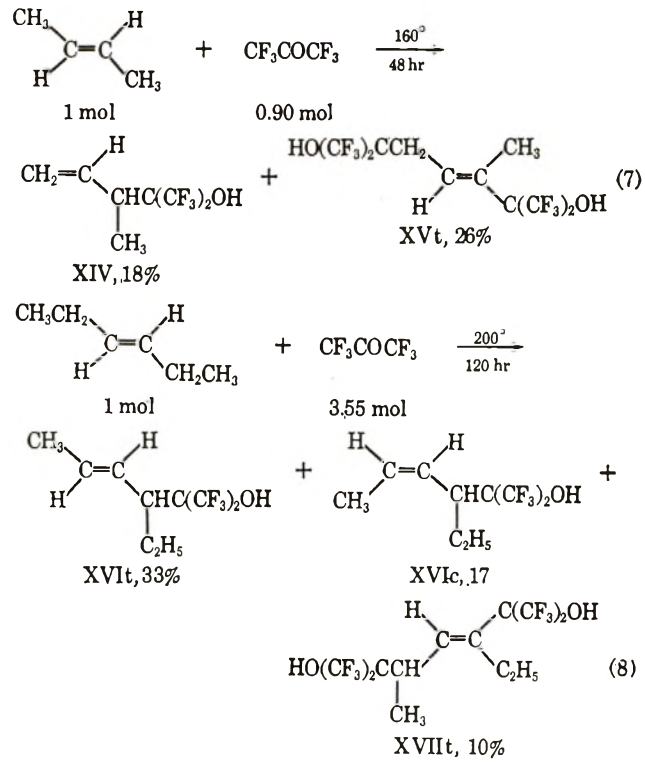


(5)



(6)

The 2- and 3-alkenes studied were still less reactive, and again *trans* 1:1 products (reaction 8, XVIt > XVIc) are favored. However, reactions giving 2:1 products are stereoselective—only *trans* isomers are observed. *cis*-2-Butene is less reactive than *trans*-2-butene. Even under more drastic conditions (186°, 72 hr), *cis*-2-butene (1 mol) with hexafluoroacetone (0.91 mol) gave only 4% XIV and 19% XVt.



(7)

(8)

In reactions 1 and 4–8, the 1:1 and 2:1 products are those expected from successive reactions with hexafluoroacetone without isomerization of either the reactant alkenes or these products. However, when these olefins are highly branched ($RCH{=}CR_2$ or $R_2C{=}CR_2$), their greater rates of acid-catalyzed isomerization (products are acidic; see below) and low reactivity with hexafluoroacetone results in their conversion into more reactive types by the former reaction prior to the completion of the latter. These factors dominate the reactions of 2-methyl-2-butene and 2,3-dimethyl-2-butene, and unexpected products result. Apparently, these olefins are first isomerized to 2-methyl-1-butene or 2,3-dimethyl-1-butene, and these more reactive olefins (see above) then react with hexafluoroacetone. Accordingly, the reaction of 2-methyl-2-butene (0.34 mol) with hexafluoroacetone (0.18 mol) at 165° for 30 hr gave unreacted olefins (0.154 mol)

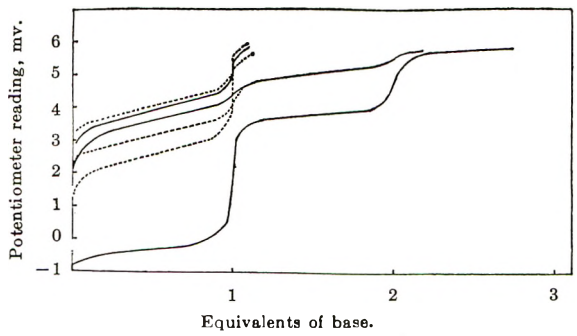
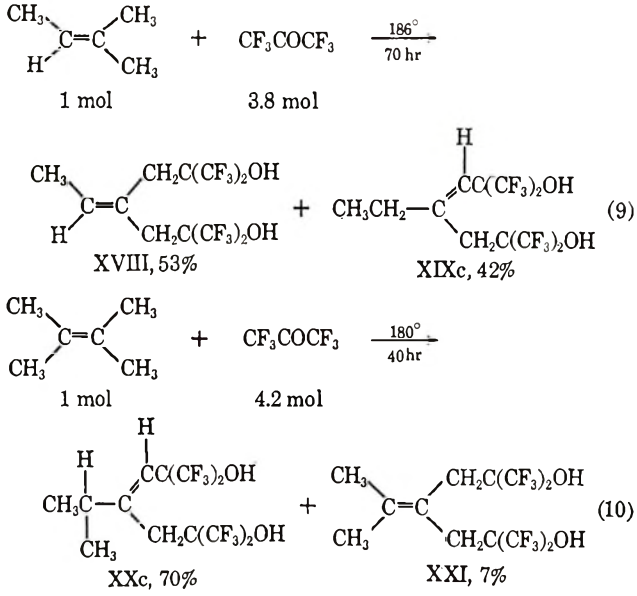


Figure 1.—Potentiometric titrations with tetrabutylammonium hydroxide in dimethylformamide of the products (solid lines) X (upper), IIc (middle), and IV (lower), and the reference substances (dotted lines) phenol (upper), 1,1,3,3,3-hexafluoropropanol-2 (middle), and acetic acid (lower).

(80% 2-methyl-2-butene and 20% 2-methyl-1-butene), a mixture of 1:1 products (0.13 mol) [the 2-alkenes, $CH_3CH{=}C(CH_3)CH_2C(CF_3)_2OH$, 72% *trans* and 8% *cis*, and 20% of the 1-alkene, $CH_2{=}C(C_2H_5)CH_2C(CF_3)_2OH$], and XVIII and XIXc (0.013 mol). Since only the 1-alkene can react further to give XVIII and XIXc, the major 2-alkene 1:1 products must also isomerize during reaction 9. Similar evidence was obtained for the role of isomerizations in both steps of reaction 10 (see Experimental Section). Under the



above reaction conditions, no isomerization of any 2:1 products is observed since only *cis* isomers, and no *trans* ones, are observed. The greater stability of these ultimate products is important since it preserves evidence of reaction specificity, and of relative reactivity of allylic hydrogen atoms.

Reactions where such isomerizations are necessary require high temperatures and long reaction times. One possible reason that vigorous conditions (209° for 150 hr) are needed to obtain IV in the multiple reaction with 2-methylpropene is that the major 2:1 product IIc is unreactive. It is isomerized to the other such product III that reacts to give IV. Also, with the 2-methyl-1-alkenes, reaction 1 is much faster than reactions 2 or 3. In the former, a reactive 2-methyl-1-alkene I is formed first. With 2-methyl-1-pentene or 2-methyl-1-undecene, initial products are the unreactive 2-alkenes [*trans*- and *cis*-$RCH{=}C(CH_3)CH_2C(CF_3)_2OH$] and the reactive 1-alkenes [$CH_2{=}C(CH_2R)CH_2C(CF_3)_2OH$]. The former must be isomerized to the latter before the observed reaction is completed.

The reaction products, and possibly hexafluoroacetone hydrate (no special precautions were taken to make reaction mixtures anhydrous), probably serve as acidic catalysts for these isomerizations. Since 1,1,1,3,3,3-hexafluoro-2-propanol is acidic (pK_a = 9.3),[10] these products were expected to be. Their potentiometric titrations (Figure 1) show that the 1:1 product X is slightly more acidic than phenol, the first dissociation constant of the 2:1 product IIc is greater than that of phenol but less than that of 1,1,1,3,3,3-hexafluoro-2-propanol, and the 3:1 product IV is stronger than acetic acid. Interestingly, the second dissociation constant of IV is approximately equal to the first dissociation constant of IIc.

The order of olefin reactivity suggested above ($CH_3CR{=}CH_2$ > $RCH{=}CH_2$ > *trans*-$RCH{=}CHR$ > *cis*-$RCH{=}CHR$ > $RCH{=}CR_2$ > $R_2C{=}CR_2$, R = alkyl) is also confirmed by an analysis of the relative rates of the competing reactions (A, olefin + CF_3COCF_3 → 1:1 product, *vs.* B, 1:1 product + CF_3COCF_3 → 2:1 product) that is possible with those experiments in which neither the olefin nor the 1:1 product was completely consumed [reactions 1, 7 (also that with *cis*-2-butene), and 8]. For example, the average mole fraction of 2-methylpropene (0.35, initial 0.50 and final 0.20) and that of I (0.30, initial 0 and final 0.60) and the ratio of rates of formation of I, and of IIc and III, from the yield ratio [(I + IIc + III)/(IIc + III)] permit calculation of the approximate ratio of rate constants for the two successive reactions (k_A/k_B = 3.4 at 25°). Here, therefore, the first reaction (A) is faster than the second (B).

With the other reactions so examined, the reverse is observed. The reaction (7) of hexafluoroacetone with the 1:1 product XIV is faster than that with *trans*-2-butene (k_B/k_A = 3.0 at 160°), and the corresponding reactions from *cis*-2-butene occur with a greater difference in rates (k_B/k_A = 32 at 186°). As expected, the 2-butenes (RCH=CHR) are less reactive than the product XIV ($RCH{=}CH_2$). *trans*-2-Butene reacts over ten times faster than *cis*-2-butene. In the reaction (8) of *trans*-3-hexene, where both it and the first product XVI are the same type of olefin (RCH=CHR), the difference in rates is diminished (k_B/k_A = 2.1). The latter ratio is probably due in part to another factor influencing the relative rates of these reactions—the nature of the allylic hydrogen atom abstracted. A tertiary hydrogen atom is so involved in the reaction of XVI with hexafluoroacetone, while in this reaction with *trans*-3-hexene the hydrogen atom attacked is secondary (general discussion below).

The above identification of geometrical isomers among these products is based upon their nmr spectra. The absorptions due to the methylene hydrogen atoms of $-CH_2C(CF_3)_2OH$ groups *cis* to $-C(CF_3)_2OH$ groups are at lower field than those in which these groups are *trans*. The magnitude of this difference in chemical shift is apparent in the nmr spectrum of IV (methylene singlets at δ 3.58 and 3.14). Evidence for the

(10) I. L. Knunyants, M. P. Gambajan, C. Y. Chen, and E. M. Rokhlin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **684**, 633 (1962).

assignment is that the doublet due to the methylene group of the *cis* form XIc (olefinic coupling constant, J = 12 cps) is at δ 3.27 and that of the *trans* form XIt (olefinic coupling constant, J = 16 cps) is at δ 2.87. Indeed, the chemical shifts of these methylenes permit classification of the 2:1 products into three groups: (1) those with $-CH_2C(CF_3)_2OH$ *cis* to $-C(CF_3)_2OH$ (IIc, δ 3.47; VIc, 3.18; VIIIc, 3.27; XIXc, 3.23; XXc, 3.27; and XXIXc, 3.17); (2) those with these groups *trans* (IIt, δ 2.75; XIt, 2.80; XVt, 2.85); and (3) those with geminal $-CH_2C(CF_3)_2OH$ groups (III, δ 3.01; V, 3.04; VII, 3.07; XVIII, 3.05; XXI, 3.07). The methylene absorptions of the *trans* 2:1 products (group 2) resemble those in 1:1 products (I, δ 2.68; X, 2.71; XIIt, 2.67; XIIc, 2.83). The corresponding methylene group of IXc (δ 3.87) is sufficiently downfield from that of the 1:1 product from 2-phenylpropene XXXIII (δ 3.01) that IXc probably has the indicated *cis* structure (the methylene of IXt from pyrolysis experiments is at δ 3.10, see below). Again, the coupling constant between the olefinic hydrogen atoms (J = 15.5 cps) of XIIIt indicates that it is the *trans* form. Although the multiplet due to the tertiary hydrogen atom of XIIIt (3.08) is different from that of XVIIt (δ 3.34), the latter probably has the indicated *trans* structure.

The above reactions to give 2:1 products show interesting specificity. Products in a 1:1 ratio with hydrogen atoms attached to the central carbon atoms of their allylic systems react with hexafluoroacetone to give predominantly *trans* 2:1 products (reactions 5–8) while those with more bulky groups (methyl or larger) so attached give *cis* isomers (reactions 1–4, 9, and 10). Study of the molecular models of I and X suggest that the specificity is a steric effect, apparent only when the transition state is considered in three dimensions.

The molecular model of I (solid outline in Figure 2) shows that steric interaction between the $-C(CF_3)_2OH$ group and the methyl or $=CH_2$ groups restricts the former to one side of the molecule (shown below the olefinic system in Figure 2). The attack of hexafluoroacetone can then occur only from the side of the molecule away from that of the $-C(CF_3)_2OH$ group (from above as shown in the dotted outline in Figure 2). The energy of the transition state is presumably minimized by the overlap of the π electrons of the carbonyl and olefinic carbon atoms. As shown in Figure 2, the carbonyl oxygen atom can then more readily reach the methylene hydrogen atom of the $-CH_2C(CF_3)_2OH$ group whose concerted removal leads to the formation of the *cis* isomer IIc.

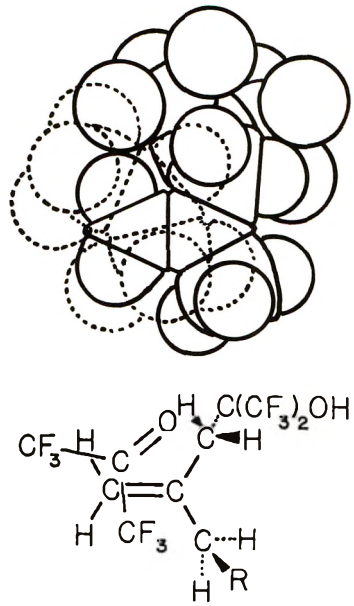
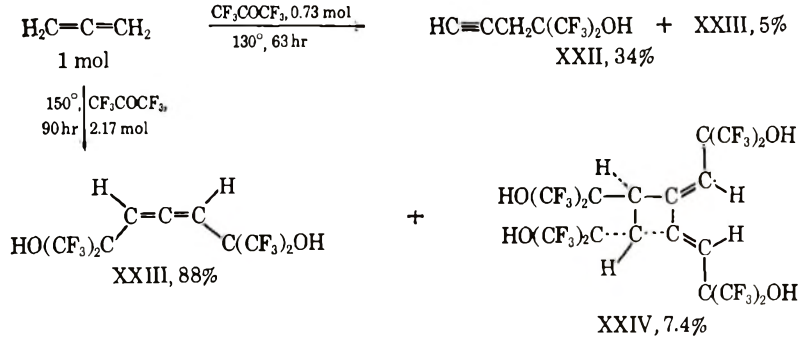


Figure 2.—Perspective drawing of molecular model of I (solid outline above, R = H below) with that of hexafluoroacetone (dotted outline) above it to illustrate its attack to give IIc.

With an hydrogen atom on the middle carbon atom of the allylic system as in X (hydrogen instead of methyl in Figure 2), reduced steric interaction between it and the $-C(CF_3)_2OH$ group permit them to be eclipsed. In this conformation, the hexafluoroacetone molecule has equal access to the allylic system both above and below it, and the methylene hydrogen atom of the $-CH_2C(CF_3)_2OH$ group in position for concerted attack from either direction is that whose removal leads to the *trans* 2:1 product XIt. Previous proposals of concerted reaction mechanisms with six-membered-ring transition states depicted in planar projection[8,9] have ignored such spatial considerations.

A mechanism involving initial formation of the carbon–carbon bond to give a zwitterion intermediate (see below) has been proposed.[11] Such a picture is in keeping with the above discussion if the carbonium ion center preserves the planarity of the olefin-derived system, as it might be expected to do. In fact, this concept is useful in explaining the reaction (11) of allene with hexafluoroacetone. The structure of XXIV is indicated by its ultraviolet [conjugated diene: λ_{max} 241 mμ (ϵ 18,000)], nmr (4 H–OH singlet, 2 H olefinic singlet, and 2 H singlet for ring hydrogen atoms), mass (molecular ion 744) spectra, and steric considerations. Molecular models show that the $-C(CF_3)_2OH$ groups are too large for two of them to be *cis* on the

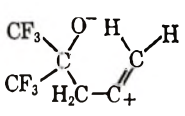


(11)

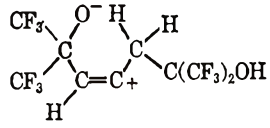
(11) R. L. Adelman, Abstracts of the 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, p K6.

cyclobutene ring, and for the other two to be in the alternative configuration with the $-C(CF_3)_2OH$ groups and olefinic hydrogen atoms transposed.

Obviously, the carbonyl bond of hexafluoroacetone is not of sufficient length to accomplish concerted carbon–carbon bond formation and hydrogen abstraction in either step of its reaction with allene. However, if the zwitterions XXV and XXVI are formed first, the next step to complete the reaction is possible.

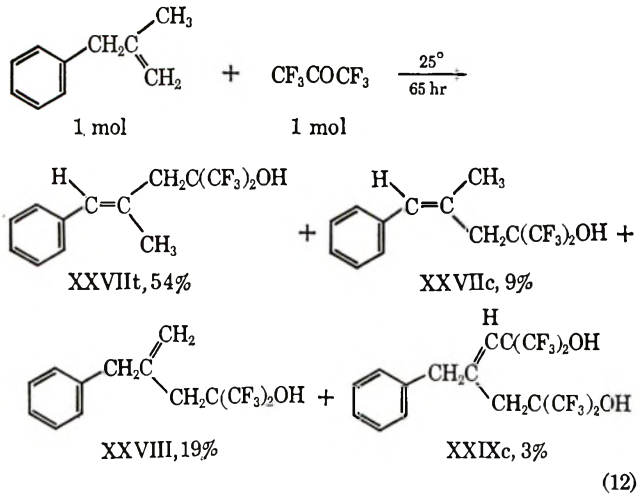


XXV



XXVI

Apparently, the steric effect of the phenyl group is not sufficient to affect the selectivity of this reaction as the $-C(CF_3)_2OH$ group does. The dominant 1:1 product of the reaction (12) of 2-methyl-3-phenylpropene (analogous to I) with hexafluoroacetone is XXVIIt (I gives IIc). The XXVIIc formed is probably due



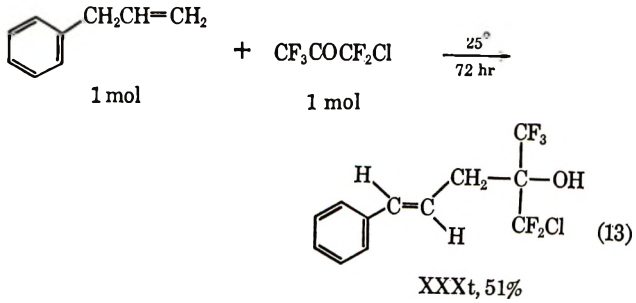
1 mol + CF_3COCF_3 (1 mol), 25°, 65 hr

XXVIIt, 54% + XXVIIc, 9%

XXVIII, 19% + XXIXc, 3%

(12)

to a limited steric effect of the phenyl group. The following reaction (13) of 3-phenylpropene gave only the *trans* product XXXt.



1 mol + CF_3COCF_2Cl (1 mol), 25°, 72 hr

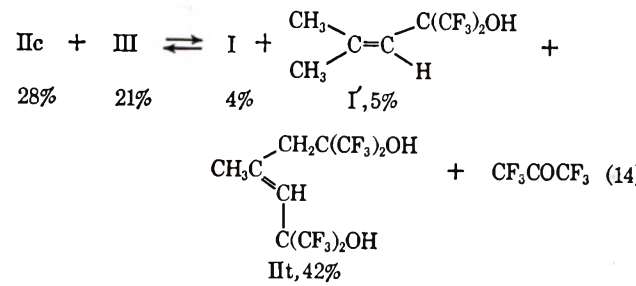
XXXt, 51% (13)

Reaction 12 provides a striking example of the influence of steric effects upon the relative reactivities of allylic hydrogen atoms. Since acid-catalyzed isomerization of the 1:1 products is probably limited at 25°, their yields indicate that, in the competition between the methyl and benzylic hydrogen atoms of 2-methyl-3-phenylpropene, the latter are more reactive (63% XXVIIt and XXVIIc and 22% XXVIII—3% then consumed to give XXIXc). However, the further reaction of XXVIII with hexafluoroacetone gave only XXIXc and none of the isomeric styrene, $C_6H_5CH{=}C(CH_2C(CF_3)_2OH)_2$.

The molecular model of XXVIII indicates the reason for exclusive attack upon a methylene hydrogen atom of its $-CH_2C(CF_3)_2OH$ group. The steric requirements of the $-C(CF_3)_2OH$ and the phenyl groups are so large that they tend to be on opposite sides of the plane of the olefinic and methylene carbon atoms (phenyl in place of the upper hydrogen atom of the methyl group of Figure 2, R = C_6H_5). The smaller phenyl group permits attack by the hexafluoroacetone molecule on its side where one of the methylene hydrogen atoms of the $-CH_2C(CF_3)_2OH$ group is accessible (again only the *cis* isomer XXIXc is formed) while the bulky $-C(CF_3)_2OH$ group obstructs the other side where the benzylic hydrogen atoms are.

Such steric effects undoubtedly play a role in other reactions in determining the relative yields of the two 2:1 products formed. The secondary hydrogen atom of the $-CH_2(CF_3)_2OH$ group involved in the reaction of I to give IIc is more reactive than the primary ones of its methyl group that are attacked to give III. This kind of secondary hydrogen atom is less reactive than those of the alkyl methylenes ($C_2H_5CH_2-$ or $C_8H_{17}CH_2-$) in the second steps of reactions 2 (88% V and 5% VIc) or 3 (74% VII and 15% VIIIc). A low reactivity of the tertiary hydrogen atom of the 1:1 product, $CH_2{=}C(CH(CH_3)_2)CH_2C(CF_3)_2OH$, is indicated in its reaction (10) to give 70% XXc and 7% XXI. Presumably, steric repulsion between its two methyl and $-C(CF_3)_2OH$ groups again tends to keep that tertiary hydrogen atom on the unreactive side of the molecule.

Bomb tube pyrolyses of mixtures of IIc and III and of IXc give all of the possible products of their β-hydroxy olefin degradation[12] and isomerization. The evidence supports the above nmr indentifications of *cis* and *trans* isomers and indicates relative stabilities. A neat sample of 60% IIc and 40% III at 275° for 24 hr gave the mixture which is shown in 14 below.



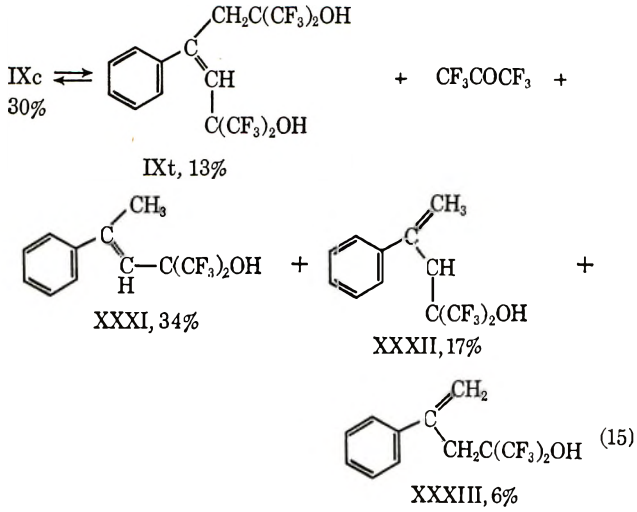
IIc + III ⇌ I + I′, 5% + IIt, 42% + CF_3COCF_3 (14)

28% 21% 4%

Equilibrium is here approached by interconversion of the 2:1 products and I and by acid-catalyzed isomerizations. The structure assignments of IIc and IIt are confirmed since IIt is shown to be more stable than IIc. Further, the nmr spectrum of IIt is that characteristic of all such *trans* isomers (methylene singlet at δ 2.73). Also, the rates of formation of IIc, IIt, and III are faster than their rates of degradation, and IV is unstable (none observed), under these conditions.

(12) R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **81**, 6443 (1959); **82**, 4918 (1960); *J. Org. Chem.*, **25**, 129 (1960).

In the similar pyrolysis of IXc (250°, 72 hr) the mixture obtained suggests that degradation reactions of IXt and IXc are faster than their formation (eq 15).



Again, the methylene singlet of IXt (δ 3.10) is at higher field than that of IXc (δ 3.87) to confirm the isomeric identification. This degradation and isomerization are too slow to be observed at 184° for 48 hr (conditions of reaction 4). As further evidence for the stability of these 2:1 products, other methods of olefin isomerization (trifluoroacetic acid and perchloric acid at reflux for 48 hr, and palladous chloride in boiling acetic acid for 48 hr) gave back unchanged IXc. Hence, nearly quantitative conversions into 2:1 products occur over a wide range of temperature before their yields are limited and the products multiplied by degradation and isomerization.

Experimental Section

Reactions of Alkenes with Hexafluoroacetone.—With gaseous olefins and this ketone, each of the two reactants was distilled from its supply tank into an evacuated 500-ml stainless steel bomb held at −80°. To determine the weight of each, the bomb was weighed before and after each addition. With liquid olefins, a weighed amount was added to the bomb before it was evacuated. Then each reaction mixture was held at the reaction temperature with rocking for the period specified below. All yields are based upon the olefin used.

2-Methylpropene.—After a reaction mixture containing 2-methylpropene (7.86 g, 0.14 mol) and hexafluoroacetone (23.2 g, 0.14 mol) had been held at 25–30° for 78 hr, the bomb was opened and unreacted 2-methylpropene was allowed to escape. Distillation of the reaction product gave I (18.7 g, 0.084 mol, 60%): bp 117°; ^{1}H nmr in CCl_4 with TMS, 3 H singlet at δ 1.91, 2 H singlet at 2.59, 1 H–OH singlet at 3.17, 1 H narrow multiplet at 4.98 (J = 1.0 cps), and 1 H narrow multiplet at 5.17 (J = 1.3 cps).

Anal. Calcd for $C_7H_8F_6O$: C, 37.8; H, 3.6; F, 51.3. Found: C, 37.6; H, 3.5; F, 51.0.

The distillation residue solidified. Its nmr analysis indicated that it was a mixture of 90% IIc and 10% III (10.9 g, 20%; see below).

With 2-methylpropene (4.5 g, 0.08 mol) and hexafluoroacetone (35.0 g, 0.21 mol) similarly held at 25–30° for 72 hr, the reaction product contained 90% IIc and 10% III (nmr, 25.0 g, 0.064 mol, 80%) after it had been washed with methylene chloride to remove I and reactants. A white solid product (72.0 g, 0.185 mol, 94%) similarly obtained from a reaction of 2-methylpropene (11.0 g, 0.196 mol) and hexafluoroacetone (67.0 g, 0.404 mol) held at 180° for 72 hr was shown by nmr analysis to contain 60% IIc and 40% III. These two products were separated by column chromatography (Fluorosil, Matheson, 60–200 mesh) to give pure III (eluted with 50:50 benzene–petroleum ether of bp 30–60°) [mp 149–150°; ^{1}H nmr in acetone-d_6 with TMS, 4 H singlet at δ 3.01; 2 H broad singlet at 5.33, and 2 H–OH singlet at 6.95; mass spectrum, molecular ion 388, 0.39%; 370, 0.78%; 369, 7.5%; 350, 3.6%; 319, 7.5%; 281, 2.8%; 261, 2.9%; 221, 2.2%; 203, 4.0%; 183, 1.7%; 165, 1.8%; 151, 1.7%; 145, 1.9%; 97, 2.7%; 73, 1.6%; 69, 7.5%; 55, 4.3%; 43, 2.0%; 41, 1.9%; and 39, 2.0% all of Σ_{28}; three base peaks, 369, 319, and 69; metastables, 331.0, 370 → 350; 315.7, 388 → 350; 262.2, 388 → 319; 247.5, 319 → 281; 242.5, 281 → 261; 182.8, 221 → 201; and 165.0, 203 → 183] and IIc (eluted with benzene and benzene–ethyl ether) (mp 142.8–144°; ^{1}H nmr in acetone-d_6 with TMS, 3 H singlet at δ 2.09, 2 H singlet at 3.27, 1 H broad singlet at 5.65, and 2 H–OH singlet at 7.33).

Anal. Calcd for $C_{10}H_8F_{12}O_2$: C, 30.9; H, 2.1; F, 58.7. Found, IIc: C, 31.2; H, 2.3; F, 59.0. Found, III: C, 31.0; H, 2.2; F, 58.5.

With a reaction mixture containing 2-methylpropene (6.7 g, 0.12 mol) and hexafluoroacetone (90.0 g, 0.542 mol) held at 209° for 150 hr, a solid product (62.8 g) was obtained. It was triturated with methylene chloride (100 ml), and the portion of it that remained undissolved (12 g) was removed on a filter. Evaporation of the methylene chloride solution gave IV (50.8 g, 0.092 mol, 77%): mp 106–107° after recrystallization from carbon tetrachloride; ^{1}H nmr in acetone-d_6 with TMS, 2 H singlet at δ 3.14, 2 H singlet at 3.58, 1 H singlet with fine splitting at 5.98; and 3 H–OH singlet at 7.27; mass spectrum, molecular ion 554, 0.02%; 536, 0.61%; 515, 0.58%; 498, 1.1%; 485, 1.9%; 477, 1.3%; 468, 0.84%; 467, 6.5%; 449, 1.4%; 447, 0.84%; 429, 3.9%; 428, 1.3%; base peak 427, 10.5%; 387, 0.95%; 385, 1.7%; 379, 0.84%; 349, 1.7%; 347, 1.2%; 327, 0.95%; 279, 3.4%; 147, 1.2%; 145, 1.1%; 97, 2.6%; and 69, 7.4%, all of Σ_{28}; metastables, 457.8, 497 → 477; 456.9, 498 → 477; 449.7, 485 → 467; 437.8, 477 → 457; 427.9, 467 → 447; 409.9, 449 → 429; 407.9, 447 → 427; 390.4, 467 → 427; 287.9, 427 → 407; and 351.8, 387 → 369.

Anal. Calcd for $C_{13}H_8F_{18}O_3$: C, 28.2; H, 1.5; F, 61.7. Found: C, 28.3; H, 1.6; F, 61.7.

Nmr analysis of the solid that did not dissolve in methylene chloride showed that it contained IV (72 mol %, 9.42 g, 0.017 mol, 14%), IIc (14.5 mol %, 1.32 g, 0.0034 mol, 2.9%), and III (13.5 mol %, 1.24 g, 0.032 mol, 2.7%).

The reaction of 2-methylpropene (8.4 g, 0.15 mol) with hexafluoroacetone (77.0 g, 0.464 mol) at 200° for 60 hr gave IIc (7.0 g, 0.020 mol, 13%), III (6.5 g, 0.017 mol, 11%), and IV (63.6 g, 0.115 mol, 76%).

2-Methyl-1-pentene.—Hexafluoroacetone (73 g, 0.44 mol) with this alkene (16.8 g, 0.20 mol) at 180° for 40 hr gave a product mixture (77 g, nmr analysis showed 95% V and 5% VIc) that crystallized when it cooled. The major product V was purified by five recrystallizations from carbon tetrachloride (73.2 g, 0.176 mol, 88%): mp 101.6–103.5°; ^{1}H nmr in acetone-d_6 with TMS, 3 H triplet at δ 0.98 (J = 7.5 cps), 2 H quintet at 2.12 (J = 7.5 cps), 4 H singlet at 3.04, 1 H triplet at 5.78 (J = 7.5 cps), and 2 H–OH singlet at 7.34.

Anal. Calcd for $C_{12}H_{12}F_{12}O_2$: C, 34.6; H, 2.9; F, 54.8. Found: C, 34.5; H, 2.7; F, 54.7.

The presence of VIc (3.8 g, 0.0092 mol, 4.6%, nmr) in the crude product was indicated (nmr methylene singlet at δ 3.18).

2-Methyl-1-undecene.—This olefin (33.6 g, 0.200 mol) and hexafluoroacetone (74 g, 0.45 mol) were held at 180° for 40 hr, and the product mixture (95 g) was crystallized upon cooling. This crude product contained 83% VII and 17% VIIIc (nmr integration of methylene singlets of VII, δ 3.07, and VIIIc, 3.27). Recrystallization from methylene chloride gave pure VII (74.0 g, 0.148 mol, 74%): mp 76–77.8°; ^{1}H nmr in acetone-d_6 with TMS, 3 H triplet at δ 0.92 (J = 6.0 cps), 12 H broad envelope at 1.34, 2 H multiplet at 2.24, 4 H broad singlet at 3.07, 1 H triplet at 5.80 (J = 7.0 cps), and 2 H–OH broad singlet at 7.08.

Anal. Calcd for $C_{18}H_{24}F_{12}O_2$: C, 43.2; H, 4.8; F, 45.6. Found: C, 43.3; H, 4.7; F, 45.9.

2-Phenylpropene.—Hexafluoroacetone (68 g, 0.41 mol) and this styrene (23.6 g, 0.200 mol) were heated at 184° for 48 hr. The crystalline product was nearly pure IXc (86.8 g, 0.193 mol, 97%): mp 141.5–142.5° after recrystallization from carbon tetrachloride;[4,5] ^{1}H nmr in acetone-d_6 with TMS, 2 H singlet at δ 3.87, 1 H singlet at 6.06, 5 H multiplet (two large peaks) at 7.52, and 2 H–OH broad singlet at 7.92; mass spectrum, molecular ion system 452, 0.09%; 451, 0.78%; 450, 4.7%; 381, 1.6%; base peak 363, 8.6%; 345, 1.2%; 293, 1.1%; 284, 1.3%; 232, 1.1%; 197, 3.6%; 196, 4.4%; 177, 2.1%; 147, 1.0%;

146, 1.2%; 145, 2.1%; 117, 3.8%; 116, 1.6%; 115, 4.6%; 103, 1.6%; 97, 2.4%; 91, 2.2%; 78, 1.4%; 77, 1.9%; 69, 6.2%; 51, 1.5%; 50, 1.0%; 39, 1.2%; and 28, 2.0%, all of Σ_{28}; metastables, 345.9, 381 → 363; 327.9, 363 → 345; 325.1, 364 → 344; 324.1, 363 → 343; 322.6, 450 → 381; 306.2, 345 → 325; 287.4, 363 → 323; 276.0, 311 → 293; 274.3, 313 → 393; 159.8, 196 → 177; 159.0, 197 → 177; 113.0, 117 → 115; and 94.4, 145 → 117.

Propene.—This olefin (15.5 g, 0.37 mol) with hexafluoroacetone (133.0 g, 0.80 mol) was held at 170° for 48 hr. After this reaction mixture had cooled, the bomb valve was opened to allow unreacted ketone to escape. The white solid that had precipitated from the reaction mixture was separated on a filter, and it was shown to be XIc (6.0 g, 0.014 mol, 4%): mp 136–137° from chloroform; ^{1}H nmr in acetone-d_6 with TMS, 2 H doublet at δ 3.27 (J = 6.8 cps), 1 H doublet at 5.68 (J = 12.0 cps), 1 H two triplets at 6.30 (J = 12.0 and 6.8 cps), and 2 H–OH singlet at 6.85. Distillation of the filtrate gave X (10.0 g, 0.048 mol, 13%) [bp 98°; ^{1}H nmr in CCl_4 with TMS, 2 H doublet at δ 2.71 (J = 6.8 cps), 1 H–OH singlet at 2.98 and 3 H vinyl multiplet with 1 H doublet at 5.28 (J = 17.8 cps), 1 H doublet at 5.35 (J = 9.5 cps), and 1 H multiplet at 5.92 (J = 17.8 and 9.5 cps apparent)] and XIt (112.5 g, 0.301 mol, 82%) [bp 175.5–176.5°; ^{1}H nmr in acetone-d_6 with TMS, 2 H doublet at δ 2.80 (J = 7.0 cps), 1 H doublet at 5.67 (J = 16.0 cps), 1 H two triplets at 6.33 (J = 16.0 and 7.0 cps), and 2 H–OH singlet at 5.62; mass spectrum, molecular ion 374, 0.11%; 356, 0.97%; 317, 2.6%; 315, 3.7%; base peak 305, 16.0%; 287, 11.8%; 267, 10.9%; 235, 5.6%, 219, 1.9%; 217, 2.6%, 205, 1.4%; 69, 2.7%; and 44, 2.7% all of Σ_{28}; metastables: 278.3, 317 → 297; 270.1, 305 → 287; 258.5, 297 → 277; 248.7, 347 → 305, 287 → 267; 233.7, 305 → 267; 228.5, 267 → 247; 214.0, 267 → 239; 200.6, 239 → 219; and 200.3, 235 → 217].

Anal. Calcd for $C_6H_6F_6O$: C, 34.6; H, 2.9; F, 54.8. Found: C, 34.9; H, 3.2; F, 55.2.

Anal. Calcd for $C_9H_6F_{12}O_2$: C, 28.9; H, 1.6; F, 60.9. Found (XIc): C, 28.8; H, 1.3; F, 60.7. Found (XIt): C, 28.7; H, 1.7; F, 60.8.

1-Butene.—A reaction mixture containing this olefin (24.0 g, 0.43 mol) and hexafluoroacetone (117.0 g, 0.71 mol) was held at 208° for 80 hr. Distillation then gave a mixture of XIIt and XIIc (69.0 g, 0.311 mol, 73%) [bp 119–120.5°; ^{1}H nmr of XIIt in CCl_4 with TMS, 3 H doublet at δ 1.76 (J = 5.0 cps), 2 H doublet at 2.67 (J = 6.2 cps), 1 H–OH singlet at 3.10 and 2 H multiplet at 5.70 (J = 6.2 and 5.0 cps apparent); presence of XIIc shown by upfield peak of methyl doublet at δ 1.65; downfield peak of methylene doublet at 2.83; integration shows 75% XIIt and 25% XIIc] and XIIIt (45.0 g, 0.116 mol, 27%) [bp 186.5–187°; ^{1}H nmr in acetone-d_6 with TMS, 3 H doublet at δ 1.36 (J = 7.0 cps), 1 H quintet at 3.08 (J = 8.0 cps), 2 H–OH singlet at 3.20, 1 H doublet at 5.78 (J = 15.5 cps), 1 H two doublets at 6.58 (J = 15.5 and 8.0 cps)].

Anal. Calcd for $C_7H_8F_6O$: C, 37.9; H, 3.6; F, 51.3. Found: C, 38.2; H, 3.7; F, 51.0.

Anal. Calcd for $C_{10}H_8F_{12}O_2$: C, 30.9; H, 2.1; F, 58.7. Found: C, 31.1; H, 2.2; F, 58.4.

A reaction mixture containing 1-butene (16.0 g, 0.285 mol) and hexafluoroacetone (25.0 g, 0.151 mol) held at 25° for 72 hr gave a mixture of XIIt and XIIc (93:7, bp 119–120.5°, 13.0 g, 0.059 mol, 40%).

***trans*- and *cis*-2-Butenes.**—*trans*-2-Butene (29.4 g, 0.52 mol) with hexafluoroacetone (78.0 g, 0.47 mol) at 160° for 48 hr gave XIV (21.0 g, 0.095 mol, 18%) [bp 119.5–120.5°; ^{1}H nmr in CCl_4 with TMS, 3 H doublet at δ 1.32 (J = 7.2 cps), 1 H "quintet" (broad peaks) at 2.88 (J = 7.2 cps), 1 H–OH singlet at 3.20, 3 H vinyl multiplet with 1 H doublet at 5.25 (J = 15.0 cps), 1 H doublet at 5.32 (J = 10.5 cps), and 1 H multiplet at 5.93] and XVt (53.0 g, 0.137 mol, 26%) [bp 185°; ^{1}H nmr in acetone-d_6 with TMS, 3 H singlet at δ 1.87; 2 H doublet at 2.85 (J = 8.0 cps), 1 H–OH singlet at 3.09, 1 H–OH singlet at 3.21, and 1 H triplet at 6.28 (J = 8.0 cps)].

Anal. Calcd for $C_7H_8F_6O$: C, 37.9; H, 3.6; F, 51.3. Found: C, 37.9; H, 3.7; F, 51.5.

Anal. Calcd for $C_{10}H_8F_{12}O_2$: C, 30.9; H, 3.1; F, 58.7. Found: C, 31.2; H, 3.3; F, 59.1.

cis-2-Butene (40 g, 0.71 mol) with hexafluoroacetone (108 g, 0.65 mol) even under more vigorous conditions (186° for 72 hr) gave lower conversions to XIV (6.0 g, 0.027 mol, 4%) and XVt (53.5 g, 0.138 mol, 19%).

***trans*-3-Hexene.**—This alkene (10 g, 0.12 mol) with hexafluoroacetone (70 g, 0.42 mol) at 200° for 120 hr gave a liquid product (21 g). Its distillation gave a mixture of XVIt and XVIc (14.7 g, 0.059 mol, 49%): bp 142° and 44–45° (10 mm); ^{1}H nmr of XVIt in CCl_4 with TMS, 3 H triplet at δ 0.94 (J = 8.5 cps), 2 H multiplet at 1.43 (J = 8.5 cps), 3 H pair of doublets at 1.90 (J = 6.5 and 1.0 cps), 1 H multiplet at 2.61, 1 H–OH singlet at 3.19, and 2 H multiplet at 6.05, downfield two quartets at 6.08 (J = 17.0 and 6.5 cps); part due to XVIc, methyl doublet pair at δ 1.78 (J = 7.0 and 2.0 cps); downfield part of olefinic multiplet shows two smaller quartets at 6.30 (J = 11.0 and 6.5 cps); integration of methyl doublet of each shows 65% XVIt and 35% XVIc.

Anal. Calcd for $C_9H_{12}F_6O$: C, 43.2; H, 4.8; F, 45.6. Found: C, 43.2; H, 4.7; F, 45.6.

Further distillation gave XVIIt (5.0 g, 0.012 mol, 10%): bp 40° at 0.08 mm; ^{1}H nmr in CCl_4 with TMS, 3 H triplet at δ 1.08 (J = 7.5 cps), 3 H doublet at 1.28 (J = 7.8 cps), 2 H quartet at 2.36 (J = 7.5 cps), 2 H–OH singlets at 3.00 and 3.21, 1 H multiplet at 3.34 (two quartets) (J = 11.0 and 7.0 cps), and 1 H doublet at 6.13 (J = 11.0 cps).

Anal. Calcd for $C_{12}H_{12}F_{12}O_2$: C, 34.6; H, 2.9; F, 54.9. Found: C, 34.9; H, 2.8; F, 55.2.

2-Methyl-2-butene.—With this olefin (8.3 g, 0.12 mol) and hexafluoroacetone (76 g, 0.46 mol) at 186° for 70 hr, a white solid product (46 g) was obtained. The crude product contained 56% XVIII (25.8 g, 0.064 mol, 53%) [^{1}H nmr in acetone-d_6 with TMS, 3 H doublet at δ 1.70 (J = 7.0 cps), 4 H broad singlet at 3.05, 1 H quartet at 5.78 (J = 7.0 cps), 2 H–OH broad singlet at 6.70] and 44% XIXc (20.2 g, 0.050 mol, 42%) [^{1}H nmr in acetone-d_6 with TMS 3 H triplet at δ 1.09 (J = 7.5 cps), 2 H quartet at 2.33 (J = 7.5 cps), 2 H singlet at 3.23, 1 H broad singlet at 5.67, and 2 H–OH broad singlet at 6.70]. Six recrystallizations from carbon tetrachloride gave a mixture of 80% XVIII and 20% XIXc (nmr) that nevertheless melted sharply at 126–127°.

Anal. Calcd for $C_{11}H_{10}F_{12}O_2$: C, 32.9; H, 2.5; F, 56.7. Found: C, 32.9; H, 2.5; F, 56.9.

Since products XVIII and XIXc are those expected from 2-methyl-1-butene, such olefin isomerization was confirmed as follows. A reaction mixture containing pure 2-methyl-2-butene (24.0 g, 0.34 mol) [^{1}H nmr in CCl_4 with TMS, 3 H doublet at δ 1.54 (J = 8.5 cps), 6 H singlet at 1.56, and 1 H quartet with fine splitting at 5.15; Varian Aerograph A-90-P, 5 ft × 0.25 in. column packed with 20% Dow silicone 710 on Chromosorb W, isothermal 70°, He flow rate 1.18 ml/sec, retention time 1.17 min] single peak] and hexafluoroacetone (30 g, 0.18 mol) was held at 165° for 30 hr. Distillation gave recovered olefin (10.8 g, 0.154 mol) [bp 38–40° (80% 2-methyl-2-butene, nmr above, and 20% 2-methyl-1-butene); ^{1}H nmr in CCl_4 with TMS, 3 H triplet at δ 1.00 (J = 7.0 cps), 3 H singlet at 1.63, 2 H quartet at 1.98 (J = 7.0 cps), and 2 H broad singlet, fine splitting at 4.63; vpc as above two peaks, retention times 0.92 and 1.16 min] and a mixture of three 1:1 products (31 g, 0.13 mol, 38%) (bp 133°). The latter contained 80% $CH_3CH{=}C(CH_3)CH_2C(CF_3)_2OH$, 90% *trans* and 10% *cis* [vpc as above, retention time 6.0 min; ^{1}H nmr of *trans* isomer in CCl_4 with TMS, 3 H doublet at δ 1.67 (J = 7.0 cps), 3 H singlet at 1.72, 2 H singlet at 2.67, 1 H–OH singlet at 3.22, and 1 H quartet at 5.51 (J = 7.0 cps); *cis* form indicated by methyl doublet at δ 1.92 (J = 7.5 cps), and smaller quartet in olefin region], and 20% $CH_2{=}C(C_2H_5)CH_2C(CF_3)_2OH$ [vpc as above, retention time 4.84 min; ^{1}H nmr in CCl_4 with TMS, 3 H triplet at δ 1.03 (J = 7.3 cps), 2 H quartet at 2.18 (J = 7.3 cps), 2 H singlet at 2.77, 1 H–OH singlet at 3.22, 1 H broad singlet at 5.00, and 1 H broad singlet at 5.18].

Anal. Calcd for $C_8H_{10}F_6O$: C, 40.7; H, 4.3; F, 48.3. Found: C, 40.6; H, 4.5; F, 48.1.

The distillation residue (5.0 g, 0.013 mol of XVIII, 55%, and XIXc, 45%; 4%) solidified when it cooled.

2,3-Dimethyl-2-butene.—2,3-Dimethyl-2-butene (8.4 g, 0.10 mol) with hexafluoroacetone (70 g, 0.42 mol) at 180° for 40 hr also gave a mixture of products (32 g) that solidified upon cooling. Nmr analysis showed that it contained 90% XXc (28.8 g, 0.069 mol, 69%) [^{1}H nmr in acetone-d_6 with TMS, 6 H doublet at δ 1.13 (J = 7.0 cps), 1 H heptet at 2.42 (J = 7.0 cps), 2 H singlet at 3.27, 1 H singlet at 5.65, and 2 H–OH broad singlet at 8.28], and 10% XXI (3.2 g, 0.0077 mole, 8%) (^{1}H nmr in acetone-d_6 with TMS, 6 H singlet at δ 1.75, 4 H singlet at 3.07, and 2 H–OH broad singlet at 8.28). Here five recrystallizations (CCl_4) gave pure XXc: mp 123.8–125.2°; mass spec-

trum, molecular ion 416, 0.87%; 401, 0.20%; 398, 0.20%; 397, 0.20%; 347, 0.50%; 250, 1.6%; 249, 6.2%; 235, 2.7%; 231, 1.3%; 207, 1.7%; 147, 1.2%; 145, 1.4%; 127, 1.1%; 97, 1.7% 85, 4.7%; 69, 1.9%; 67, 1.9%; 65, 1.9%; 55, 3.8%; 53, 1.5%; base peak 43, 9.7%; 41, 7.4%; 39, 3.0%; and 29, 1.4%, all of Σ_{28}; metastables, 380.8, 416 → 298; 289.4, 416 → 347, 329 → 309; 214.3, 249 → 331; 200.4, 235 → 217; 196.1, 249 → 221; 182.3, 235 → 207; 178.8, 249 → 211; 172.1, 249 → 207; and 159.0, 197 → 177.

Anal. Calcd for $C_{12}H_{12}F_{12}O_2$: C, 34.6; H, 2.9; F, 54.8. Found: C, 34.3; H, 2.9; F, 54.9.

With 2,3-dimethyl-2-butene (14 g, 0.17 mol) (vpc as in 2-methyl-2-butene experiment, one peak, retention time 3.36 min; ^{1}H nmr in CCl_4 with TMS, singlet at δ 1.61) and hexafluoroacetone (20 g, 0.12 mol) at 170° for 24 hr, the unreacted olefin was isomerized, and two 1:1 products (vpc) were observed. Distillation gave a mixture (7.6 g, 0.09 mol, bp 56–75°) of unreacted 2,3-dimethyl-2-butene (85%) (above retention time and nmr) and 2,3-dimethyl-1-butene (15%) [vpc retention time 1.45 min; ^{1}H nmr in CCl_4 with TMS, 6 H doublet at δ 1.00 (J = 6.7 cps); 3 H singlet at 1.62, 1 H multiplet at 2.62, and 2 H broad singlet at 4.63]. The 1:1 products [10.6 g, 0.042 mole, 25%, bp 83° (90 mm)] then distilled. Vpc and nmr analysis showed that this mixture contained 70% $CH_2{=}C(CH(CH_3)_2)CH_2C(CF_3)_2OH$ [vpc as above, retention time 5.9 min; ^{1}H nmr in CCl_4 with TMS, 6 H doublet at δ 1.08 (J = 6.8 cps), 1 H heptet at 2.27 (J = 6.8 cps); 2 H singlet at 2.74; 1 H–OH singlet at 3.59; 1 H broad singlet at 5.01, and 1 H broad singlet at 5.22] and 30% $(CH_3)_2C{=}C(CH_3)CH_2C(CF_3)_2OH$ (vpc retention time 11.1 min; ^{1}H nmr in CCl_4 with TMS, 9 H singlet at δ 1.67, 2 H singlet at 2.82, and 1 H–OH singlet at 3.17).

Anal. Calcd for $C_9H_{12}F_6O$: C, 43.2; H, 4.8; F, 45.6. Found: C, 43.1; H, 5.0; F, 45.5.

The distillation residue (90% XXc and 10% XXI, 10 g, 0.024 mol, 14%) solidified upon cooling (see above).

Allene.—This diene (15.0 g, 0.37 mol) and hexafluoroacetone (45 g, 0.27 mol) were held at 130° for 63 hr, and a colorless liquid product (35 g) was obtained. Its distillation gave XXII (25.9 g, 0.126 mol, 34%): bp 94°; ^{1}H nmr in CCl_4 with TMS, 1 H triplet at δ 2.23 (J = 2.5 cps), 2 H doublet at 2.88 (J = 2.5 cps), and 1 H–OH singlet at 3.51.

Anal. Calcd for $C_6H_4F_6O$: C, 35.0; H, 2.0; F, 55.3. Found: C, 34.7; H, 2.0; F, 55.4.

The distillation residue (5.0 g, 0.02 mol, 5%) was the 2:1 product XXIII described below.

In another such reaction, allene (14 g, 0.35 mol) and hexafluoroacetone (126.0 g, 0.76 mol) were heated at 150° for 90 hr. After the reaction mixture had cooled and had been evacuated, the white product (125 g) solidified. The solid that remained undissolved when benzene (200 ml) was added to the crude product was purified by vacuum sublimation to give XXIV (10 g, 0.013 mol, 7.4%): mp 228–229°; ^{1}H nmr in acetone-d_6 with TMS, 2 H singlet at δ 4.37, 2 H singlet at 6.28, and 4 H–OH singlet at 7.92; uv spectrum, λ_{max} 241 mμ (ϵ 18,600); mass spectrum, molecular ion 744, 0.91%; 687, 1.4%; 676, 2.1%; 675, 10.2%; 657, 2.5%; 637, 1.1%; 577, 0.62%; 559, 0.71%; 491, 0.67%; 471, 1.3%; 421, 1.2%; 373, 0.70%; 191, 1.6%; 169, 1.0%; 167, 1.3%; 163, 1.1%; 147, 2.5%; 97, 5.5%; base peak 69, 20.3%; and 28, 1.5%, all of Σ_{28}; metastables: 639.5, 675 → 657; 621.5, 657 → 639; 617.6, 657 → 637; and 612.4, 744 → 675.

Anal. Calcd for $C_{18}H_8F_{24}O_4$: C, 29.0; H, 1.1; F, 61.3. Found: C, 28.9; H, 1.1; F, 61.2.

Evaporation of the benzene solution gave a solid product that was also sublimed (50°) to give XXIII[6] (115 g, 0.309 mol, 88%): mp 70–71°; ^{1}H nmr in acetone-d_6 with TMS, 2 H singlet at δ 5.87 and 2 H–OH singlet at 6.38; mass spectrum, molecular ion 372, 0.72%; 354, 6.7%; 335, 4.7%; 303, 3.2%; 285, 3.3%; 253, 2.2%; 236, 2.7%; 215, 1.5%; 213, 1.7%; 191, 4.8%; 169, 4.7%; 119, 1.5%; 97, 4.7%; 89, 1.5%; base peak 69, 16.7%; 39, 2.3%; and 28, 1.5%, all of Σ_{28}; metastables, 336.9, 372 → 354; 317.0, 354 → 335; 246.8, 372 → 303; 246.4, 285 → 265; and 229.4, 354 → 285.

Anal. Calcd for $C_9H_4F_{12}O_2$: C, 29.0; H, 1.1; F, 61.3. Found: C, 28.8; H, 1.1; F, 61.1.

The dimerization of XXIII to give XXIV apparently is catalyzed by acid. Samples of XXIII (1 g) were sealed in glass ampoules and heated for various times. Since XXIII is soluble in benzene and XXIV is not, these reaction mixtures were triturated with benzene; the XXIV that remained undissolved gave a measure of the extent of reaction. At 150 and 180° for 60 hr, no XXIV was formed, while at 200° (60 hr), 3% conversion into XXIV occurred. Extensive decomposition of XXIII took place when it was so heated at 250° for 12 hr. When 1 drop of concentrated hydrochloric acid and XXIII (1 g) were heated at 200° for 60 hr, a 10% conversion to XXIV was observed.

2-Methyl-3-phenylpropene.—The mixture of this olefin (19 g, 0.14 mol) and the ketone (23 g, 0.14 mol) was held at 25–30° in a shaking bomb for 65 hr. Some unreacted ketone escaped when the bomb was opened. Nmr analysis of the crude product (37 g, 0.12 mol, 86%) indicated 55% XXVIIt, 15% XXVIIc, and 30% XXVIII. The distillation gave little separation of these three products, bp 62–63° at (0.25 mm). Nmr and vpc analysis (F & M 500 chromatograph, 0.25 in. × 5 ft column with 20% Dow silicone 710 on Chromosorb W, isothermal 152°, He flow rate 1.2 ml/sec, retention times of XXVIIc and XXVIII 4.5 min and XXVIIt 6.2 min) gave these compositions (fraction 1, 1.0 g, 20% XXVIIt, 27% XXVIIc, and 53% XXVIII; fraction 2, 4.85 g, 45% XXVIIt, 18% XXVIIc, and 37% XXVIII; and fraction 3, 21.1 g, 61% XXVIIt, 13% XXVIIc, and 26% XXVIII). Fraction 4 was nearly pure XXVIIt (7.3 g, 98%): ^{1}H nmr in CCl_4 with TMS, 3 H singlet at δ 1.98, 2 H singlet at 2.82, 1 H–OH singlet at 3.00, 1 H broad singlet at 6.45, and 5 H singlet at 7.24. It was further purified by preparative vpc.

Anal. Calcd for $C_{13}H_{12}F_6O$: C, 52.4; H, 4.1; F, 38.2. Found: C, 52.5; H, 4.1; F, 38.0. Found (fraction 3): C, 52.5; H, 3.9; F, 38.3.

This study gave the nmr spectra of XXVIIc (^{1}H nmr in CCl_4 with TMS, 3 H singlet at δ 2.03, 2 H singlet at 2.93, 1 H–OH singlet at 3.00, 1 H broad singlet at 6.68, and 5 H singlet at 7.22) and XXVIII [^{1}H nmr in CCl_4 with TMS, 2 H singlet at δ 2.60, 1 H–OH singlet at 3.00, 2 H singlet at 3.45, 2 H multiplet at 5.09 (J = 1.2 cps), and 5 H singlet at 7.21]. It further gave the yields of XXVIIt (0.075 mol, 54%), XXVIIc (0.013 mol, 9%), and XXVIII (0.026 mol, 19%). That the major geometrical isomer is XXVIIt [phenyl *trans* to $-CH_2C(CF_3)_2OH$] and the minor one XXVIIc is based upon a comparison of the chemical shifts of their olefinic hydrogen atoms (XXVIIt, δ 6.45; XXVIIc, δ 6.68). The olefinic hydrogen absorption of IIt [δ 5.46, *cis* to $-CH_2C(CF_3)_2OH$ and *trans* to methyl as in XXVIIt] is at higher field than that of IIc [δ 5.65, *cis* to methyl and *trans* to $-CH_2C(CF_3)_2OH$ as in XXVIIc].

The distillation residue (2 g) crystallized. Complete vacuum sublimation of it gave two fractions, both pure XXIXc: mp 75–76°; ^{1}H nmr in acetone-d_6 with TMS, 2 H singlet at δ 3.17, 2 H–OH singlet at 3.28, 2 H singlet at 3.71, 1 H broad singlet at 5.79, and 5 H singlet at 7.28.

Anal. Calcd for $C_{16}H_{12}F_{12}O_2$: C, 41.4; H, 2.6; F, 49.1. Found: C, 41.5; H, 2.7; F, 49.1.

The chemical shift of the olefinic hydrogen atom of XXIXc (δ 5.79) indicates the structure given rather than that of the alternative substituted styrene. The α-olefinic hydrogen atoms of such styrenes absorb at lower field (XXVIIt, δ 6.45, and XXVIIc, δ 6.68).

The Reaction of 2-Methylpropene with 1,3-Dichloro-1,1,3,3-tetrafluoropropanone.—A reaction mixture containing this olefin (10.7 g, 0.19 mol) and ketone (83.2 g, 0.42 mol) was held at 120° for 72 hr. After the bomb and its contents had cooled, remaining reactants were allowed to escape, and the reaction product (72.0 g, 0.16 mol, 84%) solidified. Its vpc analysis (above chromatograph and column, isothermal 110°, He flow rate 1.18 ml/sec) showed that it contained two substances (65%, retention time 12.3 min, and 35%, retention time 13.1 min). The one of longer retention time, $H_2C{=}C[CH_2(CF_2Cl)_2OH]_2$ (25.2 g, 0.056 mol, 29%) (mp 104.5–106°; ^{1}H nmr in $CDCl_3$ with TMS, 4 H singlet at δ 3.11, 2 H–OH broad singlet at 4.16, and 2 H singlet at 5.20) was obtained pure after five recrystallizations from carbon tetrachloride.

Anal. Calcd for $C_{10}H_8F_8Cl_4O_2$: C, 26.5; H, 1. ; F, 33.5. Found: C, 26.3; H, 1.7; F, 33.4.

The other product, *cis*-$CH_3C[CH_2C(CF_2Cl)_2OH]{=}CHC(CF_2Cl_2)OH$ (46.8 g, 0.103 mol, 54%) (mp 73–74°; ^{1}H nmr in CCl_4 with TMS, 3 H singlet at δ 2.07, 2 H singlet at 3.20, 1 H broad singlet at 5.62, 2 H–OH broad singlet at 5.73) was purified by column chromatography of the recrystallization liquors on alumina wherein it was eluted with benzene. It is presumed to be the *cis* isomer since its nmr spectrum resembles that of IIc. The product from evaporation of the benzene solution was then sublimed.

Anal. Calcd for $C_{10}H_8F_8Cl_4O_2$: C, 26.5; H, 1.8; F, 33.5; Cl, 31.2. Found: C, 26.3; H, 1.7; F, 33.3; Cl, 31.1.

The Reaction of 3-Phenylpropene with Chloropentafluoropropanone.—A solution containing this olefin (80.7 g, 0.68 mol) and this ketone (124.5 g, 0.68 mol) was held at 25° for 72 hr. Distillation gave only XXXt (102 g, 0.36 mol, 53%): bp 63–65° (0.3 mm); ^{1}H nmr in $CDCl_3$ with TMS, 2 H doublet at δ 3.28 (J = 6.5 cps); 1 H–OH singlet at 3.00, 1 H pair of triplets at 6.09 (J = 16.0 and 6.5 cps), 1 H doublet at 6.58 (J = 16.0 cps), and 5 H singlet at 7.28.

Anal. Calcd for $C_{12}H_{10}F_5ClO$: C, 47.9; H, 3.4; F, 31.6; Cl, 11.8. Found: C, 48.1; H, 3.4; F, 31.7; Cl, 11.9.

Thermal Studies.—A bomb tube containing I (2 g, 0.0090 mol) was heated at 300° for 16 hr. When this reaction mixture cooled, a white solid (0.89 g) precipitated. It was collected on a filter and was washed with methylene chloride. Nmr analysis showed that it contained 45% IIc and 55% III. The oil remaining (0.90 g) after the methylene chloride had been removed from the filtrate contained unreacted I and IIt (7:3 molar proportions, nmr analysis) and a small amount of polyisobutene. Major products therefore were IIc (0.39 g, 0.0010 mol), IIt (0.39 g, 0.0010 mol), and III (0.50 g, 0.0013 mol). I (0.51 g, 0.0023 mol) remained unreacted.

The product mixture (2 g, 90% IIc and 10% III) was unchanged after it was held at 150° for 24 hr in a sealed tube. However, extensive reaction occurred when a mixture of 60% IIc and 40% III (14.5 g, 0.0374 mol) was similarly heated at 275° for 24 hr. When it cooled, part of reaction mixture crystallized. It was triturated with carbon tetrachloride (50 ml). Solid products (8.2 g) were separated on a filter, and an oil (5.7 g) remained after carbon tetrachloride had been distilled from the filtrate. Both were analyzed by nmr and vpc methods (Varian Aerograph temperature-programmed chromatograph; 20% SE 30 on Chromosorb P, 0.25 in. × 5 ft; initial temperature 52° increased 10°/min; He flow rate 1 ml/sec; retention times—I, 2.33 min; I′, 2.53 min; IIt, 8.42 min; and IIc and III, 9.0 min). The solid contained 49 mol % IIc (4.02 g, 0.0104 mol), 38 mol % III (3.11 g, 0.0080 mol), and 13 mol % IIt (1.07 g, 0.0028 mol); the oil contained 78 mol % IIt (4.93 g, 0.013 mol, total in both fractions 0.0158 mol), 10 mol % I (0.34 g, 0.0015 mol), and 11 mol % I′ (0.37 g, 0.0017 mol).

Pure IIt (n^{25}D 1.3598; ^{1}H nmr in $CDCl_3$ with TMS, 3 H singlet at δ 2.15, 2 H singlet at 2.73, 2 H–OH singlet at 3.45, and 1 H broad singlet at 5.46; mass spectrum, molecular ion at 388, 0.48%; 369, 2.1%; 350, 2.8%; 319, 7.1%; 281, 3.7%; 261, 3.7%; 145, 3.4%; 69, 11.4%; 44, 5.5%; 43, 2.1%; base peak at 40, 16.2% all of Σ_{39}) was obtained by preparative vpc of the oil fraction.

Anal. Calcd for $C_{10}H_8F_{12}O_2$: C, 30.9; H, 2.1; F, 58.7. Found: C, 30.8; H, 2.2; F, 58.5.

Less extensive reaction was observed when a sample containing 90% IIc and 10% III was held at 250° for 16 hr. Analysis as above showed IIc (54 mol %), III (18 mol %), and IIt (28 mol %).

The bomb tube pyrolysis of IXc (5.0 g, 0.011 mol) contrasts with those above since the three possible 1:1 products are more important. Again, part of the reaction mixture solidified as it cooled, but here vigorous gas (CF_3COCF_3) evolution occurred when the bomb tube was opened. Trituration with carbon tetrachloride (25 ml) as before gave a solid product (unreacted IXc, 1.5 g, 0.0033 mol) and an oil (2.4 g). Nmr and vpc analysis (as above, except initial temperature 75° with 10° increase per min; retention times—XXXII, 10.55 min; XXXIII, 11.7 min; XXXI, 12.1 min; IXc, 13.25 min; and IXt, 13.65 min) showed that the oil contained 48 mol % XXXI, 25 mol % XXXII, 9 mol % XXXIII, and 18 mol % IXt. Total yields were XXXI (1.05 g, 0.0037 mol, 34%), XXXII (0.54 g, 0.0019 mol, 17%), XXXIII (0.20 g, 0.0007 mol, 6%), IXt (0.63 g, 0.0014 mol, 13%), and unreacted IXc (1.5 g, 0.0033 mol, 30%).

Pure IXt was isolated by preparative vpc (n^{25}D 1.4158; ^{1}H nmr in $CDCl_3$ with TMS, 2 H singlet at δ 3.10, 2 H–OH singlet at 4.56, 1 H broad singlet at 5.91, and 5 H singlet at 7.44; mass spectrum, molecular ion at 450, 2.9%; 381, 0.6%; 364, 0.5%; 363, 3.4%; 283, 10.0%; base peak at 214, 10.7%; 197, 10.0%; 177, 3.0%; 145, 3.1%; 129, 2.1%; 117, 3.8%; 115, 4.8%; 91, 2.5%; 77, 3.2%; 69, 4.3%; 51, 3.1%; and 39, 3.1% all of Σ_{39}). Nmr spectra of XXXI (^{1}H nmr in CCl_4 with TMS, 3 H methyl singlet at δ 2.37, 1 H–OH singlet at 3.00, 1 H broad singlet at 5.69, and 5 H singlet at 7.35), XXXII [^{1}H nmr in CCl_4 with TMS, 3 H methyl doublet at δ 2.12 (J = 1.5 cps), 1 H–OH singlet at 3.00, 1 H broad singlet at 5.69, and 5 H singlet at 7.39], and XXXIII (2 H singlet at δ 3.21, 1 H–OH singlet at 3.00, 1 H broad singlet at 5.32, 1 H broad singlet at 5.51, and 5 H singlet at 7.35) were determined from that of the oil and various preparative vpc fractions of it.

Acidities.—These potentiometric acid–base titrations were performed with a glass electrode as indicator and a saturated calomel electrode, sce, as reference; and with a Leeds and Northrup pH indicator (−700 to 0 and 0 to 700-mV scale). Each sample (References: phenol, 0.27 g; 1,1,1,3,3,3-hexafluoro-2-propanol, 0.54 g; acetic acid, 30 ml of 0.1006 N. Products: X, 0.586 g; IIc, 0.554 g; IV, 0.548 g) in dimethylformamide (100 ml) was titrated with tetrabutylammonium hydroxide (0.34 N; prepared by dilution of 1 N reagent in methanol with 2-propanol). The results are given in Figure 1.

Registry No.—I, 665-05-4; IIc, 16202-90-7; IIt, 16203-24-0; III, 16202-91-8; IV, 16202-92-9; V, 16202-93-0; VII, 16202-94-1; IXc, 16202-95-2; IXt, 16202-96-3; X, 646-97-9; XIc, 16202-98-5; XIt, 16202-99-6; XIIc, 16223-66-8; XIIt, 16203-00-2; XIIIt, 16203-01-3; XIV, 16203-02-4; XVt, 16203-03-5; XVIc, 16203-04-6; XVIt, 16203-05-7; XVIIt, 16203-06-8; XVIII, 16203-07-9; XIXc, 16203-08-0; $CH_3CH{=}C(CH_3)CH_2C(CF_3)_2OH$ (*cis*), 16203-09-1; $CH_3CH{=}C(CH_3)CH_2C(CF_3)_2OH$ (*trans*), 16203-10-4; $CH_2{=}C(C_2H_5)CH_2C(CF_3)_2OH$, 16203-11-5; XXc, 16203-12-6; $CH_2{=}C[CH(CH_3)_2]CH_2C(CF_3)_2OH$, 16203-13-7; $(CH_3)_2C{=}C(CH_3)CH_2C(CF_3)_2OH$, 16203-14-8; XXII, 16203-15-9; XXIII, 16203-16-0; XXIV, 16203-17-1; XXVIIc, 16203-18-2; XXVIIt, 16203-19-3; XXVIII, 16203-20-6; XXIXc, 16203-21-7; $CH_2{=}C[CH_2C(CF_2Cl)_2OH_2]$, 4795-96-4; *cis*-$CH_3C[CH_2C(CF_2Cl)_2OH]{=}CHC(CF_2Cl)_2OH$, 16203-23-9; XXXt, 16223-67-9; XXXI, 16204-30-1; XXXII, 16204-31-2; XXXIII, 16204-32-3.

The Photochemistry of Unsaturated Nitrogen-Containing Compounds. I. Irradiation of Benzalazine

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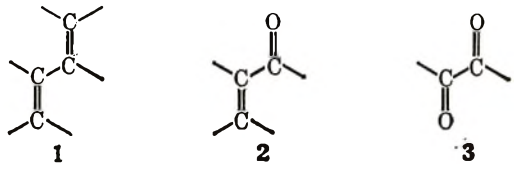
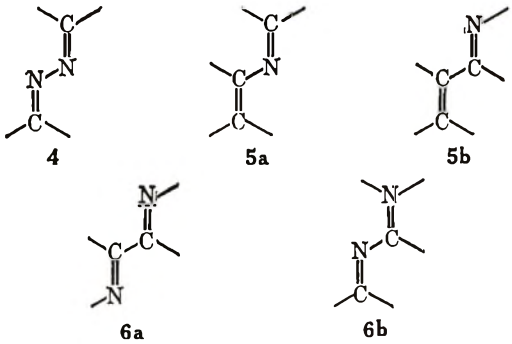
The direct irradiation of benzalazine (**7**) in methanol or benzene is shown to produce, after chromatographic separation of the irradiation mixture, *trans*-stilbene, benzonitrile, and benzaldehyde. The benzaldehyde is not present in the reaction mixture immediately after irradiation but results from a reaction occurring during isolation. Evidence is presented identifying benzaldimine (**8**) as the photochemically produced precursor of benzaldehyde. This observation is incorporated into a proposed reaction mechanism. The inability of triphenylene to sensitize this process is discussed both in terms of the excited state responsible for reaction and also in light of the previously determined capability of benzophenone to initiate photochemically the decomposition of **7**.

During the past several years one of the active areas of organic photochemistry has been the study of systems which contain two conjugated double bonds. Within this general classification of compounds the three types of molecules which have attracted the majority of attention are the dienes (**1**), the enones (**2**), and the diones (**3**). Irradiation of each of these three types of systems has produced a different and highly varied set of photochemical reactions.[1]



1 **2** **3**

In contrast to the three types of systems mentioned above, the azines[2] (**4**), the enimines (**5a,b**), and the diimines (**6a,b**) constitute several additional classes



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

6a **6b**

of compounds which possess two conjugated double bonds but which have been the subject of little photochemical investigation.[2-5] Since each of the three classifications of conjugated compounds already under study has produced an important series of photochemical processes in which the type of reaction observed varies considerably from one class of compounds to the next, a systematic consideration of the remaining, nitrogen containing systems is a logical and potentially valuable undertaking. The work reported here on the photochemistry of benzalazine (**7**) represents the initial phase of such investigation.

Before describing the results of a photochemical study of benzalazine (**7**) it is necessary to note that previous mention of the irradiation of **7** has appeared twice in the literature.[5,6] The first instance,[6] an account of work done in connection with a study of the thermal decomposition of **7**, contained the report that **7** was unreactive when exposed to light of wavelength greater than 250 mμ. In the second paper,[5] which describes an observation arising from the study of the reactions of phenyldiazomethane, it was recorded that **7**, upon irradiation in the presence of benzophenone, was decomposed to yield benzonitrile. In neither of these studies was the photochemistry of benzalazine (**7**) the primary goal of the research conducted; therefore, although several interesting observations were made, a comprehensive study of the excited-state reactions of **7** did not ensue.

Results

Direct irradiation of a methanol solution of **7** under a nitrogen atmosphere produced upon removal of solvent a deep yellow oil. Chromatography on Florisil separated the reaction mixture into four fractions: unreacted starting material, benzonitrile (38%),[7] benzaldehyde (39%), and *trans*-stilbene (4%). The product yields remained constant for different low conversions; however, irradiations in which es-

$$\underset{\mathbf{7}}{C_6H_5CH{=}NN{=}CHC_6H_5} \xrightarrow[2.\ \text{chromatographic separation}]{1.\ h\nu \text{ in benzene or methanol}} C_6H_5C{\equiv}N + C_6H_5CHO + C_6H_5CH{=}CHC_6H_5$$

sentially all of the starting material was consumed resulted in lower yields, presumably owing to the photochemical decomposition of the products (see Table I). A significant change in product yield was noted when the relatively inert benzene was used as the reaction solvent.[8] In this case the reaction mixture after chromatography gave, in addition to unreacted starting material, benzonitrile (90%), benzaldehyde (90%), and *trans*-stilbene (7%).

Irradiation of either a benzene or methanol solution of **7** with light previously passed through a Pyrex

(1) (a) O. L. Chapman, *Advan. Photochem.*, **1**, 381 (1963); (b) K. Schaffner, *ibid.*, **4**, 81 (1966); (c) R. Srinivasan, *ibid.*, **4**, 113 (1966); (d) R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., New York, N. Y., 1966, pp 32–57, 93–94, 105–150; (e) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1965).

(2) P. Beak and J. L. Miesel, *J. Amer. Chem. Soc.*, **89**, 2375 (1967).

(3) R. A. Mitsch and P. M. Ogden, *Chem. Commun.*, 59 (1967).

(4) (a) R. K. Brinton, *J. Amer. Chem. Soc.*, **77**, 842 (1955); (b) J. F. Ogilvil, *Chem. Commun.*, 359 (1965).

(5) J. E. Hodgkins and J. A. King, *J. Amer. Chem. Soc.*, **85**, 2679 (1963).

(6) H. E. Zimmerman and S. Somasekhara, *ibid.*, **82**, 5865 (1960).

(7) All yields corrected for unreacted starting material.

(8) See footnote *d*, Table I.[9]

(9) (a) L. M. Stephenson, D. G. Whitten, G. F. Vesley, and G. S. Hammond, *ibid.*, **88**, 3666 (1966); (b) J. Saltiel and L. Metts, *ibid.*, **89**, 2233 (1967).

TABLE I
IRRADIATIONS OF BENZALAZINE (7)

Reacn no.	Time, hr	% completion	Filter	Sensitizer	Solvent	% yield of products[a] Benzonitrile	Benzaldehyde	*trans*-Stilbene
1	12	21	None	None	Methanol	38	40	3
2	20	31	None	None	Methanol	38	39	4
3	75	100	None	None	Methanol	33	26	5
4	60		Pyrex[b]	None	Methanol		No reaction	
5	41	31	Vycor[c]	None	Methanol	36	38	3
6	40	9	None	None[d]	Benzene	90	90	7
7	60		Pyrex	None	Benzene		No reaction	
8	60		Pyrex	Triphenylene	Benzene		No reaction	
9[e]	*f*	*g*	Pyrex	Benzophenone	Cyclohexane	85	0	0

[a] Corrected for unreacted starting material. [b] Removes light of wavelength shorter than 280 mμ. [c] Removes light of wavelength shorter than 210 mμ. [d] It is probable that the solvent was participating in energy transfer in this reaction; however, its exact role is unclear. See ref 9a and b. [e] See ref 5. [f] Time not reported; see ref 5. [g] Per cent completion was not given but apparently was near 100; see ref 5.

filter (no transmittance at wavelengths shorter than 280 mμ) resulted in quantitative recovery of starting material. When a Vycor filter (no transmittance at wavelengths shorter than 210 mμ) was used, the reaction took place in the same manner as in the unfiltered irradiation; however, the photolysis time was doubled in order to reach the same degree of completion. For a second time no reaction was observed when an experiment was conducted using triphenylene as a triplet-state sensitizer.[10]

The photochemical reactions of benzalazine (7) are summarized in Table I.

Although benzaldehyde appeared to be one of the photoproducts, its characteristic absorption at 5.91 μ ($CHCl_3$) was absent in the ir spectrum of the crude irradiation mixture;[11] therefore, benzaldehyde must have been the product of some reaction occurring during chromatography. Control experiments showed that the starting material and the chromatographically obtained products were not affected by the isolation procedure, thus suggesting the intermediacy of some unstable photoproduct which was being transformed to benzaldehyde. Although the characteristic benzaldehyde absorption was missing, the crude ir spectrum of the irradiation mixture showed an absorption band at 6.12 μ which was present in neither the starting material nor the products but could be identified in the spectrum of a known sample of benzaldimine[12] (8). When the volatile products from the reaction mixture were distilled *in vacuo* at room temperature, the ir spectrum of the distillate appeared to be that of a mixture of benzonitrile and 8. Since one of the two established derivatives of 8 is benzaldimine hydrochloride,[12] several attempts were made to obtain this salt by saturation of the above-mentioned distillate with hydrogen chloride gas; however, no solid product could be separated from the mixture. The other established derivative of 8 is the corresponding aldehyde resulting from hydrolysis. After treatment of the distillate with water, its ir spectrum resembled that of a known mixture of benzonitrile and benzaldehyde. Reacting the hydrolysis product from the irradiation mixture with either semicarbazide hydrochloride or 2,4-dinitrophenylhydrazine resulted, respectively, in the precipitation of the semicarbazone and 2,4-dinitrophenylhydrazone of benzaldehyde; in this manner, the identity of the hydrolysis product was established to be benzaldehyde. A final but necessary requirement for the intermediacy of 8 in the proposed reaction sequence was met when 8 was converted into benzaldehyde during a control chromatography run. Thus, on the basis of spectroscopic evidence, direct hydrolysis to benzaldehyde, and chromatographic behavior, the unstable intermediate produced upon irradiation of benzalazine (7) is identified as benzaldimine (8).

(10) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4537 (1964).

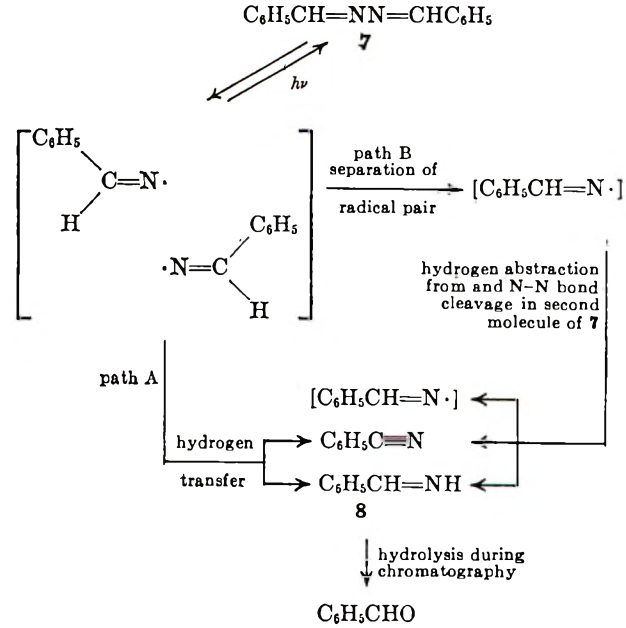
(11) The ir spectra of known mixtures showed that less that 2 mg of benzaldehyde would have been detected under these conditions; in addition, combining 2 mg of benzaldehyde with the reaction mixture at this time caused the appearance of the easily detectable carbonyl band at 5.91 μ.

(12) T. L. Tolbert and B. Houston, *J. Org. Chem.*, **28**, 695 (1963).

Discussion

A proposed mechanism for the photochemical formation of benzonitrile and benzaldehyde from benzalazine (7) is given in Scheme I. In this process it is postulated that the initial step is the photochemical cleavage of the nitrogen–nitrogen bond in 7 to produce a radical pair. The reactive species resulting from this fission can either proceed directly *via* a hydrogen transfer to give benzonitrile and benzaldimine (8) (path A)

SCHEME I
FORMATION OF BENZONITRILE AND BENZALDEHYDE FROM BENZALAZINE (7)



or they may react by an alternative route beginning with escape from the solvent cage and leading to reaction with a second molecule of **7** (path B). In reaction through path B the abstraction of a hydrogen atom from **7** produces **8** while the subsequent (or simultaneous) nitrogen–nitrogen bond cleavage in **7** leads to benzonitrile and generates a new free-radical species capable of repeating the hydrogen abstraction process. In either paths A or B, the final step in the sequence is the hydrolysis of **8** to benzaldehyde during chromatography.

In considering the justification for the proposed mechanism, several factors are of importance. First, the formation of the radical pair shown in Scheme I has considerable analogy in the photochemistry of the related α-diketone systems where the photocleavage of the central (carbon–carbon) bond is one of the frequently occurring processes.[13-17] Photochemically producing the radical pair as outlined above has the effect of creating immediately adjacent to each other, two species either one of which can act as a hydrogen source or a hydrogen acceptor in a disproportionation reaction; therefore, the transfer of a hydrogen atom at this point as depicted by path A represents a logical subsequent step. Reaction *via* path A is analogous to the reaction pathway proposed for the gas phase irradiation of acetaldazine.[4a] The alternative or, perhaps, additional mode for understanding product formation, path B, merits certain consideration owing to its resemblence to the previously suggested mechanism for the photochemical decomposition of benzalazine (**7**) in the presence of benzophenone[5] (Scheme II).

SCHEME II
PHOTOCHEMICAL FORMATION OF BENZONITRILE FROM BENZALAZINE (7) IN THE PRESENCE OF BENZOPHENONE[5]

$$(C_6H_5)_2C{=}O \xrightleftharpoons{h\nu} (C_6H_5)_2C{=}O^*$$

$$C_6H_5CH{=}N{-}N{=}CHC_6H_5 + (C_6H_5)_2C{=}O^* \rightleftharpoons C_6H_5\dot{C}{=}N{-}N{=}CHC_6H_5 + (C_6H_5)_2\dot{C}OH$$

$$C_6H_5\dot{C}{=}N{-}N{=}CHC_6H_5 + (C_6H_5)_2C{=}O \rightleftharpoons 2C_6H_5C{\equiv}N + (C_6H_5)_2\dot{C}OH$$

$$2(C_6H_5)_2\dot{C}OH \rightleftharpoons \text{benzpinacol}$$

Since reaction by either path A or B leads to a result which is consistent with the experimental finding that benzonitrile and the precursor of benzaldehyde must form with equal probability (equal molar quantities of benzonitrile and benzaldehyde are always isolated when the photochemical reaction is run to different low conversions), a definitive statement concerning the relative importance of these two processes must await the further investigation now in progress. The validity of the final portion of the proposed reaction mechanism, namely, the existance of benzaldimine (**8**) as a photoproduct and its subsequent conversion to benzaldehyde, rests in the demonstration given earlier in detail (see results) that **8**, and not benzaldehyde, is present in the reaction mixture immediately after irradiation of **7** and is totally converted into benzaldehyde during chromatography.

It is informative to compare certain portions of this work with the previously mentioned irradiation of benzalazine (**7**) in the presence of benzophenone.[5] Since excited benzophenone is capable not only of hydrogen abstraction but also of triplet energy transfer,[18] benzonitrile could have resulted either from a hydrogen abstraction process such as that given in Scheme II or by a transfer of triplet energy from benzophenone to **7** followed by a different series of reactions, possibly similar with those shown in Scheme I. One method for resolving this problem consists of replacing benzophenone (E_t = 69 kcal/mol[9a]) with a compound such as triphenylene (E_t = 67 kcal/mol[9a]) which is capable of transferring triplet excitation of essentially equal energy but is not readily able to hydrogen abstract. When an experiment was run using triphenylene as a sensitizer, no measurable amount of photochemical reaction was observed; thus, a clear indication is provided that hydrogen abstracting ability is an important element in the light induced formation of benzonitrile from benzalazine (**7**)–benzophenone mixtures. This experiment, however, provides no evidence concerning other aspects of the mechanism shown in Scheme II.

The identity of the excited state responsible for the observed photochemical reaction is as yet unknown; however, the existing experimental data do provide some information pertaining to this question. It is reasonable to assume that the triplet energy for benzalazine (**7**) is not considerably greater than those values found in the related diene-type, systems shown in Table II.[19-23] On the basis of such a comparison it would appear unlikely that the triplet energy of **7** would be greater than that of triphenylene; consequently, in a sensitization experiment triphenylene should easily transfer triplet excitation to **7**. Since no reaction was observed when triphenylene was used as an energy transfer agent, it seems reasonable to conclude that the lowest energy triplet state of **7** is not capable of reaction. In comparison with the

TABLE II
TRIPLET ENERGIES IN DIENE-TYPE SYSTEMS

Compd		Triplet energy,	
No.	Name	kcal/mol	Ref
1	Butadiene	59.6	*a*
2	Isoprene	60.0	*a*
3	1,3-Hexadiene	53.5	*a*
4	Biacetyl	57.2	*b*
5	Benzil	57.3	*b*
6	Cyclohexenone	61	*c*

[a] See ref 21 and 22. [b] See ref 9a. [c] See ref 23.

(13) H. A. Staab and J. Ipaktschi, *Tetrahedron Lett.*, 583 (1966).
(14) H. A. Staab and J. Iptaktschi, *Angew. Chem., Intern. Ed. Engl.*, **5**, 320 (1966).
(15) P. A. Leermakers, P. C. Warren, and G. F. Vesley, *J. Amer. Chem. Soc.*, **86**, 1768 (1964).
(16) N. C. Yang and A. Morduchowitz, *J. Org. Chem.*, **29**, 1654 (1964).
(17) G. S. Hammond, P. A. Leermakers, and N. J. Turro, *J. Amer. Chem. Soc.*, **83**, 2395 (1961).
(18) L. B. Jones and G. S. Hammond, *ibid.*, **87**, 4219 (1965).
(19) Although it would be of interest to determine whether the lowest triplet state of benzalazine (**7**) is n − II* or II − II* in nature, this is not necessarily a critical feature in comparing the triplet energy of **7** with those of the compounds listed in Table II since this group contains triplet states which are both of the II − II* (butadiene, isoprene, and 1,3-hexadiene) and n − II* (biacetyl[20]) variety.
(20) H. E. Zimmerman, R. W. Binkley, J. J. McCullough, and G. A. Zimmerman, *ibid.*, **89**, 6589 (1967).
(21) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).
(22) R. S. H. Liu, N. J. Turro, and G. S. Hammond, *J. Amer. Chem. Soc.*, **87**, 3406 (1965).
(23) E. Y. Lam, D. Valentine, and G. S. Hammond, *ibid.*, **89**, 3482 (1967).

lowest triplet state, the lowest energy singlet is no more reactive. Irradiation of **7** with light of wavelength greater than 280 mμ produced no reaction even though there was considerable absorption of light by **7** due to the long wavelength absorption band (λ_{max} 303 mμ (methanol)). Combining the two observations described above leads to the unusual conclusion that the reactivity of **7** is derived from an excited state other than the lowest singlet or triplet.

Although *trans*-stilbene is a minor product resulting from the irradiation of **7**, the mechanism for its formation is of interest owing to the existance of several possible reaction pathways each of which finds some precedent in the chemical literature. Work designed to select among these several possibilities is now in progress.

Experimental Section[24]

Direct Irradiation of Benzalazine (7) in Methanol.—In a typical run 208.3 mg (1.000 mmol) of benzalazine[25](**7**) in 300 ml of anhydrous methanol[26] was irradiated for 20 hr at 23° with constant stirring using a 100-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis. No filter was used.

After 20 hr, the solvent was removed by distillation *in vacuo* below 40°, producing a distillate which was transparent in the uv spectrum and leaving a yellow oil. The residual oil was chromatographed on a 78 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 20 ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 1.0 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 1.0 l. of 1:24 ether–hexane; 0.5 l. of 1:12 ether–hexane; and 0.5 l. of 1:6 ether–hexane.

Fractions 16–30 yielded 2.4 mg (4%) of crystalline *trans*-stilbene, mp 121–122° (lit.[27] mp 124°). This material was identical in ir spectrum and showed no mixture melting point depression with a known sample. Fractions 90–120 yielded 144 mg of benzalazine (**7**) as yellow crystals, mp 92–93°. Fractions 123–139 afforded 12.7 mg (39%) of a slightly yellow oil which gave the ir spectrum of benzaldehyde. Treatment of these fractions with semicarbazide hydrochloride according to the method of Shriner, Fuson, and Curtin[28] produced benzaldehyde semicarbazone, mp 220–222° (lit.[28] mp 222°). Fractions 140–167 gave 12.0 mg (38%) of a clear oil identical in ir and uv spectra with a known sample of benzonitrile.

Irradiation of Benzalazine (7) in Methanol Using a Vycor Filter.—The type and amount of materials used and the irradiation procedure were identical with that described in the direct irradiation in methanol except that a vycor filter was placed between the light source and the reaction mixture and the irradiation time was increased to 41 hr.

The irradiation mixture was chromatographed on a 76 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 500 ml fractions were collected. The column was eluted as follows: 3.5 l. of 1:19 ether–hexane and 0.5 l. of 1:9 ether–hexane.

Fraction 1 gave 2.0 mg (3%) of crystalline *trans*-stilbene, mp 120–122°. Fractions 2 and 3 gave 144 mg of benzalazine (**7**) as a yellow solid, mp 90–93°, yielding, after 1 recrystallization from petroleum ether (35–60°), 139 mg of benzalazine (**7**), mp 93–94°. Fractions 5 and 6 afforded 12.7 mg (38%) of benzaldehyde, identified by ir spectroscopy. Fractions 7 and 8 yielded 11.5 mg (36%) of benzonitrile, identified by ir spectroscopy.

Irradiation of Benzalazine (7) in Methanol Using a Pyrex Filter.—The procedure and the identity and quantity of the compounds used corresponded exactly to the direct irradiation in methanol except that a Pyrex filter was placed between the light source and the reaction mixture and the irradiation time was increased to 60 hr. The chromatographic adsorbent and elution scheme were the same as used in the direct irradiation.

Fractions 90–135 afforded 207 mg of crystalline benzalazine (**7**), mp 92–93°.

Direct Irradiation of Benzalazine (7) in Benzene.—The type and amount of compounds used and the experimental procedure were the same as in the direct irradiation in methanol except that the reaction solvent was benzene and the irradiation time became 40 hr.

The irradiation mixture was chromatographed on a 76 × 2.5 cm florisil column slurry packed in 1:9 ether–hexane; 20 ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 0.5 l. of 1:24 ether–hexane; and 1.0 l. of 1:12 ether–hexane.

Fractions 15–35 yielded 1.1 mg (7%) of crystalline *trans*-stilbene. Fractions 96–115 gave 190 mg of benzalazine (**7**) as a crystalline yellow solid, mp 91–93°. Fractions 116–125 afforded 8.6 mg (90%) of benzaldehyde which was identified by ir spectroscopy. Fractions 126–150 yielded 8.1 mg (90%) of benzonitrile, also identified by ir spectroscopy.

Irradiation of Benzalazine (7) in Benzene Using a Pyrex Filter.—The procedure and the identity and quantity of the compounds used were exactly that employed in the direct irradiation in methanol except that a Pyrex filter was placed between the light source and the reaction mixture, benzene was used as an irradiation solvent, and the irradiation time was 60 hr. The chromatographic adsorbent and the elution scheme were the same as used in the direct irradiation in methanol.

Fractions 95–130 afforded 206 mg of crystalline benzalazine (**7**), mp 92–93°.

Irradiation of Benzalazine (7) in Benzene Using Triphenylene as a Sensitizer.—In a typical run 52.1 mg (0.25 mmol) of benzalazine (**7**) and 280 mg (1.22 mmol) of triphenylene in 300 ml of benzene were irradiated for 60 hr. The experimental procedure used, including the chromatographic separation, was the same as that used in the direct irradiation in methanol except that a Pyrex filter was placed between the light source and the reaction mixture.

Fractions 100–127 from the chromatography yielded 53.7 mg of yellow solid, mp 89–93°, producing after recrystallization from petroleum ether, 52.0 mg of benzalazine (**7**), mp 92–94°.

Test of the Stability of Benzalazine (7) under the Reaction and Isolation Conditions.—Benzalazine (**7**) (208.3 mg, 1.000 mmol) was dissolved in 300 ml of anhydrous methanol and stirred for 60 hr at 25°, and the solvent was removed by distillation *in vacuo* below 40°. The residual solid was chromatographed on a 77 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 20 ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 1.0 l. of 1:24 ether–hexane; 0.5 l. of 1:12 ether–hexane; and 0.5 l. of 1:6 ether–hexane.

Fractions 90–135 yielded 206 mg of benzalazine (**7**), mp 93–94°.

Test of the Stability of Benzonitrile during Chromatography.—Benzonitrile (63 mg, 0.61 mmol) was chromatographed on a 79 × 2.5 cm column of Florisil slurry packed in 1:9 ether–hexane; 500-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 0.5 l. of 1:24 ether–hexane; and 2.0 l. of 1:12 ether–hexane.

Fractions 7 and 8 gave 59 mg of benzonitrile identified by ir spectroscopy.

Test of the Stability of Benzaldehyde during Chromatography.—Benzaldehyde (52 mg, 0.49 mmol) was chromatographed on a 78 × 2.5 cm column of Florisil slurry packed in 1:9 ether–hexane; 500-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:49 ether–hexane; 0.5 l. of 1:24 ether–hexane; and 2.5 l. of 1:12 ether–hexane.

Fraction 8 gave 52 mg of benzaldehyde identified by ir spectroscopy.

Identification of Benzaldimine[12] (8) as an Intermediate in the Photolysis of Benzalazine (7).—A 208.3-mg (1.000 mmol) sample of benzalazine (**7**) in 300 ml of anhydrous methanol was irradiated according to the procedure described in the direct irradiation in methanol. After 75 hr, the solvent was removed by distillation *in vacuo* below 40°, giving a distillate which was transparent in

(24) All melting points were taken on a Fisher–Johns block and are corrected.

(25) T. Curtius and R. Jay, *J. Prakt. Chem.*, **39**, 45 (1889).

(26) In methanol benzalazine shows absorption maxima at 303 (ε 37,800) and 217 mμ (ε 17,900) with shoulders at 324 (ε 17,200) and 309 (ε 34,000) mμ.

(27) A. Michaelis and H. Lange, *Ber.*, **8**, 1314 (1875).

(28) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, pp 218 and 283.

the uv spectrum and leaving a residual yellow oil. The ir spectrum of this oil showed no absorption at 5.91 μ (C=O in benzaldehyde) but did exhibit absorption at 6.12 μ [(C=N in benzaldimine (8)]. The volatile photoproducts were removed *in vacuo* from the reaction mixture at 25° leaving a solid yellow residue and giving as a distillate a clear oil. The ir spectrum of the oil was that of a mixture of benzonitrile and 8 with no benzaldehyde present.[29] Addition of 1.0 ml of water to the distillate, stirring for 10 hr, extraction with ether, and evaporation of the ether gave a second oil whose ir spectrum appeared to be that of a mixture of benzaldehyde and benzonitrile. Treatment of this oil with semicarbazide hydrochloride according to the method of Shriner, Fuson, and Curtin[28] led to the isolation of benzaldehyde semicarbazone, mp 220–222° (lit.[28] mp 222°).

(29) The benzaldimine used for comparison was synthesized according to the procedure given in ref 12.

Conversion of Benzaldimine (8) into Benzaldehyde during Chromatography.—Benzaldimine (8) (52.1 mg, 0.49 mmol) was chromatographed on a 76 × 2.5 cm column of Florisil slurry packed in 1:9 ether–hexane: 20-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 1.0 l. of 1:24 ether–hexane; and 0.5 l. of 1:12 ether–hexane.

Fractions 120–140 afforded 45 mg of benzaldehyde, identified by ir spectroscopy and its semicarbazone derivative, mp 218–220° (lit.[28] mp 222°).

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Arylation by Aromatic Nitro Compounds at High Temperatures. IV. Nitrobenzene with Toluene and Toluene-α-d_3

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Nitrobenzene reacts with toluene at 600° to give the arylation product, methylbiphenyl, in addition to biphenyl and the toluene dehydro dimers (bibenzyl, methyldiphenylmethane, and dimethylbiphenyl). Most of the biphenyl contains one benzene ring from toluene and nitrobenzene each; some consists of benzene rings solely from one reactant. Toluene and toluene-α-d_3, pyrolyzed at low conversion, give only the dehydro dimers. The total amount and distribution differ markedly from that resulting in the nitrobenzene reaction. Apparently, in the absence of added free radicals, toluene pyrolyzes largely by a nonradical mechanism.

Earlier papers described the reactions of nitrobenzene with benzene[1] and with its fluorinated derivatives.[2] To extend these studies to compounds containing benzylic hydrogens, we examined the reactions of aromatic nitro compounds with a series of methylated benzenes and naphthalenes. This paper describes the reactions of nitrobenzene with toluene and toluene-α-d_3 and of nitrobenzene-d_5 with toluene, as well as the pyrolysis of toluene-α-d_3 alone.

Experimental Section

Materials. The reagents and standards for gas chromatography, except as noted below, were purchased from Aldrich Chemicals and used as received. Where purity was critical, the reagent was analyzed and, if necessary, purified by distillation, crystallization, and gas chromatography.

Table I shows the source and melting (or boiling) points of the ten $C_{14}H_{14}$ isomers used as gas chromatography standards. Methyldiphenylmethanes were prepared from methylbenzyl bromides rather than the chlorides as Senff described.[3] Reaction with benzene in the presence of ferric chloride was vigorous, and careful addition was necessary to keep the reaction under control.

Dimethylbiphenyls were prepared by stirring and refluxing mixtures of iodotoluenes and copper at atmospheric pressure for 24 hr, instead of in a bomb tube as described by Ullmann.[4] Unsymmetrical dimethylbiphenyls were made from equimolar mixtures of two iodotoluenes. They were not isolated; their retention times were determined by comparison with authentic symmetrical dimethylbiphenyls.

TABLE I

Compound	Synthesized according to	Yield, mol %	Mp (bp), °C Found	Lit.
Bibenzyl	Purchased, Aldrich	...	52	52
2-Methyldiphenylmethane	*a*	54	(279–281)	(279–282)
3-Methyldiphenylmethane	*a*	48	(265–269)	(268–269)
4-Methyldiphenylmethane	*b*	38	(280–282)	(279–280)
2,2′-Dimethylbiphenyl	*c*	33	15–17	17.8
2,3′-Dimethylbiphenyl	*c*	...	...	(265–267)
2,4′-Dimethylbiphenyl	*c*	...	...	(272–260)
3,3′-Dimethylbiphenyl	*c*	38	(285–287)	(286–287)
3,4′-Dimethylbiphenyl	*c*	...	...	(288–289)
4,4′-Dimethylbiphenyl	Purchased, Aldrich	...	120–121	122

[a] See ref 3. [b] A. Behr and N. A. van Dorp, *Ber.*, **7**, 18 (1874). [c] See ref 4.

Toluene-α-d_3 was prepared in 45 mol % yield by reduction of benzotrichloride in D_2O with zinc dust.[5] It had the following isotopic composition: 2.3% d_2, 96.2% d_3, 1.0% d_4, 0.3% d_5, and 0.2% d_6. Nitrobenzene-d_5 was prepared in 50 mol % yield by nitrating benzene-d_6 with nitrogen pentoxide in carbon tetrachloride according to Haines and Adkins.[6] Its isotopic composition was 96.9% d_5 and 3.1% d_4.

Procedure.—Arylations were run in a Vycor tube filled with Vycor beads in an electric furnace maintained at 600 ± 1° under pure dry nitrogen with contact times of 9–12 sec. The vapors were condensed in a bulb at −60°, the condensate was distilled to recover unreacted material, and the residue was analyzed.

In a typical experiment, a solution of 5.011 ml (0.05 mol) of nitrobenzene in 26.6 ml (0.25 mol) of toluene was passed through a Vycor tube at 600° under nitrogen flowing at 20 cc/minute. Contact time was 9.5 sec. The vapors were condensed in a bulb at −60°; the condensate was distilled to recover 20 ml of toluene and give 6.9 g of products, the composition of which is shown in Table II.

(1) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 3224 (1967).
(2) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **32**, 3114 (1967).
(3) P. Senff, *Ann.*, **220**, 230 (1883).
(4) F. Ullmann and G. H. Meyers, *ibid.*, **332**, 42 (1904).
(5) E. K. Fields and S. Meyerson, forthcoming publication.
(6) L. B. Haines and H. Adkins, *J. Amer. Chem. Soc.*, **47**, 1419 (1925).

TABLE II

PRODUCTS FROM THE REACTION OF NITROBENZENE WITH TOLUENE AND TOLUENE-α-d_3[a]

Product	Relative intensities in low-voltage spectra[b] Toluene	Toluene-α-d_3
Aniline	3	5
Phenol-d_0	22	45[c]
-d_1	...	26[c]
Biphenyl-d_0	42	42
-d_1	...	33
-d_2	...	10
Fluorene-d_0	7	...
-d_2	...	10
Methylbiphenyl-d_0 and diphenylmethane-d_0	100	...
$C_{13}H_{10}D_2$, considered to be diphenylmethane-d_2	...	9
$C_{13}H_9D_3$, considered to be methylbiphenyl-d_3	...	91
$C_{14}(H + D)_{14}$ isomers	61	79

[a] Reaction conditions were 600°, 9.5 sec contact time, and a mole ratio of nitrobenzene to toluene of 0.05:0.25. The weight of products from nitrobenzene + toluene was 6.9 g and that from nitrobenzene + toluene-α-d_3 was 7.0 g. [b] Normalized to a value of 100 for total $C_{13}(H + D)_{12}$. [c] Tentative assignments; shown subsequently (see text) to contain contributions from deuterated anilines as well as phenols.

Table III shows the composition of the dimethylbiphenyls derived from mixtures of two iodotoluenes. The unsymmetrical isomer, as would be expected statistically, was predominant in each case.

TABLE III

Dimethylbiphenyl	Area, %
From *o*- and *p*-Iodotoluenes	
2,2′-	29.5
2,4′-	42.7
4,4′-	19.5
From *o*- and *m*-Iodotoluenes	
2,2′-	25.7
2,3′-	41.5
3,3′-	25.1
From *m*- and *p*-Iodotoluenes	
3,3′-, 3,4′-, 4,4′-	95.1% of total product[a]

[a] Overlapping peaks for the three constituents.

Best separation of $C_{14}H_{14}$ isomers was achieved on a 20 ft × 0.25 in. column of 10% OV-1 on Chromosorb W. Of the 6 dimethylbiphenyls containing a methyl group in each benzene ring, the 2,2′ isomer was cleanly resolved; the 2,3′ and 2,4′ overlapped somewhat, and the 3,3′, 3,4′, and 4,4′ isomers overlapped considerably.

Gas chromatograms for the $C_{14}H_{14}$ isomers from nitrobenzene and toluene showed identical retention times for 3-methyldiphenylmethane and 2,2′-dimethylbiphenyl, as well as much overlapping of the peaks for 2,4′-dimethylbiphenyl, bibenzyl, 2- and 4-methyldiphenylmethane, and 3,3′-dimethylbiphenyl.

Mass Spectrometry and Gas Chromatography.—Analyses were performed with a Consolidated Model 21-103c mass spectrometer with the inlet system at 250 or 325°; with a directly coupled gas chromatograph–mass spectrometer combination[7] also employing a 21-103c instrument with an electron multiplier in place of the Faraday-cup detector; and by gas chromatography on a column of polyethylene glycol sebacate on Chromosorb W. Mass spectra were measured at the conventional 70 ionizing volts and at low voltage (7.5 V, uncor). For the low-voltage measurements, the repellers were maintained at an average potential of 3 V, the exact values being selected to give maximum sensitivity. Precise mass measurements to distinguish among the overlapping phenol and aniline peaks in the spectrum of the reaction products from nitrobenzene and toluene-α-d_3 were made by peak matching on a Consolidated Model 21-110 double-focusing mass spectrometer.

Relative intensities in the low-voltage (7.5 V, uncor) mass spectra of product mixtures were taken as a first approximation to relative concentrations. Sensitivity, *i.e.*, the proportionality factor between parent-peak intensity and concentration, differs from one compound to another. However, closely related compounds have roughly equal sensitivities at the ionizing voltage employed in our work.[8] For example, the same sample was analyzed by both low-voltage mass spectrometry and gas chromatography, and the ratios of peak intensities and areas, respectively, of a series of compounds are given in Table IV. In any case, the use of relative intensities is perfectly valid for intercomparison of concentration ratios of identical components in separate samples,[9] within the limits of reproducibility of the low-voltage data.

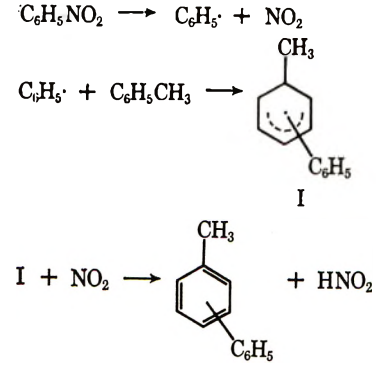
TABLE IV

Compounds	Ratios: Low-voltage mass spectrometry	Ratios: Gas chromatography
Biphenyl/fluorene	6.0	6.16
$C_{14}H_{14}$ isomers/biphenyl	2.39	2.89
Toluene/$C_{14}H_{14}$ isomers	1.37	1.30

Results and Discussion

Nitrobenzene and Toluene.—The major products from the reaction of nitrobenzene with toluene and toluene-α-d_3 are listed in Table II. The product formed in greatest concentration results from arylation by the phenyl radical from nitrobenzene (Scheme I). Distribution (area %) of methylbiphenyl isomers, determined by gas chromatography, was (*meta* and *para* were only partially separated) as follows: *ortho*, 22.5%; *meta* 35.3%; and *para*, 42.2%. This distribution differs considerably from that obtained by Dannley and Zaremsky[10] (% by ir analysis) from phenylation of toluene by benzoyl peroxide at 75°: *ortho*, 65%; *meta*, 19%; and *para*, 16%. Hey and Williams[11] found an even higher proportion of *ortho* phenylation, 71%.

SCHEME I



Our estimate of the methylbiphenyl isomer distribution may differ slightly from the initial product distri-

(7) R. S. Gohlke, *Anal. Chem.*, **31**, 535 (1959); L. P. Lindeman and J. L. Annis, *ibid.*, **32**, 1742 (1960); J. T. Watson and K. Biemann, *ibid.*, **36**, 1135 (1964).

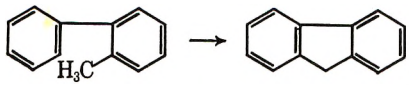
(8) G. F. Crable, G. L. Kearns, and M. S. Norris, *ibid.*, **32**, 13 (1960).

(9) S. Meyerson and E. K. Fields, *Chem. Commun.*, 275 (1966).

(10) R. L. Dannley and B. Zaremsky, *J. Amer. Chem. Soc.*, **77**, 1588 (1955).

(11) D. H. Hey and G. H. Williams, *J. Chem. Phys.*, **23**, 757 (1955).

bution because of thermal intramolecular dehydrogenation of the *ortho* isomer to give fluorene (eq 1). Fluo-



$$+ H_2 \qquad (1)$$

rene and fluorene-d_2 are formed to about the same extent from toluene and toluene-α-d_3, respectively. Adding the amount of fluorene, determined by gas chromatography, to that of *o*-methyldiphenylmethane gives the distribution: *ortho*, 28.3%; *meta*, 32.7%; and *para*, 39.0%. This isomer distribution still is quite different from those obtained by the authors quoted.

In view of the drastically different conditions involved in our arylation different isomer distributions might be anticipated, especially in light of the induced decomposition of benzoyl peroxide by many reactants. Such decomposition is in fact invoked by Dannley

$$C_6H_5\cdot + C_6H_5CH_3 \longrightarrow C_6H_6 + C_6H_5CH_2\cdot$$

$$C_6H_5CH_2\cdot + (C_6H_5CO_2)_2 \longrightarrow (C_6H_5)_2CH_2 + C_6H_5CO_2\cdot + CO_2$$

and Zaremsky to explain the presence of 15% diphenylmethane among the $C_{13}H_{12}$ products on the basis that the rate of decomposition of benzoyl peroxide in toluene is higher than first order.[12]

Diphenylmethane was also formed, 11.4% of the $C_{14}H_{14}$ isomers estimated by mass spectrometry, 9.6% estimated by gas chromatography. It may result from induced decomposition of nitrobenzene by the benzyl radical. An alternative source may be the

$$C_6H_5CH_2\cdot + C_6H_5NO_2 \longrightarrow C_6H_5CH_2C_6H_5 + NO_2$$

reaction of the relatively stable benzyl radical with a phenyl radical from nitrobenzene, as in the sequence in Scheme II.

SCHEME II

$$C_6H_5NO_2 \longrightarrow C_6H_5\cdot + NO_2$$

$$NO_2 + C_6H_5CH_3 \longrightarrow HNO_2 + C_6H_5CH_2\cdot$$

$$C_6H_5CH_2\cdot + C_6H_5\cdot \longrightarrow C_6H_5CH_2C_6H_5$$

The apparent proportion of aniline to phenol was about 1:7 and 1:14 in the toluene-d_0 and -d_3 cases, respectively. The discrepancy suggests that the toluene-d_3 reaction probably produced some aniline-d_1 and -d_2, which were obscured by phenol-d_0 and -d_1. This inference was confirmed by precise mass measurements made at low voltage (14 V, uncor) on the high-resolution mass spectrometer, which indicated the isotopic anilines and phenols given in Table V.

TABLE V

	Number of D atoms	Intensity, arbitrary scale division	Isotopic distribution, %
Aniline	0	1.0	42
	1	0.9	37
	2	0.5	21
		Total 2.4	
Phenol	0	7.2	71
	1	3.0	29
		Total 10.2	

The aniline/phenol ratio of 1:4 is *ca.* twice that found in the unlabeled counterpart. The difference may be due, in part at least, to differences in ionizing voltages employed in the high and low resolution measurements. In both cases, however, phenol intensity is substantially greater than that due to aniline.

Phenol probably arises *via* a nitro–nitrite rearrangement[1] (eq 2). The formation of more phenol-d_0

$$C_6H_5NO_2 \longrightarrow C_6H_5ONO \longrightarrow C_6H_5O\cdot + NO$$

$$\downarrow RH$$

$$C_6H_5OH \qquad (2)$$

than phenol-d_1, despite the fivefold excess of trideuterated toluene, would seem to rule out preferential abstraction of benzylic hydrogen atoms. Alternatively, by analogy with the preferred formation of unlabeled phenol in the reaction of nitrobenzene with 5 mol of benzene-d_6,[1] the reaction might involve an intermediate derived from two molecules of nitrobenzene, in which the phenoxy radical as it forms has ready access to a source of hydrogen. The ratios of unlabeled phenol to phenol-d_1 in the reactions of nitrobenzene with toluene-α-d_3 and with benzene-d_6,[1] both present in fivefold excess, were 2.4 and 1.7, respectively. The difference may simply reflect the additional protium atoms and the smaller number of deuterium atoms available in the former reaction.

Biphenyl constituted an appreciable amount of the product. In other reactions involving phenyl radical in the liquid phase, dimerization has been minor or absent in the presence of aromatic systems to which this highly energetic radical can add.[13,14] In the present study, moreover, biphenyl-d_1 from nitrobenzene and toluene-α-d_3 was almost as plentiful as unlabeled biphenyl, and there was an appreciable amount of biphenyl-d_2.

To help identify the source of so much biphenyl, we treated nitrobenzene-d_5 with toluene under the same conditions as nitrobenzene with toluene-α-d_3. The isotopic distribution is shown in Table VI. In the mass region starting at 166, there was so much overlapping of chemical species containing varying numbers of deuterium atoms as to render interpretation extremely difficult. Luckily, the biphenyl region, masses 154–164, was clear of such interference.

The most abundant species is biphenyl-d_5, evidently fron arylation of toluene by the phenyl-d_5 radical with subsequent loss of the methyl group (eq 3). However, about half as much biphenyl-d_4 is present; this suggests that either there is intramolecular exchange of protium

(12) K. Nozaki and P. D. Bartlett, *J. Amer. Chem. Soc.*, **68**, 1680 (1946).

(13) Phenyl radical formed in a variety of ways in the presence of benzene, phenanthrene, and anthracene does not recombine to give biphenyl, but adds to the aromatic systems instead. See J. D. Burr, J. M. Scarborough, J. D. Strong, R. I. Akawie, and R. A. Meyer, *Nucl. Sci. Eng.*, **11**, 218 (1961); G. W. Taylor, *Can. J. Chem.*, **35**, 739 (1957).

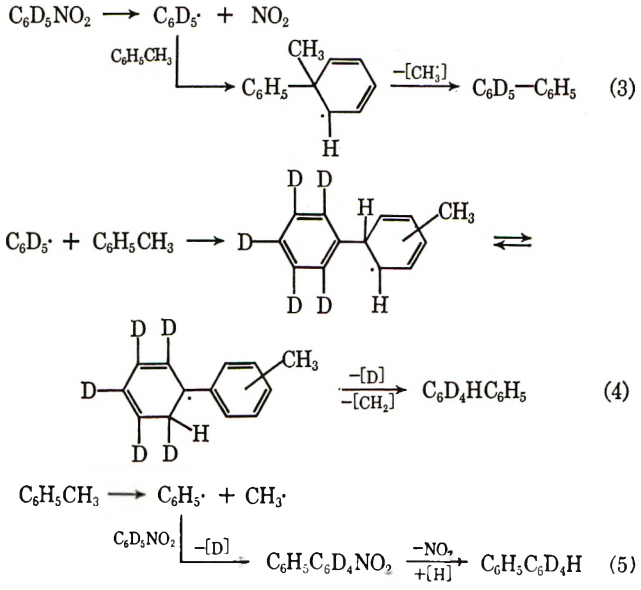
(14) The electron spin resonance of phenyl radical at 77°K indicates that the unpaired electron remains in the sp^2 orbital of the carbon atom at which scission occurs. The σ type localized structure can account for the high reactivity of the phenyl radical: J. E. Bennett, B. Mile, and A. Thomas, *Chem. Commun.*, 265 (1965). In a different context, the difference between the ionization potential of the phenyl radical (9.20 eV) and that of benzene (9.50 eV) just barely exceeds the combined uncertainties of the measurements: I. P. Fisher, T. F. Palmer, and F. P. Lossing, *J. Amer. Chem. Soc.*, **86**, 2741 (1964). The near-equality of the two values constitutes further evidence that the odd electron is not coupled into the π system but remains highly localized. In contrast, the ionization potential of the resonance-stabilized benzyl radical (7.76 eV) [J. B. Farmer, I. H. S. Henderson, C. A. McDowell, and F. P. Lossing, *J. Chem. Phys.*, **22**, 1948 (1954)] is considerably lower than that of toluene (9.0 eV) [S. Meyerson, J. D. McCollum, and P. N. Rylander, *J. Amer. Chem. Soc.*, **83**, 1401 (1961)].

TABLE VI
ISOTOPIC COMPOSITION OF BIPHENYL FROM NITROBENZENE-d_5 AND TOLUENE[a]

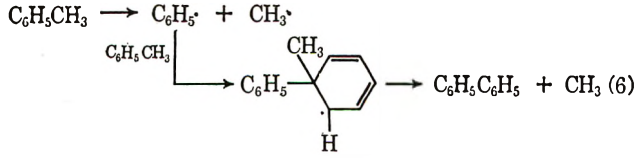
Mol wt	Number of D atoms	Rel concn, %[b]
154	0	19
155	1	2
156	2	1
157	3	3
158	4	18
159	5	34
160	6	2
161	7	1
162	8	5
163	9	11
164	10	4

[a] Reaction conditions were a mole ratio of nitrobenzene-d_5 to toluene of 1:5, 600°, and 9 sec contact time. [b] From relative intensity in the low-voltage (7.5 V, uncor) mass spectrum.

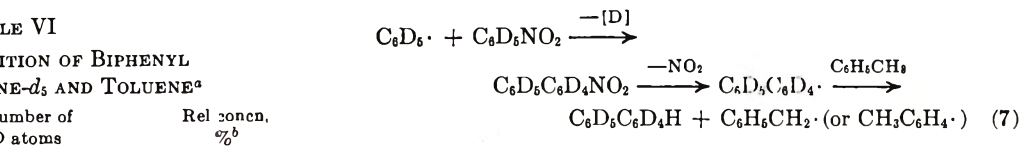
and deuterium in the intermediate cyclohexadienyl radical with subsequent loss of a methyl radical or CH_2 group (eq 4), or that biphenyl-d_4 arises by way of a phenyl radical derived from toluene (eq 5). There is



evidence for both eq 4 and 5. Product of molecular weight 172 was formed in relative concentration 35 on the scale of Table VI; this is attributed chiefly to methylbiphenyl-d_4. Intramolecular interchange of deuterium and protium has been demonstrated in the reaction of nitrobenzene with benzene-d_6,[1] in which biphenyl-d_6 formed in about equal amount to the normal arylation product, biphenyl-d_5. Biphenyl-d_0 in Table II, about the same concentration as biphenyl-d_4, must be derived solely from toluene, and is most readily explained by phenylation of toluene by phenyl radical derived from toluene, followed by loss of methyl radical (eq 6).



The formation of three times as much biphenyl-d_9 as -d_{10}, the expected product of dimerization of C_6D_5 radical, strongly suggests its formation by eq 7.



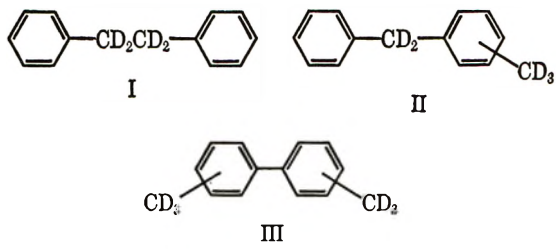
Toluene Alone.—To determine whether the products in Tables II and VI may be derived from toluene alone or require reaction with nitrobenzene, we pyrolyzed toluene and toluene-α-d_3 alone under the identical conditions used in the nitrobenzene reaction. Pyrolysis of toluene is a well-documented reaction, and it would appear unnecessary to repeat it. However, there are discrepancies in the literature.

In 1867 Berthelot passed toluene through a glowing red porcelain tube and obtained hydrogen, methane, acetylene, benzene, and bibenzyl, as well as aromatic hydrocarbons with condensed rings.[15] The possibility that isomers of bibenzyl were present was posed both by Berthelot and by the editors of Beilstein who abstracted his work.[16]

Since that time, some investigators have found bibenzyl as the only $C_{14}H_{14}$ isomer;[17] others have evidence for the formation of dimethylbiphenyls as well.[18] Blades, Blades, and Steacie identified a dimethylbiphenyl among the products from toluene at 722°, and assumed it was a secondary product derived from bibenzyl.[19] Blades and Steacie[20] pyrolyzed impure toluene-α-d_3 at 722° and 0.45-sec contact time and obtained H_2, HD, and D_2. They suggested that hydrogen atoms were being abstracted from the ring. Cleavage of ring (in competition with side chain) carbon–hydrogen bonds, which could most simply lead to dimethylbiphenyl formation, has been suggested to account for anomalous kinetic data[18] and for labeling results in pyrolysis of toluenes-3-d and -4-d.[21] Badger and Spotswood[22] pyrolyzed toluene at 700° for an unspecified contact time and identified 23 products, among which was 4,4′-dimethylbiphenyl.

The last-named authors obviously employed such severe conditions as to cause many secondary reactions. In our pyrolyses of toluene and toluene-α-d_3 we used 600° and a contact time of 6 sec, which gave about 0.1% conversion into the dehydro dimers, $C_{14}H_{14}$, and no other products. The parent ions from toluene-α-d_3 had the following isotopic composition: mass (D atoms, relative abundance, %), 186 (4, 80.3%), 187 (5, 6.8%), and 188 (6, 12.9%). If deuterium atoms are only in benzylic or α positions and undergo no exchange during pyrolysis, and if species derived from isotopic impurities in the toluene-α-d_3 are ignored, the dimers containing four, five, and six deuterium atoms must represent bibenzyl (I), methyldiphenylmethanes (II), and dimethylbiphenyls (III), respectively. Any ex-

(15) M. Berthelot, *Ann.*, **142**, 254 (1867).
(16) F. K. Beilstein, "Handbuch der organische Chemie," Vol. 5, Springer-Verlag, Berlin, 1922, p 283.
(17) C. Graebe, *Ber.*, **7**, 48 (1874); P. Ferko, *ibid.*, **20**, 622 (1887); H. Meyer and A. Hofmann, *Monatsh.*, **37**, 684 (1916); L. R. Herndon and E. E. Reid, *J. Amer. Chem. Soc.*, **50**, 3069 (1928); M. Szwarc, *J. Chem. Phys.*, **16**, 128 (1948); *Chem. Rev.*, **47**, 75 (1950); M. Szwarc and J. S. Roberts, *J. Chem. Phys.*, **16**, 609 (1948); F. Hein and H. J. Mesee, *Ber.*, **76**, 430 (1943); K. U. Ingold and F. P. Lossing, *Can. J. Chem.*, **31**, 30 (1953); L. A. Errede and J. P. Cassidy, *J. Org. Chem.*, **24**, 1890 (1959).
(18) M. Takahashi, *Bull. Chem. Soc. Jap.*, **33**, 801 (1960).
(19) H. Blades, A. T. Blades, and E. W. R. Steacie, *Can. J. Chem.*, **32**, 298 (1954).
(20) H. Blades and E. W. R. Steacie, *ibid.*, **32**, 1142 (1954).
(21) M. Takahashi, *Bull. Chem. Soc. Jap.*, **33**, 808 (1960).
(22) G. B. Badger and T. M. Spotswood, *J. Chem. Soc.*, 4420 (1960).



I II III

tensive exchange is ruled out by the close agreement in isotopic composition of the recovered toluene (0.3% d_1, 2.5% d_2, 95.9% d_3, 0.9% d_4, 0.3% d_5, 0.1% d_6) with that of the starting material (2.3% d_2, 96.2% d_3, 1.0% d_4, 0.3% d_5, 0.2% d_6).[23] The dimer isotopic distribution found corresponds to the approximate isomer distribution (mol %): I, 87; II, 5; and III, 8.[24]

The question raised by Berthelot, whether dimethylbiphenyls result from the pyrolysis of toluene, thus appears to have been answered. We tried to determine bibenzyl, the three methyldiphenylmethanes, and six dimethylbiphenyls by gas chromatography, but overlapping was so extensive that the value of this type of analysis was limited.

By contrast, the breakdown of isomers into the three groups, bibenzyl, methyldiphenylmethanes, and dimethylbiphenyls, by the number of deuterium atoms, as shown in Table VII, is clean and unambiguous. This analytical method is of considerable value when (a) extensive scrambling has not occurred and (b) position isomers within each group need not be determined.

TABLE VII

C_{14} ISOMERS FROM TOLUENE-α-d_3 ALONE AND WITH NITROBENZENE[a,b]

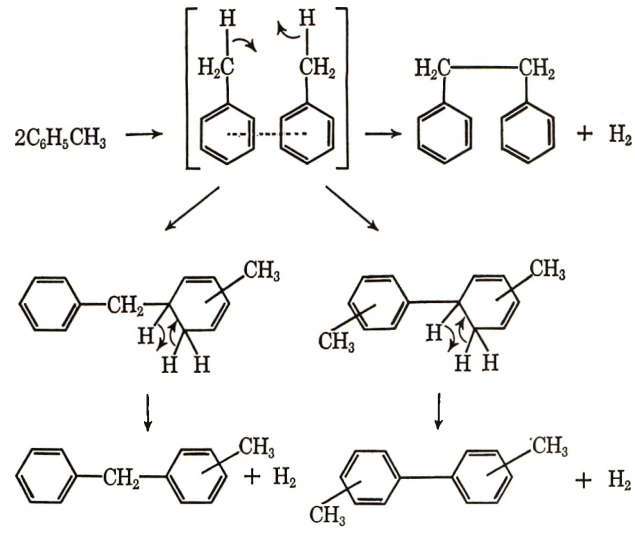
		% of total ^{14}C fraction			
		Alone		With nitrobenzene	
Mass	Probable structure	Rel intensity	Ratio	Rel intensity	Ratio
186	$C_6H_5CD_2CD_2C_6H_5$	80.3	11.8	44	2.4
187	$C_6H_5CD_2C_6H_4CD_3$	6.8	1	18	1
188	$CD_3C_6H_4$–$C_6H_4CD_3$	12.9	1.9	38	2.1

[a] Reaction conditions were toluene, 0.25 mol; nitrobenzene 0.05 mol; 600°; and 9.5-sec contact time. [b] The weight of the C_{14} fraction alone was 0.015 g and with nitrobenzene it was 1.15 g.

The C_{14} isomers from toluene-α-d_3 pyrolyzed alone and with nitrobenzene are compared in Table VII. In addition to the 80-fold greater weight of product in the nitrobenzene reaction, the proportions of the three groups are so markedly different as to demand different dominant mechanisms in the two reactions.

A free-radical mechanism for the pyrolysis of toluene has been generally accepted (ref 22, and references cited therein). We propose, instead, that in the absence of added free-radical precursors, toluene decomposes largely by way of a bimolecular complex (see Scheme III) which can either lose hydrogen intramolecularly to give bibenzyl, or collapse to a benzyl- or tolylmethylcyclohexadiene. The cyclohexadiene in turn loses hydrogen intramolecularly to give methyldiphenylmethane or dimethylbiphenyl. A similar mechanism

SCHEME III



involving a phenylcyclohexadiene intermediate was invoked to explain the scrambling of protium and deuterium in benzene-d at 690° and 21-sec contact time.[23]

In the presence of other free radicals, as in our nitrobenzene reaction, toluene pyrolysis indeed seems to go by a free-radical mechanism involving benzyl and tolyl radicals (eq 8).

$$C_6H_5CH_3 + R\cdot \longrightarrow C_6H_5CH_2\cdot + CH_3C_6H_4\cdot + RH \qquad (8)$$

$$C_6H_5CH_2CH_2C_6H_5 + C_6H_5CH_2C_6H_4CH_3 + CH_3C_6H_4C_6H_4CH_3$$

The large difference in bond strengths of aromatic and benzylic carbon–hydrogen bonds (bond, D (kcal/mol): C_6H_5–H, 112;[25] $C_6H_5CH_2$–H, 85[26]) would seem to render hydrogen abstraction from the benzene ring unlikely in the presence of available benzylic hydrogen. However, abstraction of hydrogen from aromatic rings by various radicals occurs *via* addition to give cyclohexadienyl radicals;[27] the reported parameters are therefore not applicable,[28] and the formation of almost as much dimethylbiphenyl as bibenzyl in Table VII seems reasonable.

Effect of Benzylic Substituents.—To see if benzylic substituents influence the composition of the product in the reaction with nitrobenzene, we compared the major products from benzotrifluoride and toluene under identical conditions, as shown in Table VIII. Toluene was somewhat more reactive, as the total yield of products was about 50% greater than from benzotrifluoride, and no nitro compound survived. This may be added evidence for induced decomposition. The product distributions were generally similar. However, in several groups of isomers the nature of products differed sharply.

(23) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 21 (1966).

(24) Relative parent-peak sensitivities, measured at the low-voltage conditions employed here, of some of the isomers, taken as representative of the three isomer groups, are bibenzyl, 0.565; 2-methyldiphenylmethane, 0.825; 3,3′- and 4,4′-dimethylbiphenyls, 1.00.

(25) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworth and Co. Ltd., London, 1958, pp 270–289.

(26) R. Walsh, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **88**, 650 (1966), and references cited therein.

(27) R. D. Giles and E. Whittle, *Trans. Faraday Soc.*, **62**, 128 (1966), and earlier references therein; M. Levy and M. Szwarc, *J. Amer. Chem. Soc.*, **77**, 1949 (1955); A. P. Stefani, L. Herk, and M. Szwarc, *ibid.*, **83**, 4732 (1961); A. P. Stefani and M. Szwarc, *ibid.*, **84**, 3661 (1962).

(28) A. S. Rodgers, D. M. Golden, and S. W. Benson, *ibid.*, **89**, 4578 (1967).

TABLE VIII
COMPARISON OF PRODUCTS FROM TOLUENE AND BENZOTRIFLUORIDE WITH NITROBENZENE[a,b]

Products, X = F or H	Rel concn[c] Benzotrifluoride	Toluene
Phenol	7	22
Biphenyl	25	42
Nitrobiphenyl	12	...
Trifluoromethylbiphenyl, $C_{13}H_{14}$	100	100
$X_3CC_6H_4C_6H_4CX_3$ and isomers	42	61
Terphenyl	5	5
X_3C-Terphenyl and isomers	21	8
$(X_3C)_2$-Terphenyl and isomers	21	7

[a] Reaction conditions were 600°; contact time, 9.5 sec; and a mole ratio of nitrobenzene to $X_3C-C_6H_5$ of 1:5. [b] The total weight of products from benzotrifluoride was 4.4 g and that from toluene was 6.9 g. [c] From relative intensities in the low-voltage (7.5 V, uncor) mass spectrum, normalized to X_3C-biphenyl = 100.

The product from benzotrifluoride containing two rings and one methyl group was apparently, in view of the retention of all three fluorine atoms, solely trifluoromethylbiphenyl, whereas that from toluene contained a substantial contribution from the isomeric diphenylmethanes. In the product containing two rings and two methyl groups, benzotrifluoride gave only bis(trifluoromethyl)biphenyl; toluene gave bibenzyl and dimethylbiphenyl in almost equal amounts, as well as an appreciable amount of methyldiphenylmethane (Table VI). This difference apparently follows as a consequence of the difference in bond dissociation energies of C_6H_5C-F and C_6H_5C-H,[29] which makes fluorine abstraction unlikely when hydrogen is available in the same molecule. Only in the absence of hydrogen is fluorine abstracted, as in the reaction of nitrobenzene with hexafluorobenzene.[2] Even in the latter case the fluorine was retained to a considerable extent through intramolecular exchange with hydrogen, and hexafluorobiphenyl was formed in about the same concentration as pentafluorobiphenyl.

Registry No.—Nitrobenzene, 98-95-3; toluene, 108-88-3; toluene-α-d_3, 1124-18-1; nitrobenzene-d_5, 4165-60-0.

Acknowledgment.—The authors are greatly indebted to D. K. Albert of the American Oil Co. for his assistance in the gas chromatographic analyses.

(29) C_6H_5C-F, D = 120 kcal/mol;[26] C_6H_5C-H, D = 85 kcal/mol.[26]

Kinetics of the Reversible Reaction of Piperidine with 2,4-Dinitroanisole in Methanol Solution[1]

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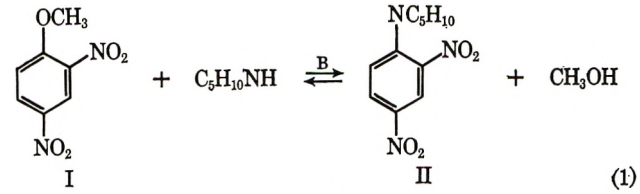
2,4-Dinitroanisole reacts with piperidine in methanol to form 2,4-dinitrophenylpiperidine (eq 1). The reaction is reversible, and the equilibrium constant at 67.9° is about 100 l. mol^{-1}. The reaction rate has been determined in both directions as a function of $NaOCH_3$ concentration. Catalysis by methoxide ion is strong, and the second-order rate coefficient (k_A) for the forward reaction is related to $[NaOCH_3]$ in a nearly linear fashion. The forward reaction in the absence of $NaOCH_3$ is catalyzed by methoxide ion generated by the basic dissociation of piperidine in methanol, and probably also by piperidine. A side reaction which produces 2,4-dinitrophenol, *via* SN2 displacement by piperidine at methyl carbon (eq 2), is important in the absence of $NaOCH_3$; its rate has been estimated.

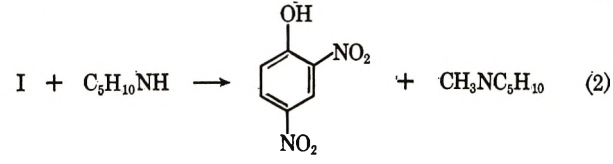
The reaction of 2,4-dinitrodiphenyl ether with piperidine to form 2,4-dinitrophenylpiperidine is strongly catalyzed by bases.[3,4] The formally similar reaction of ethyl formate with *n*-butylamine to form *n*-butylformamide is also very responsive to base catalysis.[5] We therefore expected that bases would catalyze the reaction of 2,4-dinitroanisole (I) with piperidine to form 2,4-dinitrophenylpiperidine (II). Accordingly, a kinetic investigation of this reaction in methanol solution was undertaken.

Subsequent to our work, the same reaction in 10% dioxane–90% water was investigated by Bunnett and Bernasconi[4] and by Bernasconi.[6]

Years ago, Cahn[7] examined the reactions of several nitroanisoles with refluxing neat piperidine. He reported that 2,4-dinitroanisole gave 2,4-dinitrophenylpiperidine quantitatively within 15 min on the water bath. This indicates piperidinodemethoxylation at aromatic carbon, since 2,4-dinitrophenylpiperidine was not formed by heating 2,4-dinitrophenol with piperidine at reflux. In contrast, 2,4,6-trinitroanisole was quantitatively converted to picric acid within 1 min under the same conditions. Also, 2-methyl-4-nitroanisole gave almost 100% of 2-methyl-4-nitrophenol within 1 hr at reflux. The latter two examples suggest that nucleophilic displacement at methyl carbon occurred, although Cahn recognized hydrolysis due to traces of water to be



I II (1)



(2)

(1) (a) Supported, in part, by the National Science Foundation. (b) Based on the Ph.D. Thesis of R. H. Garst, Brown University, June, 1964; *Dissertation Abstr.*, **25**, 4404 (1965).
(2) University of California at Santa Cruz, Santa Cruz, Calif.
(3) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, **87**, 3879 (1965).
(4) J. F. Bunnett and C. Bernasconi, *ibid.*, **87**, 5209 (1965).
(5) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).
(6) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).
(7) R. S. Cahn, *J. Chem. Soc.*, 1121 (1931).

an alternative possibility. Tertiary amines are known to react with 4-substituted 2,6-dinitroanisoles *via* displacement at the methyl carbon.[8]

Our work indicates that both types of reaction occur between piperidine and 2,4-dinitroanisole in methanol. Displacement at aromatic carbon (eq 1) predominates and can be made nearly quantitative by suitable adjustment of conditions. This reaction is strongly catalyzed by sodium methoxide. Also, the reverse of this reaction can be made to occur quantitatively; it is, of course, also catalyzed by sodium methoxide.

Experimental Section

Materials.—Methanol was purified by the magnesium method.[9] Piperidine was purified as we have previously described.[3] Commercial 2,4-dinitroanisole was recrystallized four times from diethyl ether containing a small amount of petroleum ether (bp 30–60°): mp 94.8–96.5°. N-(2,4-Dinitrophenyl)piperidine, mp 92–94.5°, was crystallized from absolute ethanol. Solutions of sodium methoxide in methanol were prepared and stored after Reinheimer, *et al.*[10] "Quenching solution" was prepared by mixing 1 l. each of distilled water and 95% ethanol with 200 g of concentrated hydrochloric acid solution. N-Methylpiperidine, bp 104° (uncor), $n^{20}D$ 1.4373, was prepared from piperidine by the Leuckart reaction.[11] Proton magnetic resonance and infrared spectra confirmed its structure and high purity.

Spectra of Reactants and Products.—Suitably dilute solutions were prepared in solvents as noted below, and spectra were recorded by means of a Bausch and Lomb Spectronic 505 spectrophotometer. Wavelengths of maximum absorption (mμ) and the associated molar extinction coefficients (ϵ) were as follows: I in CH_3OH, 254 (7190), 293 (10,700); I in quenching solution, 258 (8390), 297 (10,600); 2,4-dinitrophenol in CH_3OH, 355 (14,700); 2,4-dinitrophenol in 0.1 *M* $NaOCH_3$ in CH_3OH, 356 (14,800); 2,4-dinitrophenol in quenching solution, 257 (10,900); II in CH_3OH, 377 (14,700); II in quenching solution, 390 (15,100). Neither I nor 2,4-dinitrophenol absorbs measurably in quenching solution at 390 mμ.

Kinetic Procedure.—Reaction solutions were prepared at room temperature by combination of appropriate volumes of standard methanolic solutions of reactants (or, in some cases, the appropriate weight of pure piperidine), and dilution to the mark in a volumetric flask with methanol. Aliquots were pipetted into nitrogen-filled Pyrex ampoules which were then flushed with nitrogen and sealed with a flame. All the ampoules for a run were immersed in the thermostat at the same time. Ampoules were removed at recorded times and plunged into cold water. They were quickly opened, and the contents were transferred quantitatively to a volumetric flask and diluted to the mark with quenching solution. The absorption at 390 mμ was determined by means of a Beckman Model DU spectrophotometer. Pseudo-first-order kinetics were obeyed in all runs, and the pseudo-first-order rate coefficient (k_ψ) was determined in the usual way from the "infinity" absorbance and the absorbance of samples taken at various times.[12]

The rate of reaction of sodium methoxide with I, to form 2,4-dinitrophenol, was determined in one run.[13] The technique was generally as described above. However, after the ampoules were cooled to room temperature and opened, a 5-cc portion of the reaction solution was diluted to 50 cc with methanol, and the absorbance at 356 mμ was measured. The spectrum of the "infinity" sample between 200 and 500 mμ was recorded; it matched that of 2,4-dinitrophenol in 0.1 *M* $NaOCH_3$ in CH_3OH.

Reaction temperature for all runs was 67.9°. Rate coefficients are symbolized, and were reckoned, as follows: $k^*_r = k_\psi$ for the special case of reaction 1, reverse; $k_r = k^*_r/[OCH_3^-]$, second-order rate coefficient for reaction 1, reverse; k^*_f = pseudo-first-order rate coefficient for reaction 1, forward, reckoned as $(A_\infty/A_{quant})\cdot k_\psi$, where A_∞ is the observed infinity absorbance and A_{quant} is the infinity absorbance calculated for quantitative conversion of I to II; $k_A = k^*_f/[C_5H_{10}NH]$, second-order rate coefficient for reaction 1, forward; k^*_P = pseudo-first-order rate coefficient for side reaction(s) to reaction 1, forward, in absence of $NaOCH_3$, reckoned as $k_\psi - k^*_f(1 + K_e\cdot[C_5H_{10}NH])/(K_e[C_5H_{10}NH])$ (K_e is the equilibrium constant for reaction 1); $k_P = k^*_P/[C_5H_{10}NH]$, second-order rate coefficient for side reaction(s) to reaction 1, forward.

Our method for reckoning the last four coefficients calls for comment. When piperidine is in large excess, eq 1 and 2 constitute a system of the type

$$A \underset{k_b}{\overset{k_a}{\rightleftharpoons}} B \qquad (3)$$

$$A \xrightarrow{k_c} C \qquad (4)$$

For reaction 3 alone, it is known[15] that the slope in a plot of ln $(A_\infty - A)$, where A_∞ is the final (equilibrium) absorbance, *vs.* time is $k_a + k_b$, and that k_a can be reckoned as A_∞/A_{quant} times said slope (if the absorbance measured is due only to B). Moreover, if reactions 3, forward, and 4 are competitive irreversible reactions, it is known that the slope in a plot of ln $(A_\infty - A)$ *vs.* time is $k_a + k_c$, and that k_a can be reckoned as A_∞/A_{quant} times said slope.[16]

The procedure we have used for evaluating k^*_f and k^*_P (above) represents amalgamation of these two familiar procedures. It is not rigorous, for the true "infinity" value for reactions 3 and 4 in competition will represent complete conversion of A and B into product C. On the other hand, if the equilibrium concentration of reactant A is small and k_c is small, the condition of equilibrium between A and B will not drift rapidly toward C and a "quasi-infinity" condition will be attained after eight or ten half-lives of reaction 3. The chief intrusion of reaction 4 will then be direct competition with reaction 3 as the initial state progresses to the "quasi-infinity" state. Under such conditions, which prevailed in most of our experiments concerning reaction 1, forward, the treatment we have used is approximately correct.

Detection of 2,4-Dinitrophenol as a By-product.—"Infinity" samples from reactions of I with 0.2, 0.4, and 0.6 *M* piperidine (without piperidine hydrochloride) were examined. It was assumed that 2,4-dinitrophenol was the by-product containing 2,4-dinitrophenyl groups. On the basis of this assumption, solutions were prepared mimicking the "infinity" solutions from these runs; these solutions contained 2,4-dinitrophenylpiperidine in the concentrations indicated by the absorbance at 390 mμ of acid-quenched "infinity" samples plus 2,4-dinitrophenol as needed to account for the rest of the starting 2,4-dinitroanisole. The spectra of all six solutions, the three actual "infinity" solutions and the three mimics, as diluted with methanol and as diluted with *ca.* 1 *M* HCl in 47% ethanol, were determined between 200 and 500 mμ. In all six cases there was an appreciable difference in the spectra of the methanol-diluted and the acid-diluted samples, and each pair of actual and mimic "infinity" solutions showed qualitatively and quantitatively the same spectra when diluted in a given way. This substantiates the assumption which was made.

We now consider the possibility that 2,4-dinitrophenol was formed by reaction of methoxide ion with 2,4-dinitroanisole. Methoxide ion is generated by the basic dissociation of piperidine in methanol, for which K_b is 7.3×10^{-6}.[17] For the piperidine concentrations represented in Table II, $[OCH_3^-]$ is reckoned to range from 0.85×10^{-3} to 2.1×10^{-3} (except in the presence of piperidine hydrochloride). Making use of the probable second-order rate coefficient for the dinitroanisole–methoxide reaction

(8) M. Kohn and F. Grauer, *Monatsh. Chem.*, **34**, 1751 (1913); E. Hertel and H. Lührmann, *Z. Elektrochem.*, **45**, 405 (1939).

(9) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 360.

(10) J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. C. Cochran, and E. W. Barr, *J. Amer. Chem. Soc.*, **80**, 164 (1958).

(11) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(12) J. F. Bunnett and J. J. Randall, *ibid.*, **80**, 6020 (1958).

(13) Recently several investigators[14] have studied the kinetics and equilibrium for combination of sodium methoxide with 2,4-dinitroanisole to form the usual Jackson–Meisenheimer complex. Under the conditions of our experiments, the equilibrium concentration of that complex was very small.

(14) (a) C. H. Rochester, *J. Chem. Soc.*, 2404 (1965); J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966); (b) C. F. Bernasconi, unpublished work.

(15) *Cf.* A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, p 186.

(16) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957).

(17) J. R. Schaefgen, M. S. Newman, and F. H. Verhoek, *ibid.*, **66**, 1847 (1944).

determined in this research, we reckon the contribution of this reaction to the pseudo-first-order coefficients in Table II to be not greater than 2.7×10^{-8} sec^{-1}. This is only about one-hundredth the actual magnitude of the side reaction, tabulated as k^*_P in Table II. This is clearly not the principal side reaction.

Detection of N-Methylpiperidine as a By-product.—A solution (75 ml) of I (0.0667 *M*), piperidine (0.4 *M*), and piperidine hydrochloride (0.0667 *M*) in methanol was flushed with nitrogen gas, sealed in a Pyrex tube, and heated 1080 hr at 68°. The tube was cooled to room temperature and opened, and the contents were acidified to pH 1 by dropwise addition of aqueous HCl. The solvents were evaporated by means of a rotary vacuum evaporator, distilled water was added, and the mixture was heated to 60°. The lumps were crushed, and the mixture was cooled and filtered. The collected solids were discarded, and the filtrate was evaporated to dryness as above. The dry residue was treated with 3.0 g of sodium amide in pyridine, and the resulting slurry was filtered under nitrogen pressure through a fritted-glass plate. To a sample of the filtrate, a weighed amount of acetone was added as internal standard, and the mixture was analyzed by glpc, using 10% Carbowax 4000 on 42–60 mesh Johns-Manville C-22 Silocel firebrick. The peak for N-methylpiperidine was sharp; the retention time was the same as that of an authentic sample. The peak area, corrected for molar response, indicated that 0.174 g (36%) of N-methylpiperidine had been formed. Another sample of the pyridine filtrate was subjected to mass spectrometric analysis; peaks at *m/e* 98 (MW − 1 for N-methylpiperidine), 84 (MW − 1 for piperidine), and 79 (pyridine) were strong, and the yield of N-methylpiperidine was indicated to be slightly higher than estimated by glpc.

Concentrations of reactants as listed in the tables refer to room temperature. However, all the second- and third-order rate coefficients given in the tables and in the text have been corrected to take account of solvent expansion between room temperature and 67.9°; the correction factor used was 1.06.

Results and Discussion

Reaction of 2,4-Dinitroanisole with $NaOCH_3$.—A conceivable side reaction was nucleophilic displacement by methoxide ion on methyl carbon of I, forming methyl ether and 2,4-dinitrophenol.[13] Reaction was indeed observed to occur at 67.9°, between 0.10 *M* $NaOCH_3$ and 4.24×10^{-4} *M* 2,4-dinitroanisole, and ultimately the ultraviolet spectrum of the solution matched that of 2,4-dinitrophenol in methanolic $NaOCH_3$. Also, a sample of the "infinity" solution diluted with excess "quenching solution" (*ca.* 1 *M* HCl in 47% ethanol) matched that of 2,4-dinitrophenol in the same solvent.

The rate of this reaction was followed by the increase of absorbance at 356 mμ, an absorption maximum for the 2,4-dinitrophenoxide ion. The pseudo-first-order rate coefficient was 1.2×10^{-6} sec^{-1}. The reaction order in sodium methoxide was not established, although it was found that 2,4-dinitroanisole is stable in methanol free of this base. If the reaction is first order in methoxide ion, the second-order rate coefficient is 1.2×10^{-5} M^{-1} sec^{-1}.

We cannot exclude the possibility that this reaction is hydroxydemethoxylation at aromatic carbon, hydroxide ion having been formed by reaction of methoxide ion with traces of water in the solvent.

Reaction of 2,4-Dinitrophenylpiperidine with Methanol, Catalyzed by Sodium Methoxide.—This tertiary amine was found to be stable in methanol at 67.9°. However, in the presence of sodium methoxide a reaction occurred and ultimately all the 2,4-dinitrophenylpiperidine was destroyed, for the "infinity" solution showed no trace of the characteristic absorption of II at 390 mμ. The ultraviolet spectrum of this solution matched that of 2,4-dinitroanisole in methanol. Thus, the reverse of reaction 1 occurred.

Reaction rate was determined as a function of sodium methoxide concentration, the decrease in absorption at 390 mμ being followed. Our data are presented in Table I. The rate was higher at higher methoxide concentrations, but the second-order rate coefficient (k_r) diminished somewhat as the base concentration increased.

TABLE I

REACTION OF 2,4-DINITROPHENYLPIPERIDINE WITH METHANOL, CATALYZED BY SODIUM METHOXIDE[a] AT 67.9°

$[NaOCH_3]$, *M*	$10^6 k^*_r$, sec^{-1}	$10^4 k_r$, l. mol^{-1} sec^{-1}
0.0145	3.88	2.83
0.036	8.84	2.56
0.073	16.9	2.46
0.109	24.2	2.32
0.146	30.2	2.19
0.218	40.5	1.96
0.328	54.9	1.77

[a] Initial substrate concentration in all runs: 1.92×10^{-4} *M*.

Reaction of 2,4-Dinitroanisole with Piperidine (without $NaOCH_3$).—The reaction velocity was determined as a function of piperidine concentration; results are presented in Table II. The kinetics are complicated by three factors: (i) the reaction progresses to a state of equilibrium which, at low piperidine concentrations, provides an appreciable amount of unreacted 2,4-dinitroanisole; (ii) there is a side reaction which consumes 2,4-dinitroanisole forming something other than 2,4-dinitrophenylpiperidine, as shown by the fact that "infinity" concentrations of the latter are considerably less than called for by the equilibrium constant; and (iii) the formation of 2,4-dinitrophenylpiperidine is catalyzed by base, certainly by methoxide ion and probably also by piperidine.

The side reaction is that of piperidine with 2,4-dinitroanisole to form N-methylpiperidine and 2,4-dinitrophenol, *via* SN2 attack of piperidine on methyl carbon. The formation of 2,4-dinitrophenol was demonstrated by the ultraviolet spectra of product mixtures, and N-methylpiperidine was detected as a product by gas–liquid partition chromatography (glpc) and by mass spectrometric analysis.

In a situation of competing reversible and irreversible reactions, as represented by eq 1 and 2, "infinity" conditions are attained only when all the reactants have been transformed into the products of the irreversible step. However, if the irreversible reaction is slow and there is but little of the common reactant present at equilibrium, conditions which are fulfilled in the present work, the system may be treated approximately as competing independent first-order reactions. This question is discussed in detail in the Experimental Section. By this treatment, pseudo-first-order coefficients (k^*_P) for the side reaction were computed, and they were converted into second-order coefficients (k_P) by dividing by the piperidine concentration.

The k_P values (Table II) differ considerably. We are inclined to think that the variation is not real, and that the proper value of this coefficient is best indicated by the first experiment in Table II, a run in which piperidine hydrochloride was present. Under the conditions of that run, equilibrium lay strongly on the side of 2,4-dinitrophenylpiperidine and the side reaction accounted for nearly half of the products formed. In the other

TABLE II

REACTION OF 2,4-DINITROANISOLE WITH PIPERDINE IN METHANOL AT 67.9°

[Substrate]$_0$ × 10^4, M	[$C_5H_{10}NH$]	Yield, %	Cor yield,[a] %	10^6k_ψ, sec^{-1}	$10^6k^*_f$, sec^{-1}	10^6k_A, M^{-1} sec^{-1}	$10^6k^*_P$, sec^{-1}	10^6k_P, M^{-1} sec^{-1}
2.87	0.600[b]	55.8	56.8	9.55	5.6	8.9	4.1	7.1
5.00	0.600	92.3	94.0	45.3	44	69.7	2.7	4.8
2.87	0.600	93.0	94.5	45.0	44	69.7	2.5	4.3
5.00	0.400	86.9	89.0	22.0	20	47.8	2.4	6.3
2.87	0.399	87.3	89.5	26.5	24	58.0	2.8	7.4
17.9	0.250	78.2	81.3	10.8	8.9	33.8	2.0	8.6
5.00	0.200	73.9	77.6	9.54	7.4	35.2	2.1	11.3
17.9	0.100	59.6	65.6	3.13	2.0	18.7	1.08	11.4

[a] "Cor yield" is the yield of 2,4-dinitrophenylpiperidine (from photometric data) plus the amount of 2,4-dinitroanisole which should be in equilibrium with it. [b] Piperidine hydrochloride (0.102 M) also present.

TABLE III

REACTION OF 2,4-DINITROANISOLE WITH PIPERIDINE, CATALYZED BY SODIUM METHOXIDE, IN METHANOL AT 67.9° [a]

[$NaOCH_3$], M	[Substrate]$_0$, × 10^4, M	10^4k_ψ, sec^{-1}	Yield, %	Cor yield,[b] %	10^4k_A, M^{-1} sec^{-1}	$10^2k_A/[OCH_3^-]$, M^{-2} sec^{-1}	K_e,[c] M^{-1}
0.010	8.98	0.735	91	96	3.70	3.91	136
0.010	3.59	0.812	92	97	4.08	4.31	150
0.030	3.59	1.82	90	95	9.16	3.23	127
0.050	3.59	2.54	98	103	12.8	2.71	108
0.070	1.80	2.87	90	95	14.4	2.18	89
0.100	1.44	4.54	97	102	22.8	2.41	103
0.130	1.44	5.45	98	103	27.4	2.23	99
0.182	1.44	7.37	97	102	37.1	2.16	105
0.327	1.44	11.2	96	101	53.9	1.74	98

[a] Piperidine 0.20 M in all runs. [b] See footnote *a*, Table II. [c] Computed from kinetic data.

experiments with 0.6 M piperidine, the side reaction was a very small percentage of the whole and its rate, being reckoned as a difference between large quantities, could not be estimated very precisely. In the experiments at low piperidine concentrations, the approximate kinetic analysis employed is somewhat less justified.

The pseudo-first-order coefficients for reaction 1 in the forward direction are given (Table II) as k^*_f, and the corresponding second-order coefficients ($k^*_f/[C_5H_{10}NH]$) are tabulated as k_A. It is obvious that k_A increases with piperidine concentration, except that it is much lower in the presence of piperidine hydrochloride. Since a principal effect of the latter salt is to repress basic dissociation of piperidine to form methoxide ion, we conclude that the increase in k_A with piperidine concentration is mainly due to catalysis by methoxide ion. This conclusion is supported by the fact that one can approximate the k_A values in Table II by multiplying the catalytic coefficient for methoxide ion (see below) by the methoxide ion concentrations reckoned from the K_b value. Reaction 1, forward, may also be catalyzed by piperidine, but our data are not suitable for estimating the magnitude of such catalysis.

It is interesting that the enhancement of k_A for reaction 1, forward, by piperidine in methanol is mainly due to catalysis by methoxide ion. In contrast, the augmentation of k_A for the analogous reaction of piperidine with 2,4-dinitrodiphenyl ether in 60% dioxane–40% water, on addition of excess piperidine, is mainly due to catalysis by the amine itself.[3] Also, reaction 1 in 10% dioxane–90% water is strongly catalyzed by piperidine.[6]

Reaction of 2,4-Dinitroanisole with Piperidine, Catalyzed by $NaOCH_3$.—In a series of kinetic runs, sodium methoxide concentration was varied as piperidine concentration was held constant at 0.2 M. Under these conditions, one can estimate from the equilibrium constant for reaction 1 (*ca.* 100) that the ratio of I to II at equilibrium should be 1:20. The observed photometric yields of 2,4-dinitrophenylpiperidine (Table III) were multiplied by $^{21}/_{20}$ in order to obtain "corrected yields," which represent the per cent of the starting dinitroanisole accounted for by photometric analysis of the "infinity" solutions. With but three exceptions, the corrected yields are 100 ± 3%. This testifies to the magnitude of experimental error in our product analysis. Yields lower than 97% tend to occur at lower methoxide concentrations where side reactions as discussed above are relatively more serious.

The k_A values for reaction 1, forward, rise with increase in sodium methoxide concentration. The relationship is plotted as Figure 1. The third-order catalytic coefficient, $k_A/[OCH_3^-]$, diminishes as the base concentration augments (Table III). A similar effect was observed in respect to the reverse reaction; see Table I.

The fact that the "corrected yields" of 2,4-dinitrophenylpiperidine in Table III are near to 100% shows that side reaction 2 is insignificant at higher $NaOCH_3$ concentrations. It does not respond, or responds very weakly, to catalysis by bases. Recently Gregory and Bruice[18] have reported that the SN2 reactions of several amines with methyl iodide in water show simple second-order kinetics, with no evidence of base catalysis by the amines, and it has been known for some time that reactions of amines with 2,4-dinitrochlorobenzene and several other aromatic substrates in protic solvents are not base-catalyzed.[19] It appears that nucleophilic *attack* by amines in such solvents is not assisted by bases, and that catalysis when observed involves rate-limiting steps following the initial attack.

(18) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).
(19) J. F. Bunnett and R. H. Garst, *ibid.*, **87**, 3875 (1965).

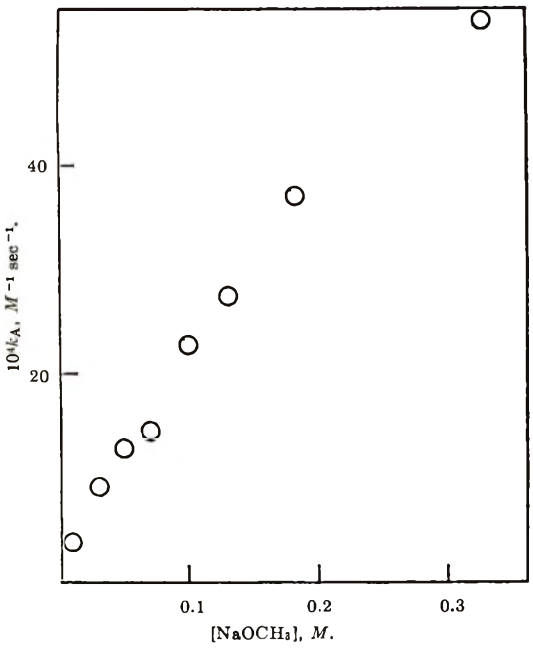


Figure 1.—Dependence of second-order rate coefficient (k_A) for the forward reaction on $NaOCH_3$ concentration; data of Table III.

Division of the present third-order catalytic coefficients by k_r values at corresponding $NaOCH_3$ concentrations should give K_e, the equilibrium constant for reaction 1 in the forward direction. The necessary k_r values were interpolated graphically from data in Table I, and the resulting K_e values are presented in Table III. Among the last six values, the average K_e is 100 ± 5 l. mol^{-1}. The larger estimates of K_e at lower methoxide concentrations possibly are due to the incursion of side reactions, especially in the forward rate determination.

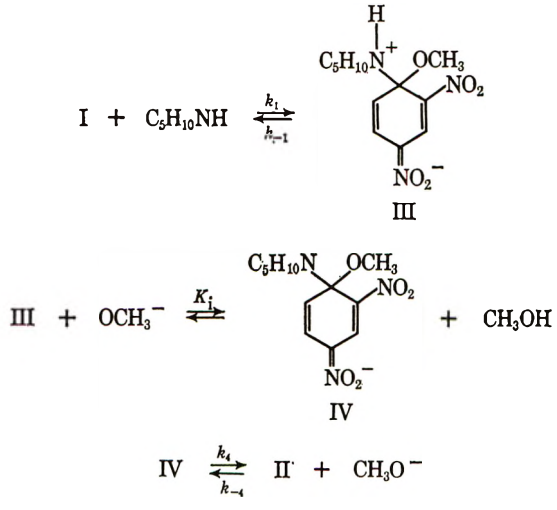
Equilibrium Measurement.—The equilibrium constant, K_e, for eq 1 was also estimated directly from measurement of absorption at 390 mμ after equilibrium had been attained. Because of the side reactions of 2,4-dinitroanisole, it was necessary that equilibrium be attained quickly. Also, the extent of side reactions could be minimized by having a rather high concentration of piperidine which would drive the reaction to the right as written. On the other hand, if it were driven too far to the right, the equilibrium constant could not be measured accurately.

In our experiments, solutions 9.58×10^{-5} M in 2,4-dinitroanisole and of various known concentrations of $NaOCH_3$ and piperidine were prepared and, in sealed ampoules with a nitrogen gas atmosphere, were allowed to react at 67.9° for ten half-lives, as indicated by rate measurements. The ampoule contents were then diluted to standard volume with *ca.* 1 M HCl in 47% ethanol, and absorption at 390 mμ was measured. With 0.1 M piperidine, K_e was 105, 119, and 109, respectively, with [$NaOCH_3$] 0.05, 0.10, and 0.20 M. With 0.05 M piperidine, K_e was 83, 86, and 81, at the respective $NaOCH_3$ concentrations. These estimates confirm in a general way the K_e (100 l. mol^{-1}) of kinetic origin, which we consider to be more reliable.

The K_e of 100 M^{-1} corresponds to $\Delta G°$ of −3100 cal.

Reaction Mechanism.—Several aromatic nucleophilic substitution reactions involving amine reagents have now been found to be base catalyzed.[3,4,6,12,20,21] The mechanism indicated by those studies is written in Chart I in the form most suitable for the present reaction. The second step of this mechanism is a fast proton-transfer equilibrium with equilibrium constant K_i. We have omitted from Chart I a step commonly included in such a mechanism, namely, the uncatalyzed or solvent-catalyzed transformation of intermediate complex III to products. It is omitted only because we have no evidence for it from the present study.

CHART I



The general expression for k_A in terms of rate coefficients for specific steps[12] is written for the mechanism of Chart I as eq 5. This expression calls for k_A to be

$$k_A = \frac{k_1K_ik_4[OCH_3^-]}{k_{-1} + K_ik_4[OCH_3^-]} \quad (5)$$

linearly dependent on [OCH_3^-] when $k_{-1} \gg K_ik_4$[OCH_3^-], independent of [OCH_3^-] when K_ik_4[OCH_3^-] $\gg k_{-1}$, and curvilinearly dependent on [OCH_3^-] with ever-diminishing slope when neither inequality is extreme.

The dependence of k_A on methoxide concentration found in the present work (Figure 1) is nearly linear, but the plot is slightly curved in a sense allowed by eq 5. The form of the plot suggests that k_{-1} is larger than K_ik_4[OCH_3^-] but not so much larger that the latter term may be dismissed from the denominator. This interpretation means that step 4 is almost wholly rate limiting, in either direction, at low $NaOCH_3$ concentrations, but that rate limitation is increasingly shared with step 1 as the methoxide concentration increases.

An alternative interpretation of the decrease in k_r in Table I and of k_A/[OCH_3^-] in Table III is that sodium methoxide exerts a negative salt effect on the reaction in both directions, but this seems unlikely in view of Bernasconi's discovery that the rate coefficient for attack of $NaOCH_3$ on 2,4-dinitroanisole, to form the usual Jackson–Meisenheimer complex, increases as the $NaOCH_3$ concentration increases.[14b]

Another mechanistic possibility is that methoxide ion catalyzes the first step of the intermediate complex mechanism, I and piperidine and CH_3O^- reacting in

(20) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3217 (1965).
(21) F. Pietra and A. Fava, *Tetrahedron Lett.*, 1535 (1963); C. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, **49**, 103 (1966).

one concerted step to form IV and CH_3OH. A linear dependence on methoxide ion concentration would be expected, except as it might be modified by salt effects. We cannot exclude this possibility on the basis of our present results, but we consider it unlikely because no strong catalysis of this type has been encountered in other aromatic nucleophilic substitutions involving amine reagents.

Bunnett and Bernasconi[4] found reaction 1 in 10% dioxane–90% water to exhibit curvilinear dependence of k_A on hydroxide ion concentration. Their study was conducted at constant ionic strength, and the curvature could not be attributed to a salt effect. Comparison of the two studies shows that the relative rates of reversion of intermediate III to reactants and progression to products are altered by change of solvent and base.

By the principle of microscopic reversibility, the reverse of reaction 1 must occur by the same mechanism, in the other direction. The reverse mechanism in Chart I is a reasonable one.

Registry No.—I, 119-27-7; II, 839-93-0; methanol, 67-56-1; piperidine, 110-89-4; sodium methoxide, 124-41-4.

The Reaction of Diphenylphosphinous Chloride with Benzoyl Peroxide[1]

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The reaction of equimolar quantities of diphenylphosphinous chloride, Ph_2PCl (**1**), and benzoyl peroxide in refluxing benzene produces a mixture of benzoyl chloride, benzoic anhydride, and diphenylphosphinic anhydride, $Ph_2P(O)OP(O)Ph_2$ (**2**). In addition, a mixed anhydride, $PhC(O)OP(O)Ph_2$ (**3**), is detected. The first step of the reaction is an oxygen transfer from peroxide to **1** to form benzoic anhydride and diphenylphosphinyl chloride (**4**) In a secondary reaction **4** interacts with benzoic anhydride to give a mixture of benzoyl chloride, **3**, and benzoic anhydride. Mixed anhydride is thus not a primary product but is formed by a metathesis between benzoic anhydride and **4** or/and by an equilibration of benzoic anhydride with **2**.

The reaction between peroxides and trivalent phosphorus compounds may proceed by either a homolytic or a heterolytic route, or by a combination of the two, the products giving some indication of the favored route.[2-4] Thus, the reaction of benzoyl peroxide with triphenyl or tri-*n*-butyl phosphine (eq 1, R = Ph, *n*-Bu)

$$PhC(O)OO(O)CPh + R_3P \longrightarrow PhC(O)O(O)CPh + R_3P \longrightarrow O \quad (1)$$

yields the corresponding phosphine oxide and benzoic anhydride,[5,6] the net effect being the transfer of an oxygen atom to phosphorus. In this case the involvement of ionic intermediates is established.[7,8] However, a radical mechanism is thought to operate in the reaction of phosphorus trichloride with benzoyl peroxide to yield carbon dioxide, benzoyl chloride, and benzene phosphonyl dichloride[9] (eq 2). Benzoyl peroxide and

$$PhC(O)OO(O)CPh + PCl_3 \longrightarrow PhC(O)Cl + PhP(O)Cl_2 + CO_2 \quad (2)$$

triethyl phosphite react in solution by the ionic route to yield benzoic anhydride and triethyl phosphate (eq 1, R = OEt), but the uncontrolled reaction in the absence of a solvent yields in addition to these products diethylphenyl phosphonate, $PhP(O)(OEt)_2$, indicating, at least in part, a homolytic route.[10]

Recently, we reported[1b] that the reaction of benzoyl peroxide with diphenylphosphinous chloride (**1**), although not homolytic, is apparently different from the general ionic type expressed by eq 1. There were isolated benzoyl chloride, and two symmetrical anhydrides, benzoic anhydride and diphenylphosphinic anhydride (**2**) (eq 3). In addition, a mixed benzoic

$$\underset{\mathbf{1}}{Ph_2PCl} + PhC(O)OO(O)CPh \longrightarrow PhC(O)Cl + {}^1/_2\underset{\mathbf{2}}{PhC(O)O(O)CPh} + {}^1/_2Ph_2P(O)O(O)PPh_2 \quad (3)$$

diphenylphosphinic anhydride (**3**) was detected but was not isolated in pure form. This paper outlines in

$$\underset{\mathbf{3}}{Ph_2P(O)O(O)CPh}$$

greater detail the results of the preliminary communication, and provides further information about the reaction path and the role of **3** in the reaction.

Results

In initial preparative-scale experiments, the reaction between **1** and benzoyl peroxide was carried out in refluxing benzene at molar concentration. Under these conditions and after an isolation procedure involving distillation and recrystallization, the final products were identified as benzoyl chloride, benzoic anhydride, and **2**. The stoichiometry corresponds roughly to eq 3. In addition, another material with a characteristic ir absorption band in the carbonyl region at 1740 cm^{-1} (which is not displayed by the other carbonyl-containing materials in the system) was detected in the

(1) (a) This investigation was supported by a grant from the Public Health Service, U. S. Department of Health, Education, and Welfare (GM 14932-01). The preliminary results (b) were published in *Chem. Ind.* (London), 120 (1967) and (c) were presented in part in a talk at the International Symposium on the Chemistry of Organic Peroxides in Berlin, DDR, Sept 1967.

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reaction mixture during work-up and as a contaminant of crops of low-melting **2** obtained from the mother liquor. Several attempts, using varying work-up procedures, to isolate a pure sample of this material from the peroxide reaction were unsuccessful.

The hitherto unknown anhydride **3** was prepared by the reaction of diphenylphosphinic acid and benzoyl chloride in the presence of 2,6-lutidine (lu), and its physical properties and chemical behavior under the

$$Ph_2P(O)OH + PhC(O)Cl + lu \longrightarrow \underset{\mathbf{3}}{Ph_2P(O)O(O)CPh} + lu\cdot HCl$$

conditions of the peroxide reaction were established. Comparison of ir spectra of pure **3** with those of samples of **2** from the peroxide reaction containing material with a band at 1740 cm^{-1} established that the latter material was **3**.

In addition to identification of products, the following observations were made. No gas (CO_2, HCl) was evolved, and neither chlorobenzene nor biphenyl was detected. The product composition was identical both in the presence and absence of catalytic amounts of cupric bromide.

Ir spectra indicated that under the chosen conditions the reaction of benzoyl peroxide with **1** proceeded rapidly. No rate measurements were therefore made under these conditions. Immediately after the addition of benzoyl peroxide, benzoic anhydride and only minor quantities of benzoyl chloride and **2** were present. As refluxing continued, the amounts of benzoyl chloride and **2** increased at the expense of the benzoic anhydride. Compound **3** could not be positively identified until the removal of benzoyl chloride by distillation.

Thus, there were clear indications that, after an initial rapid reaction, secondary interactions of the products in the reaction mixture, and possibly also during the isolation procedure, had occurred.

In order to clarify the reaction path, the reaction conditions were changed. At room temperature and in more dilute solution, the initial interaction of benzoyl peroxide and **1** was slowed down to a rate which allowed the study of the disappearance of the reactants, and the appearance of the primary products. No attempt was made to isolate the products, because it was by now known that further interaction occurs during distillation and recrystallization procedures. Instead, extensive use was made of ir spectra in following the changes and identification of products.

Under these conditions the primary products are diphenylphosphinyl chloride (**4**) and benzoic anhydride, which do not rapidly react further. However, on refluxing they were converted into the final product mixture consisting of benzoyl chloride, benzoic anhydride, and **2**. Thus, a clean separation was achieved between the initial interaction of benzoyl peroxide with **1** (eq 4), and the further interactions of the primary products, benzoic anhydride and **4** (eq 5). Additional evidence was obtained from the reaction of **4** with

$$\underset{\mathbf{1}}{Ph_2PCl} + PhC(O)OO(O)CPh \longrightarrow \underset{\mathbf{4}}{Ph_2P(O)Cl} + PhC(O)O(O)CPh \quad (4)$$

benzoic anhydride. The reaction of a synthetic mixture of these reactants proceeded only slowly at room temperature, and gave products identical with those obtained from benzoyl peroxide at reflux.

$$\underset{\mathbf{4}}{Ph_2P(O)Cl} + PhC(O)O(O)CPh \longrightarrow PhC(O)Cl + {}^1/_2\underset{\mathbf{2}}{Ph_2P(O)O(O)PPh_2} + {}^1/_2PhC(O)O(O)CPh \quad (5)$$

Further work at room temperature and high dilution showed that inhibitors, such as galvinoxyl and diphenylpicrylhydrazyl (DPPH), and also catalytic amounts of cupric bromide, have no effect on the rate or products of the reaction between benzoyl peroxide and **1**. Each of the "stable" free radicals interacted with **1**, as evidenced by a change in color and the simultaneous disappearance of the esr signal of the radical. However, the reaction mixtures still markedly inhibited the otherwise rapid autoxidation of **1**.

Each reaction system, with and without inhibitors or cupric bromide, behaved identically when the initially formed products at room temperature were refluxed. Benzoyl chloride, benzoic anhydride, and **2** were the products in each case. A synthetic mixture of **4** and benzoic anhydride at the same concentration also yielded the same mixture of products.

Further evidence was sought bearing on the role of **3** in the reaction. Careful examination of the ir spectra of samples from the reaction of benzoyl peroxide with **1** and those of synthetic mixtures of **4** and benzoic anhydride after refluxing in benzene was not conclusive because of the close proximity of the carbonyl absorptions of benzoyl chloride and **3**. It could only be concluded that **3** might be present in minor quantities. After removal of solvent and benzoyl chloride by distillation, the carbonyl peak (1740 cm^{-1}) of **3** was now clearly distinguishable. If benzoic anhydride was now removed by distillation, **3** remained as the only carbonyl-containing material in the residue, but again only in minor quantities.

A solution of **3** in refluxing benzene rapidly transformed to an equilibrium mixture containing the two symmetrical anhydrides and an appreciable proportion of **3**. The same equilibrium mixture was reached more slowly when equimolar amounts of benzoic anhydride and **2** were refluxed in benzene. The behavior at room temperature was similar, and the transformation of **3** yielded an equilibrium mixture containing a rather larger proportion of **3**.

In refluxing benzene, the two systems, **4**–benzoic anhydride and **3**–benzoyl chloride, are transformed to the same equilibrium mixture, identical with that obtained from the reaction of benzoyl peroxide with **1** (eq 3).

Each system after equilibration gave an identical mixture of products, namely benzoyl chloride, benzoic anhydride, **2**, and traces of **3** during the isolation procedure. The equilibrium does not lie completely to the right as shown by eq 3, since small changes occur when a mixture of the composition shown is refluxed in benzene.

Equilibrium in refluxing benzene was reached within 4 hr, except for the reaction of **3** with benzoyl chloride. In this case the decomposition of **3** was slower than the decomposition of **3** alone under the same conditions.

Discussion

The pathway and mechanism of the reaction of benzoyl peroxide with **1** are of interest because of the apparently different behavior from the reactions of triphenylphosphine and phosphorus trichloride.

The detection of **3**, unstable with respect to the corresponding symmetrical anhydrides, led us initially to

$$Ph_2P(O)O(O)CPh \rightleftharpoons {}^1/_2Ph_2P(O)O(O)PPh_2 + {}^1/_2PhC(O)O(O)CPh$$

the conclusion that **3** might be an important intermediate in the reaction. The formation of **3** could be rationalized through participation of a pentacovalent phosphorus addition compound, as has been discussed in other cases.[3]

$$\underset{\mathbf{1}}{Ph_2PCl} + PhC(O)OO(O)CPh \longrightarrow \left[Ph_2P(Cl)(O(O)CPh)(O(O)CPh)\right] \longrightarrow$$

$$PhC(O)Cl + \underset{\mathbf{3}}{Ph_2P(O)O(O)CPh} \longrightarrow$$

$$PhC(O)Cl + {}^1/_2Ph_2P(O)O(O)PPh_2 + {}^1/_2PhC(O)O(O)CPh$$
$$\mathbf{2}$$

This assumption was disproved by experiments at room temperature, which showed that successive steps are involved, described by eq 4 and 5.

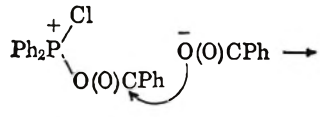
Compound **3** is clearly not an intermediate in the initial interaction of **1** and benzoyl peroxide, but is formed at some later stage.

The first step (eq 4) is formally identical with the reaction path observed in the case of the reaction of triphenylphosphine with benzoyl peroxide, *i.e.*, an oxygen transfer. The inhibition data obtained at room temperature seem to exclude a radical mechanism. This conclusion is supported also by the absence of an effect of copper salts, and the autoxidative data. It has been shown[11,12] that traces of copper salts can drastically change the rates and products of radical reactions of peroxy compounds. The absence of such an effect in the reaction of benzoyl peroxide with **1** indicates that a radical path may not be operative.

Inhibition of autoxidation of **1** by galvinoxyl and DPPH clearly demonstrates that this autoxidation is a radical process. The observation that **1** is rapidly autoxidized independent of the presence of benzoyl peroxide indicates that the radical species involved in the autoxidation play no part in the peroxide reaction.

It is probable then that the first step (eq 4) proceeds through an ionic mechanism such as that established for the reaction of triphenylphosphine.

$$Ph_2PCl + PhC(O)OO(O)CPh \longrightarrow$$



$$Ph_2P(O)Cl + PhC(O)O(O)CPh$$

The data obtained at low temperatures do not necessarily apply rigorously to the high temperature conditions, where a radical process could be partially operative. In this case, the absence of carbon dioxide in the products, inertness of the solvent, and the lack of effect of copper salts on product composition, seem also to exclude a radical mechanism.

The second step (eq 5) consists of the metathesis between **4** and benzoic anhydride. Compound **3** was not conclusively identified in this process, and if present would only be in small concentration. Separate experiments with **3** show that it decomposes to an equilibrium mixture with the two symmetrical anhydrides. It is proposed that **3** is an unstable intermediate in the second step, for which the following reaction path

$$\underset{\mathbf{4}}{Ph_2P(O)Cl} + PhC(O)O(O)CPh \longrightarrow$$

$$PhC(O)Cl + \underset{\mathbf{3}}{[PhC(O)O(O)PPh_2]}$$

$$[\underset{\mathbf{3}}{Ph_2P(O)O(O)CPh}] \rightleftharpoons$$

$${}^1/_2Ph_2P(O)O(O)PPh_2 + {}^1/_2PhC(O)O(O)CPh$$
$$\mathbf{2}$$

might be applicable, since it is difficult otherwise to visualize a simple one-step process which satisfies the overall stoichiometry of eq 5.

$$Ph_2P(O)Cl + {}^1/_2PhC(O)O(O)CPh \longrightarrow$$

$${}^1/_2\ Ph_2P(O)O(O)PPh_2 + PhC(O)Cl$$

Abundant references can be found in the literature supporting the generality of this type of interaction of acid halides with anhydrides. Thus acetic anhydride reacts with carboxylic acid chlorides[13,14] to yield the corresponding carboxylic anhydride and acetyl chloride. For example, the reaction of acetic anhydride with benzoyl chloride[13] produces an almost quantitative yield of benzoic anhydride; the presumed intermediate, acetic benzoic anhydride, which is thermally unstable,[15] is not isolated. However, the reaction of acetic anhydride with chlorides of nonmetal or metalloid chlorides may proceed only as far as a mixed anhydride which is thermally stable and can be isolated. For example, acetates result from the reaction of acetic anhydride with phosphoryl chloride,[16] silicon tetrachloride,[17] aluminum chloride,[18] and chlorodiphenylboron.[19]

$$MeC(O)O(O)CMe + PhC(O)Cl \rightleftharpoons$$

$$MeC(O)Cl + [MeC(O)O(O)CPh]$$

$$[MeC(O)O(O)CPh] \rightleftharpoons$$

$${}^1/_2MeC(O)O(O)CMe + {}^1/_2PhC(O)O(O)CPh$$

$$P(O)Cl_3 + 3MeC(O)O(O)CMe \longrightarrow$$

$$P(O)[O(O)CMe]_3 + 3MeC(O)Cl$$

$$SiCl_4 + 4MeC(O)O(O)CMe \longrightarrow Si[O(O)CMe]_4 + 4MeC(O)Cl$$

$$AlCl_3 + MeC(O)O(O)CMe \longrightarrow AlCl_2[O(O)CMe] + MeC(O)Cl$$

$$Ph_2BCl + MeC(O)O(O)CMe \longrightarrow Ph_2BO(O)CMe + MeC(O)Cl$$

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The comparative ease of detection of **3** from the peroxide reaction during work-up after removal of solvent may be due to a more favorable equilibrium in the absence of solvent. A similar situation has been recorded recently[20] involving the interaction of acetic anhydride with **2**.

Experimental Section

Melting and boiling points are uncorrected. The molecular weight determination was carried out by Rast's method. Elemental microanalyses were performed by MicroTech Laboratories, Skokie, Ill.

Diphenylphosphinous chloride, benzoyl peroxide, benzoyl chloride, benzoic anhydride, 2,6-lutidine, cupric bromide, galvinoxyl, and diphenylpicrylhydrazyl (DPPH) were commercial products. Diphenylphosphinyl chloride was prepared by air oxidation of neat diphenylphosphinous chloride[21] at 130° in 36 hr, followed by distillation at reduced pressure. Diphenylphosphinic acid was prepared by the reaction of diphenylphosphinous chloride with aqueous alkaline hydrogen peroxide.[22] Diphenylphosphinic anhydride was made by the reaction of diphenylphosphinic acid with diphenylphosphinyl chloride[23] in the presence of base, *e.g.*, 2,6-lutidine.

All experiments were carried out under nitrogen where appropriate, with exclusion of atmospheric moisture. No gas evolution was observed in the peroxide reactions.

Peroxide in the reaction mixtures could not be estimated by direct iodometric titration after addition of sodium iodide and a catalyst. Instead, ir spectra were used to follow the progress of the reactions and to confirm the characterization of isolated materials. Standard spectra were prepared for comparison purposes. The main absorption bands for each material are listed in Table I, with an indication (*) (low intensity bands have been omitted) of those bands which were most useful for characterization. Identification of mixtures was confirmed where possible by comparing spectra with those of synthetic mixtures.

TABLE I

Compounds	Ir absorptions, cm^{-1}
Ph_2PCl	1430, 1090*, 740*
$Ph_2P(O)Cl$	1435, 1250, 1235, 1120, 750, 725
PhC(O)OO(O)CPh	1785*, 1765*, 1595, 1450, 1220, 1175, 995
PhC(O)O(O)CPh	1785, 1725, 1600, 1450, 1210, 1170, 1010*, 995*, 775
$PhC(O)O(O)PPh_2$	1740*, 1450, 1435, 1260–1240 (sh), 1235, 1205, 1165, 1125, 1070, 1020–1040, 1015, 835*, 770, 745, 720
$PPh_2(O)O(O)PPh_2$	1440, 1245, 1130, 1110, 1000, 945*, 745, 725
PhC(O)Cl	1770, 1730, 1590, 1580, 1450, 1200, 1170, 870*, 775
PhC(O)OH	2500–3200*, 1690*, 1450, 1415, 1320, 1290

Reaction of Benzoyl Peroxide with Diphenylphosphinous Chloride (1) A. In Refluxing Benzene. a. In the Presence of Cupric Bromide.—Benzoyl peroxide (24.2 g, 0.1 mol) suspended in benzene (50 ml) was added dropwise during 1 hr to a refluxing solution of **1** (18 ml, 0.1 mol) and cupric bromide (0.2 g, 0.9 mmol) in benzene (50 ml). After an exothermic reaction, the mixture was refluxed for a further 3 hr. The solvent was then removed at 14 mm, and the residual oil was distilled and yielded benzoyl chloride (7.6 g, 0.0543 mol), bp 100–110° (50 mm); benzoic anhydride (10.0 g, 0.0442 mol), bp 100–138° (0.05 mm), mp 43–44.5° (ether–petroleum ether, 20–40°); and a residue. Successive crops of **2** were obtained by recrystallization of the residue from benzene and repeated addition of ether to the evaporated mother liquor to precipitate further solid material. Obtained were crop 1 (3.2 g), mp 145–148°, crop 2 (9.0 g), mp 138–143°, and crop 3 (5.0 g), mp 137–140°, to total 17.2 g (0.041 mol).

b.—Experiment a was repeated with more detailed ir monitoring of the reaction and a slight variation in work-up procedure. After the addition period (1 hr) the characteristic peaks of benzoyl peroxide (1765, 1220, and 1175 cm^{-1}) and that of **1** (1090 cm^{-1}) were not observed. Instead, benzoic anhydride (two peaks of almost equal intensity at 1010 and 995 and carbonyl absorption at 1785 cm^{-1}) and smaller proportions of benzoyl chloride (870 cm^{-1}) and **2** (945 cm^{-1}) could be detected. After refluxing for 3 hr more, the ir spectrum indicated the formation of more **2** and benzoyl chloride at the expense of benzoic anhydride, which was, however, still present. Alkaline hydrolysis of an aliquot followed by acidification and removal of insoluble diphenylphosphinic acid by filtration produced an aqueous solution which was then titrated against silver nitrate. The titration indicated that all chlorine could be converted by hydrolysis into chloride ion. After removal of benzoyl chloride (7.8 g, 0.0553 mol), bp 75° (13 mm), the ir spectrum of the residual oil showed carbonyl absorptions of similar intensity at 1780, 1740, and 1725 cm^{-1}. Crystallization of the residual oil from benzene yielded **2** (8.0 g, 0.0191 mol), mp 146–146.5°. Ether treatment of the evaporated mother liquor yielded a brownish solid (5.5 g), mp 125.5–148°; the ir spectrum of this material showed that it was **2** contaminated with anhydride **3** (only one absorption band in the carbonyl region at 1740 cm^{-1}). Evaporation of the mother liquor gave a dark residual oil (15.3 g). The ir spectrum of this oil indicated that it consisted of a mixture of benzoic anhydride with a small proportion of **2**, benzoyl chloride, and benzoic acid.

c. In the Absence of Cupric Bromide.—Experiment a, repeated with the omission of cupric bromide, gave essentially identical results. There were isolated benzoyl chloride (8.4 g, 0.060 mol), bp 105–115° (35 mm); benzoic anhydride (9.9 g, 0.0438 mol), bp 140° (0.2 mm), mp 44–44.5° (ether–petroleum ether); **2** (successive crops totaling 19.0 g, 0.045 mol); and a residue.

B. The Primary Process. Formation of Diphenylphosphinyl Chloride (4) and Benzoic Anhydride in Benzene at Room Temperature. a. In the Absence of Cupric Bromide.—A solution of benzoyl peroxide (2.42 g, 0.01 mol) in benzene (25 ml) was added to a stirred solution of **1** (2.0 ml, 2.44 g, 0.011 mol) in benzene (25 ml) at room temperature, and samples of the reaction mixture were removed periodically for ir analysis. The reaction was conducted in an atmosphere of nitrogen, and the benzene used was previously purged with nitrogen. The temperature of the reaction mixture rose from 29 to 36.5° during about 30 min; thereafter, the reaction mixture slowly cooled down to room temperature. During the first hour the slow disappearance of peroxide was followed through the decreasing intensity of the carbonyl peak at 1765 cm^{-1}. After 5 hr peroxide was not detectable, and the spectrum was completely superimposable on that of an equimolar mixture of **4** and benzoic anhydride in benzene at the same dilution.

b. In the Presence of Cupric Bromide.—The preceding experiment a, repeated in the presence of catalytic amounts of cupric bromide (0.90 mmol), produced no change in either rate or composition of products.

c. In the Presence of DPPH and Galvinoxyl.—Stock solutions of DPPH (10^{-2} *M*) and galvinoxyl (5×10^{-3} *M*) were made up in benzene which had been purged with nitrogen, and used within 12 hr. The color of DPPH stock solution (purple) was unchanged over several days, but that of galvinoxyl (brown) faded appreciably over 24 hr. When **1** (2.0 ml, 0.011 mol) was added to the stirred benzene stock solution (25 ml) of radical, a rapid (about 1 min) color change occurred, from purple to brown for DPPH, and from brown to yellow for galvinoxyl. After the color change had occurred, no esr signal was detectable in either reaction mixture.

The preceding experiment a was now repeated. The benzene solution of benzoyl peroxide was added to the resulting reaction mixture (from addition of **1** to the benzene solution of radical), in which the color change was complete and no esr signal was detectable. The ir spectra throughout the reaction, in the case of each radical, were identical with those in the absence of these additives. Thus, within the limits of the experimental method, there was no inhibition of rate or changes of products.

Inhibition of Autoxidation of Ph_2PCl (1) to $Ph_2P(O)Cl$ (4).—A solution of **1** (0.01 mol) in benzene (50 ml), which was purged with nitrogen, was stirred under a nitrogen atmosphere, and

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(21) P. Hauke and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).

(22) L. R. Ocone, *et al.*, *U. S. Dept. Comm. Office Tech. Serv., AS 262*, 806 (1961); *Chem. Abstr.*, **59**, 2853*h* (1963).

(23) R. L. Dannley and K. R. Kabre, *J. Amer. Chem. Soc.*, **87**, 4805 (1965).

oxygen was introduced at a rate of about two bubbles per second. An exothermic reaction occurred, and the conversion of **1** into **4** was completed within 20 min (by ir).

When the experiment was repeated with the addition of benzoyl peroxide (0.01 mol) just before the introduction of oxygen, the autoxidation was completed within 15 min, while benzoyl peroxide remained unaffected.

The autoxidation was now attempted with the reaction mixture resulting from addition of **1** (0.01 mol) to the benzene solution (25 ml) of DPPH, in which the color change was complete, and no esr signal was detectable. No autoxidation occurred. In the case of galvinoxyl (1×10^{-3} *M*), a strong retardation was observed.

C. The Secondary Process. Reaction of Benzoic Anhydride with Diphenylphosphinyl Chloride (4) in Benzene at Reflux.—The ir spectra of the mixtures of products obtained in experiments B (a–c) remained unchanged over a period of a few hours at room temperature. On heating at reflux for 24 hr all mixtures produced the following result. The ir spectra indicated that **2** (945 cm^{-1}) and benzoyl chloride (870 cm^{-1}) were formed at the expense of benzoic anhydride (1010 and 995 cm^{-1}), which, however, was still detectable. The spectra were identical with those of an equimolar mixture of **4** and benzoic anhydride at the same concentration which had been refluxed for 24 hr and were also identical with those of a mixture of a composition of benzoyl chloride (1.0 mol), **2** (0.5 mol), and benzoic anhydride (0.5 mol) at the same concentration which had been refluxed for 4 hr.

Preparation of Mixed Anhydride, $PhC(O)O(O)PPh_2$ (3).—Benzoyl chloride (42 g, 0.3 mol) was added over 10 min to a stirred solution of diphenylphosphinic acid (65 g, 0.3 mol) and 2,6-lutidine (32 g, 0.3 mol) in dry benzene (500 ml) below 25°. The apparatus was protected from atmospheric moisture. After 3 hr at 25°, the reaction mixture was filtered. The ir spectrum of the filtrate showed only one absorption peak (1740 cm^{-1}) in the carbonyl region. On evaporation of benzene under reduced pressure, there were obtained crop 1 (29.5 g), mp 113.5–115.5°; crop 2 (23 g), mp 119–120°; crop 3 (12.8 g) mp 121–140°; and an oily residue (24.2 g). Four recrystallizations of crop 1 from benzene at 10° yielded pure **3**, mp 123.5–124°. Material obtained by recrystallization from benzene tenaciously retained solvent, and melted rather low (110–120°). On pumping at 0.1 mm pressure for 12 hr the melting point rose to 123–124°.

Anal. Calcd for $C_{19}H_{15}O_3P$: C, 70.79; H, 4.69; mol wt, 322. Found: C, 70.63; H, 4.80; Mol wt, 320.

The ir spectrum showed only one peak in the carbonyl region (1740 cm^{-1}). Other strong absorption bands are at 1450, 1435, 1260–1240 (sh), 1235, 1205, 1165, 1125, 1070, 1020–1040, 1015, 835, 770, 745, and 720 cm^{-1}. Low intensity absorptions are at 1518 and 1105 cm^{-1}.

When this reaction was repeated at higher temperatures a mixture of the three anhydrides was produced from which pure **3** could not be readily separated.

Decomposition of 3 in Refluxing Benzene.—Compound **3** was generated in solution by the previously described reaction between **4** (23.6 g, 0.1 mol), benzoic acid (12.2 g, 0.1 mol), and 2,6-lutidine (10.7 g) in benzene (200 ml). The white suspension was refluxed for 4 hr, and 2,6-lutidine hydrochloride (13.3 g, 0.093 mol) was removed by filtration. Solvent was then removed at reduced pressure, and the residual oil was distilled to yield benzoic anhydride (6.8 g, 0.0301 mol): bp 125–143° (0.02 mm); mp 42–43.5° (ether–petroleum ether). Recrystallization of the pot residue from benzene and precipitation with ether yielded **2**: crop 1 (13.2 g, 0.0316 mol), mp 145–146.5°; crop 2 (4.4 g), mp 131–139.5°; crop 3 (1.2 g), mp 125–137°; and a residue (3.7 g). Ir spectra of crops 2 and 3 indicated that they contained traces of **3**.

The preceding experiment was repeated in order to follow the progress of the reaction by ir spectroscopy. A solution of **3** (3.2 g, 0.01 mol), mp 123–124°, in benzene (15 ml) was refluxed. After 15 hr the ir spectrum indicated the formation of a mixture of benzoic, diphenylphosphinic, and mixed anhydrides at equilibrium; *i.e.*, the ir spectrum was not significantly altered on refluxing for a further 24 hr. The equilibrium mixture is composed of approximately equal molar amounts of the three anhydrides.

Decomposition of 3 in Benzene at Room Temperature.—A solution of **3** (3.2 g, 0.01 mol), mp 123–124°, in benzene (15 ml) was left at room temperature protected from atmospheric moisture, and the progress of the decomposition followed by taking ir spectra. The rate of decomposition was slower than that in refluxing benzene. After 24 hr, slightly more **3** remained than was present in the equilibrium mixture at reflux. After 48 hr, a little more decomposition had occurred, but the amount of **3** was still slightly greater than that at reflux in benzene.

Reaction of Benzoic Anhydride and Diphenylphosphinic Anhydride (2) in Refluxing Benzene.—A solution of benzoic anhydride (2.26 g, 0.01 mol), mp 44–44.5°, and **2** (4.20 g, 0.01 mol) in benzene (30 ml) was refluxed, and the progress of the reaction was followed by ir spectroscopy. After 3 hr at reflux the ir spectrum indicated that about 65% of the benzoic anhydride remained and a corresponding amount of **3** (about 0.006 mol) had appeared. The spectrum was not altered by further reflux and corresponded to the same equilibrium mixture which was formed from **3** dissolved in benzene at reflux.

The final spectra from each experiment were completely superimposable.

Reaction of 3 with Benzoyl Chloride in Refluxing Benzene.—Compound **3** was generated in solution by the previously described reaction between diphenylphosphinic acid (2.18 g, 0.1 mol), benzoyl chloride (28.2 g, 0.2 mol), and 2,6-lutidine (10.7 g, 0.1 mol) in benzene (125 ml). The white suspension was refluxed for 4 hr, and lutidine hydrochloride (13.1 g, 0.092 mol) was removed by filtration. Solvent was then removed at reduced pressure, and the residual oil was distilled to yield benzoyl chloride (8.0 g, 0.0567 mol), bp 73° (11 mm), and benzoic anhydride (5.2 g, 0.023 mol), bp 125–140° (0.03 mm), mp 46° (ether–petroleum ether). Recrystallization from benzene and precipitation with ether yielded **2**: crop 1 (9.7 g, 0.0232 mol), mp 144.5–145.5°; crop 2 (1.4 g), mp 144–146°; crop 3 (3.4 g), mp 127–147°; and a residue (5.7 g). Ir spectra of crops 2 and 3 indicated that they consisted of **2** contaminated with **3**. The residue consisted of benzoic anhydride with a considerable proportion of **3**.

The reaction of benzoyl chloride with **3** was repeated on a smaller scale in order to follow the reaction by ir spectroscopy. A solution of benzoyl chloride (2.81 g, 0.02 mol) and **3** (6.44 g, 0.02 mol) in benzene (40 ml) was refluxed. After 4 hr, the benzoyl chloride (870 cm^{-1}) concentration remained unchanged, but **3** had decomposed to benzoic anhydride and **2**. Within the wide limits of the experimental method, not more than 50% of **3** had decomposed. The reaction had not come to equilibrium, however, since after 15 hr further decomposition of **3** had occurred, although a considerable proportion still remained.

Reaction between Diphenylphosphinyl Chloride (4) and Benzoic Anhydride.—A solution of benzoic anhydride (11.3 g, 0.05 mol) and **4** (11.8 g, 0.05 mol) in benzene (50 ml) was refluxed for 4 hr. The ir spectrum indicated the appearance of benzoyl chloride and some **2** at the expense of the benzoic anhydride. No clear conclusion could be drawn at this stage concerning the presence of **3**. After removal of the solvent, benzoyl chloride (4.4 g, 0.0312 mol), bp 70–73° (12 mm), was distilled. The ir spectrum of the residue indicated a mixture of the three anhydrides. Benzoic anhydride (5.4 g, 0.0239 mol), bp 134–136° (0.12 mm), mp 42–45°, was then removed by distillation. Recrystallization of the residue yielded **2**: crop 1 (5.1 g, 0.0122 mol), mp 147.5–148°; crop 2 (2.8 g, 0.0067 mol), mp 134–141°; and a residue (2.3 g). The ir spectrum indicated that crop 1 consisted of pure **2**, crop 2 was the same material contaminated with **3** (1740-cm^{-1} absorption), and the residue was a mixture of **2**, **3**, and benzoic anhydride.

Reaction between Benzoyl Chloride, Benzoic Anhydride, and Diphenylphosphinic Anhydride (2).—A mixture of benzoyl chloride (2.81 g, 0.02 mol), benzoic anhydride (2.26 g, 0.01 mol), and **2** (4.20 g, 0.01 mol) dissolved in benzene (40 ml) was refluxed. The progress of the reaction was followed by ir spectroscopy. Only minor changes occurred during a 4-hr period; a very small decrease in concentration of each reactant occurred, together with appearance of small shoulders at about 1740 and 835 cm^{-1}. It could only be concluded that **3** could not be present in more than very small proportions if present at all.

Registry No.—**1**, 1079-66-9; **2**, 5849-36-5; **3**, 4693-63-4; **4**, 1499-21-4; benzoyl peroxide, 94-36-0.

Acknowledgments.—The authors wish to thank The Stauffer Chemical Co. and Lucidol Division, Wallace and Tiernan, Inc., for samples of diphenylphosphinous chloride and benzoyl peroxide.

Chemistry of Tetrafluorohydrazine. IV. Addition Reactions with Halogenated Olefins, Norbornadiene, and 2,5-Dimethylfuran

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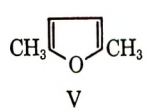
Reaction products of N_2F_4 with halogenated olefins, tetrafluorobutadiene, and norbornadiene are described. Most halogenated olefins give the normal adducts, 1,2-bis(difluoramino)alkanes, but tetrabromoethylene and dichlorohexafluorobutene give largely the products of NF_3 addition. The isomeric addition products from norbornadiene, 2,5-dimethylfuran, and tetrafluorobutadiene were isolated and characterized.

Tetrafluorohydrazine adds readily to olefins to give the corresponding 1,2-bis(difluoramino)ethanes.[1] A mixture of the 1,2- and 1,4-bis(difluoramino) adducts has been obtained from 1,3-cyclooctadiene as well as isomeric mixtures of 1,4 adducts from cyclooctatetraene and 6,6-diphenylfulvene.[2] Substituted anthracenes gave the corresponding 9,10-bis(difluoramino)-9,10-dihydroanthracenes.[1c,3a] Dehydrofluorination of these adducts to give the corresponding N-fluorimino compounds has also been studied.[1e,3,4] We wish to describe the products obtained from addition of N_2F_4 to the completely halogenated olefins Ia–g, the highly halogentated olefins Ih–j, norbornene, and the dienes IV, V, and VI.

$$\underset{\text{I}}{R_1R_2C{=}CR_3R_4} \xrightarrow[75\text{–}200^\circ]{N_2F_4} \underset{\text{IIa,b,d,e,g–j}}{R_1R_2C(NF_2)\text{–}CR_3R_4(NF_2)} + \underset{\text{IIIf}}{R_1R_2C(NF_2)\text{–}CR_3R_4(F)} \quad (1)$$

a, R_1, R_2, R_3, R_4 = F
b, R_1, R_2, R_3, R_4 = Cl
c, R_1, R_2, R_3, R_4 = Br
d, R_1, R_2 = F; R_3, R_4 = Cl
e, R_1, R_3 = F; R_2, R_4 = Cl
f, R_1, R_3 = CF_3; R_2, R_4 = Cl
g, R_1 = CF_3; R_2, R_3, R_4 = F
h, R_1, R_3 = F; R_2, R_4 = CN
i, R_1, R_3 = F; R_2 = C_6H_5; R_4 = C
j, R_1 = F; R_2 = C_6H_5; R_3, R_4 = Cl

$CF_2{=}CHCH{=}CF_2$ (IV)


(V)


(VI)

Tables I and II summarize the properties of the adducts obtained. With chloro and fluoro substituents (Ia,b,d,e,g–j) good yields of 1,2-bis(difluoramino)ethanes (IIa,b,d,e,g–j) are obtained at temperatures of 75–150°. Reaction temperatures as high as 200–225° may be utilized in these addition reactions, but above this temperature range thermal decomposition of N_2F_4 into NF_3 and nitrogen becomes extensive and interferes with the course of addition.

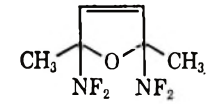
With a few of the olefins studied, so-called "abnormal" adducts were obtained. These adducts represent the addition of the elements of NF_3 to the olefinic linkage. For example, 2,3-dichlorohexafluoro-2-butene underwent reaction with N_2F_4 at 200° to give this "abnormal" adduct IIIf in 13% yield. Cesium fluoride catalysis[5,6] improved the yield in this reaction to 37%. None of the adduct II was observed. The remainder was starting olefin. Tetrabromoethylene (Ic), on the other hand, yielded the N-fluorimino compound VII in 67% yield, together with 14% of a second N-fluorimino compound, VIII. Compound

$$\underset{\text{Ic}}{CBr_2{=}CBr_2} + N_2F_4 \xrightarrow{155^\circ} \underset{\text{VII}}{CBr_2FC(Br){=}NF} + \underset{\text{VIII}}{F_2NCF(Br)C(Br){=}NF} \quad (2)$$

VII may arise from "abnormal" addition of NF_3 to tetrabromoethylene followed by elimination of BrF while compound VIII could arise by normal addition of N_2F_4 followed by elimination of a bromine molecule and internal rearrangement (see Mechanism). All of the eliminated bromine could be titrated with ethylene or 1-hexene.

Dienes react with N_2F_4 to give a mixture of 1,2 and 1,4 adducts as shown by Cantrell[2] in the 1,3-cyclooctadiene case. This was also the case with fluorinated dienes. For example, with 1,1,4,4-tetrafluorobutadiene (IV) the reaction proceeds nearly quantitatively at 38° to give a mixture consisting of 61% 1,4 and 35% 1,2 adducts.[7]

However, with 2,5-dimethylfuran the addition reaction took place at 78°, to give only one simple adduct in 43% yield, the remainder of the reaction mixture being a high-boiling residue. The product appears to be a single stereoisomer, 2,5-dimethyl-2,5-bis(difluoramino)dihydrofuran (IX), as judged by a


IX

broad singlet F^{19} nmr peak for the NF_2 group, a singlet for the vinyl protons at τ 3.74, and a triplet at τ 8.3 for the CH_3 (J_{F-H} = 2.5 cps). Addition of N_2F_4

(1) (a) R. C. Petry and J. P. Freeman, Abstracts of the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 46S; *J. Org. Chem.*, **32**, 4034 (1967); (b) A. J. Dijkstra, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc. Sect. A*, 582 (1966), 105 (1967), 864 (1967); (c) H. Cerfontaln, *ibid.*, 6602 (1965); (d) T. E. Stevens and W. H. Graham, *J. Amer. Chem. Soc.*, **89**, 182 (1967); (e) F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967).

(2) T. S. Cantrell, *ibid.*, **32**, 911 (1967).

(3) (a) A. L. Logothetis, *ibid.*, **31**, 3686 (1966); (b) A. L. Logothetis and G. N. Sausen, *ibid.*, **31**, 3689 (1966); (c) T. E. Stevens, *ibid.*, **32**, 670 (1967); (d) S. K. Brauman and M. E. Hill, *J. Amer. Chem. Soc.*, **89**, 2127, 2131 (1967).

(4) See also G. N. Sausen and A. L. Logothetis, *J. Org. Chem.*, **32**, 2261 (1967), and R. C. Petry, C. O. Parker, F. A. Johnson, T. E. Stevens, and J. P. Freeman, *ibid.*, **32**, 1534 (1967), for reaction products obtained from N_2F_4 with acetylenes and allene.

(5) R. D. Dresdner, F. N. Tlumac, and J. A. Young, *J. Amer. Chem. Soc.*, **82**, 5831 (1960), showed that cesium fluoride is a catalyst for addition of NF_3 to hexafluoropropylene in a flow system at 320°.

(6) R. J. Shozda of this laboratory obtained a 68% yield of 2-difluoraminoheptafluoropropane by reaction of NF_3 with hexafluoropropylene at 250° in a closed system using cesium fluoride as a catalyst.

(7) The authors are indebted to Dr. R. J. Shozda for this experiment.

TABLE I

PROPERTIES OF 1,2-BIS(DIFLUORAMINO)ETHANES, $R_1R_2C(NF_2)C(NF_2)R_3R_4$

Olefin	Solvent	Temp, °C	Yield, %	Bp, °C (mm)	n_D	Formula	Calcd, % C	H	F	N	Found, % C	H	F	N	Mol wt Calcd	Mol wt Found	Infrared absorption, 10.5–12 μ
$CF_2=CF_2$	None	75	93	0[a]		$C_2F_8N_2$			74.50				74.33		204	209	10.4, *10.7*, 11.45
$CF_2=CCl_2$	None	90	65	79	1.3478 (26°)	$C_2Cl_2F_6N_2$			48.11	11.83			48.03	11.41			*10.6*, 11.1, 11.5
$CCl_2=CCl_2$[b]	None	150	86	Mp 85.5–87.5		$C_2Cl_4F_4N_2$			28.16	10.38			28.19	10.17			11.0, *11.5*, 11.65
CFCl=CFCl	None	116	74	76	1.3477 (24°)	$C_2Cl_2F_6N_2$			48.11	11.83			47.89	11.87			*10.6*, 11.05, 11.35, 11.55–11.70 (d)
$CF_3CF=CF_2$	None	134	51[c]	35	<1.3000	$C_4F_{10}N_2$				11.03				10.99	254	255	
CF(CN)=CF(CN)[e]	None	157	87	64[f]		$C_4F_6N_4$[d]			52.28				50.84				*10.55*, 10.95, 11.2, 11.7
$C_6H_5CF=CFCl$	None	70	98	70 (5.0)	1.4462 (27°)	$C_8H_{12}N_2F_6Cl$[g]	34.49	1.80	40.92	10.06	35.00	1.96	40.90	10.27			10.6, 11.0, 11.2, 12.0
$C_6H_5CF=CCl_2$	None	120	59[f]	62 (0.5)	1.4814 (25°)	$C_8H_{12}N_2F_5Cl_2$[g]	32.57	1.71	32.20	9.50	33.87	1.87	31.93	9.51			10.36, 10.75, 10.98, 11.40, 11.68
Norbornene	$CHCl_3$	50	52[h]	89–94 (22)	1.4292 (25°)	$C_7H_{10}N_2F_4$	42.42	5.09	38.35	14.14	43.64	5.44	38.21	14.08			10.6, 11.3, 11.5, 11.95

[a] 1,2-Bis(difluoramino)tetrafluoroethane, bp 0°, was obtained by Bigelow and coworkers, *J. Amer. Chem. Soc.*, **83**, 5010 (1961), by the jet fluorination of $(CN)_2$. [b] Excess N_2F_4 (8 mol %) was used to obtain complete conversion of the olefin to adduct. The white solid, obtained directly from the bomb, was analytically pure. [c] Minimum yield, product was lost during work-up. [d] Mass spectrometric analysis showed *m/e* 166 (parent with loss of one NF_2 group) and smaller fragments in support of the 1:1 adduct structure. [e] Calcd for Cl, 12.73; found, 12.78. [f] About 8% $C_6H_5CF(NF_2)C(Cl)=NF$ was also obtained and separated by gc. Ir bands in 10.5–12-μ region were present at 10.75, 11.25, 11.8 μ. [g] Calcd. for Cl, 24.04; found, 23.39. [h] F^{19} nmr showed three sets of quadruplets indicating the presence of *cis-exo*, *cis-endo*, and *trans* adduct. [i] S. Proskow (to Du Pont), U. S. Patent 3,121,734 (Feb 18, 1964).

to dienes like anthracene gave both *cis* and *trans* stereoisomers[3a] and one would expect that 2,5-dimethylfuran should also give two addition products. The isolation of one stereoisomer in only 43% yield suggests that the other stereoisomer is probably also formed, but that it is unstable under the reaction conditions and is decomposed. Models indicate that in the *cis* isomer the two NF_2 groups are very crowded, while in the *trans* isomer they are not. It is tentatively proposed, therefore, that the isomer isolated is the more stable *trans*-2,5-dimethyl-2,5-bis(difluoramino)-dihydrofuran (IX).

The N_2F_4 addition reaction with norbornadiene (VI) occurs readily at 50°, and a mixture of 1:1 adducts is obtained. Gas chromatographic analysis indicated the presence of four components in a ratio of 1:1:9:1 in order of elution. These isomeric components were separated, and their structures were tentatively established by means of infrared and nmr spectroscopy.

The first eluent was assigned the structure of 2,7-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (X) of unknown stereochemistry. It showed unsaturation in the infrared at 6.1 μ, proton nmr indicated two different vinyl hydrogens, τ 3.45 and 3.70, and a single hydrogen in the bridge methylene position (τ 8.0),[8] and F^{19} nmr analysis showed the presence of two different $-NF_2$ groups. The next isomer is a symmetrical molecule and could be assigned the structure of di-*exo*-(XIa) or the di-*endo*-2,3-bis(difluoramino)bicyclo-[2.2.1]hept-5-ene (XIb). The structure is supported

(3)

by the presence of unsaturation in the infrared, 6.1 μ, two equivalent vinyl protons, τ 3.70, in the proton nmr spectrum, and two equivalent $-NF_2$ groups in the F^{19} nmr spectrum. The di-*exo* structure XIa is favored because radical attack is more likely to take place predominantly from the *exo* di-

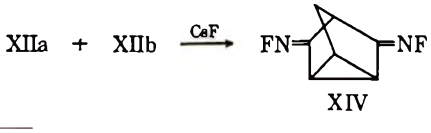
(8) The hydrogens at the highest magnetic field (τ 8.0–9.0) in the substituted norbornenes are assigned to the bridge methylene group: H. E. Simmons, Jr., *J. Amer. Chem. Soc.*, **83**, 1657 (1961).

TABLE II
F^{19} NMR SPECTRA OF DIFLUOROAMINO COMPOUNDS

1,2-Bis(difluoroamino)ethanes	Group	Chemical shift, cps[a]	Observed spin–spin coupling, cps
$F_2NCF_2CF_2NF_2$[b]	NF_2	−5057	None
	CF_2	+3332	None
$F_2NCF_2CCl_2NF_2$[b]	NF_2	−6060	None
	NF_2	−4880	None
	CF_2	+2330	Complex multiplet
$F_2NCCl_2CCl_2NF_2$	NF_2	−6608	None
$F_2NCFClCFClNF_2$[c]	NF_2	−6310, −5650, −5540, −5065	AB type
	CF	+2060, +2235	Badly split
$CF_3CF(NF_2)CF_2NF_2$[c]	NF_2	−5182	
	NF_2	−4865	
	CF_3	+268	
	CF_2	+2475	
	CF	+5626	
$NF_2CF(CN)CF(CN)NF_2$	NF_2	−5650	None
	CF	+4370	Complex multiplet
	CF	+4405	Complex multiplet
$C_6H_5CF(NF_2)CFCl(NF_2)$	NF_2	−3966, −3903	None[d]
	NF_2	−3707, −3662	None
	CF	+3627, +3792	Multiplets
	CF(Cl)	+1736, +1842	Multiplets
$C_6H_5CF(NF_2)CCl_2(NF_2)$	NF_2(C–F)	ν_A −6615, ν_B −6093,	AB, $J_a = J_b = 585$—each peak is a doublet
	NF_2(C–Cl_2)	ν_A −5464, ν_B −5154, $J = 580$	$J_{F\text{-}NF_2} = 12$)
	CF	+4726	Multiplet
$C_6H_5CF(NF_2)C(Cl)=NF$	NF	−6220	
	NF_2	ν_A −5235, ν_B −4975	AB type, $J = 514$
Norbornene adducts	NF_2	−7750 to −5800	Three sets of quadruplets, hence three stereoisomers present, *cis-exo*, *cis-endo*, *trans*

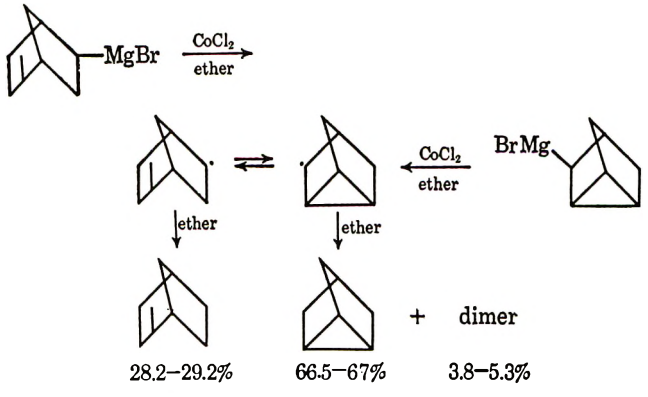
[a] Fluorine nmr spectra were obtained from a Varian Associates high-resolution nmr spectrometer and associated electromagnet. Unless otherwise indicated spectra were obtained at 56.4 Mc/sec and approximately 14,000 gauss. Spectra were calibrated in terms of displacements in cycles per second (cps) from the F^{19} resonance of 1,2-difluoro-1,1,2,2-tetrachloroethane. Negative frequency displacements are for resonances occurring at lower field than the reference. [b] The spectrum was obtained at 40 Mc/sec with reference to $CF_3CO_2H = 0$. The chemical shift recorded in the table has been recalculated to give the value at 56.4 Mc/sec with reference to 1,2-difluoro-1,1,2-2-tetrachloroethane = 0. A value of +625 cps for CF_3CO_2H at 56.4 Mc/sec was used. [c] Spectrum was determined at 40 Mc/sec with reference to 1,2-difluoro-1,1,2,2-tetrachloroethane = 0. The values given for chemical shifts are recalculated to 56.4 Mc/sec. [d] The four NF_2 peaks represent a mixture of *threo* and *erythro* isomers. The AB spectrum expected apparently approaches the A_2 system because of the large values (~600 cps) of the coupling constants and chemical shifts.

rection.[9–12] The third and most abundant component was assigned as a mixture of di-*exo*- and *endo-exo*-3,5-bis(difluoramino)tricyclo[2.2.1.0^{2,6}]heptane (XIIa and b, respectively) in about 3:2 ratio. This assignment is supported by the absence of unsaturation in the infrared and absence of vinyl protons in the proton nmr, and the presence of one kind of $-NF_2$ group for XIIa and two kinds for XIIb. Elimination of 2 mol of hydrogen fluoride from this mixture of tricyclenes, by means of cesium fluoride, gave 3,5-bis(fluorimino)-tricyclo[2.2.1.0^{2,6}]heptane (XIV). It appears to be a mixture of *syn* and *anti* isomers as indicated by the



XIV (4)

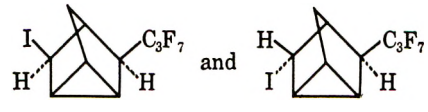
(9) D. I. Davies, J. N. Done, and D. H. Hey, *Chem. Commun.*, 725 (1966), report the following reaction.



It is concluded by the authors that the equilibrium lies toward the tricyclyl radical by about 2.3:1.

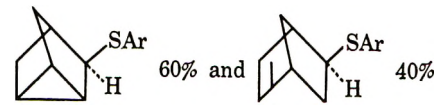
(10) The free-radical addition of arylsulfonyl halides to norbornadiene is described; S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, **26**, 2182 (1961); S. J. Cristol and D. I. Davies, *ibid.*, **29**, 1282 (1964). The amount of tricyclene product was the largest when the halide was chlorine and smallest when it was iodine. This indicates that as the chain-transfer ability of the reagent increases (I > Br > Cl) the intermediate radical corresponding to XVII has a smaller chance to equilibrate ($k_3 \approx k_2 < k_4$) and more and more 2,3-disubstituted products are obtained. The N_2F_4 species has a chain-transfer ability close to chlorine if one compares the product distribution of the norbornadiene reaction with N_2F_4 and arylsulfonyl halides, excluding any differences in steric requirements (see ref 11).

(11) Addition of 1-iodoperfluoropropane to norbornadiene gave a mixture of the nortricyclyl adducts.



The absence of any 2,3-perfluoropropyliodonorbornene is explained by the fact that both iodo and perfluoropropyl groups are bulky and will be very crowded adjacent to each other: N. Brace, *ibid.*, **27**, 3027 (1962).

(12) Thiophenols react with norbornadiene under free-radical conditions to give the following mixture.

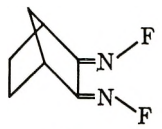


S. J. Cristol and G. D. Brindell, *J. Amer. Chem. Soc.*, **76**, 5699 (1954); S. J. Cristol, G. D. Brindell, and J. A. Reeder, *ibid.*, **80**, 635 (1958).

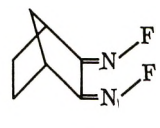
presence of two N–F resonances in the F^{19} nmr spectrum.

The last component to elute contained two isomers. The larger isomer (>90%) was assigned the *endo,exo*-2,3-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (XIII) structure. It showed unsaturation in the infrared, 6.13 μ, and two nonequivalent vinyl protons in the nmr spectrum, τ 3.50. The F^{19} nmr spectrum showed two different kinds of $-NF_2$ groups. The minor component contained a single $-NF_2$ group belonging to a symmetrical structure, presumably the di-*endo*-2,3-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (XIb).

Norbornene gave a normal adduct, 2,3-bis(difluoramino)norbornane (see Tables I and II), as a mixture of three isomers, *cis-exo* (largest), *trans-endo-exo*, and *cis-endo* (smallest). Dehydrofluorination by means of cesium fluoride in acetonitrile gave 2,3-bis(fluorimino)norbornane (XV) as a mixture of two stereoisomers, *anti-anti* (XVa) and *syn-anti* (XVb). The

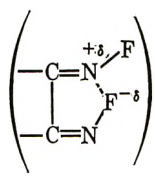


XVa



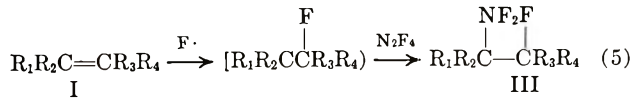
XVb

F^{19} nmr spectrum showed two peaks, one as a quadruplet of AB type, ν_A −6735, ν_B −6570 cps (J_{F-F} = 80 cps), and the other as a singlet at −5720 cps in a 2:1 ratio. The spectrum does not change by raising or lowering the temperature between −30 and 175°, or by changing solvent (neat, benzene, acetone, trifluoroacetic acid). The single nmr peak is assigned to the symmetrical isomer XVa and the quadruplet to the unsymmetrical isomer XVb. The large F–F coupling constant (80 cps) is very surprising since the two atoms are so far apart and coupling through space is usually ~1–10 cps.[3b,3d,13] It is possible that partial bonding between nitrogen and fluorine takes



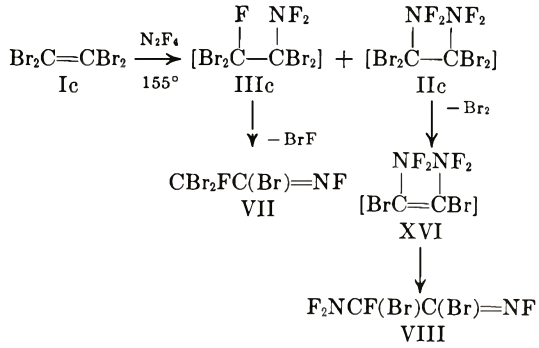
place which brings the two fluorines in close proximity and accounts for the large coupling constant. For comparison, $-NF_2$ groups attached on unsymmetrical carbon atoms give coupling constants around 600 cps (see Table II).[1e,3b,3c,4]

Mechanism.—Normal addition of N_2F_4 to olefins to give 1,2-bis(difluoramino)alkanes proceeds by a free-radical process involving difluoramino radicals ($\cdot NF_2$).[1a,b,e] The "abnormal addition" which occurs at temperatures of 150° or higher with certain olefins may proceed as shown in eq 5. Transient



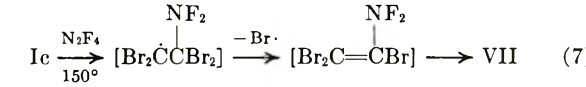
fluorine radicals are reasonable species arising from decomposition of difluoramino radicals at these elevated temperatures.[4] Bumgardner[14] obtained the "abnormal adducts" and substitution products when he irradiated mixtures of N_2F_4 and olefins. He postulated photochemical decomposition of an activated $\cdot NF_2$* to give a fluorine atom followed by addition to the olefin (eq 5).

The case of tetrabromoethylene combines both types of addition, "normal" and "abnormal," and may proceed as shown in eq 6. The intermediate



(6)

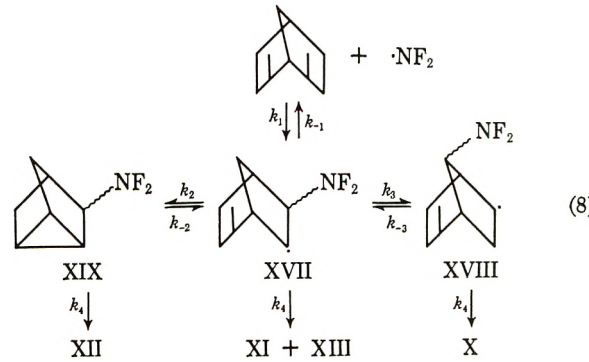
addition products, however, are not stable and in the case of IIIc the elements of BrF are lost to give VII. In the case of IIc, bromine is lost to give the vinyl–NF_2 compound XVI which rearranges to the more stable VIII.[4] Products obtained from 9,10-dibromoanthracene corresponded to the loss of bromine from the intermediate addition product.[3a] One cannot exclude, however, an alternate route in explaining the formation of VII, namely the addition of an NF_2 radical to Ic followed by expulsion of a bromine radical to give a vinyl–NF_2 compound which rearranges to VII (eq 7). A similar pathway was used by Petry,



(7)

et al.,[4] to explain the product obtained from β-bromostyrene and N_2F_4. Presumably VIII could also arise from VII *via* free-radical replacement of bromine by $\cdot NF_2$.[15]

The addition of N_2F_4 to norbornadiene gives results typical of a radical process. The initially formed intermediate XVII can react by chain-transfer reaction to give products XI and XIII or can equilibrate to the isomeric radical intermediates XVIII and XIX which in turn react with N_2F_4 or $\cdot NF_2$ to give products X and XII (eq 8). It appears that the isomerization of



(8)

(13) Long-range coupling constants, $J \sim 7$ cps, have been reported for bicyclo[2.2.1]hexane and bicyclo[2.2.1]heptane derivatives between an *endo* proton and bridge methylene protons: J. Meinwald and A. Lewis, *J. Amer. Chem. Soc.*, **83**, 2769 (1961); J. Meinwald and Y. C. Meinwald, *ibid.*, **85**, 2514 (1963).

(14) For photochemical decomposition of N_2F_4 to give a fluorine atom, see C. L. Bumgardner, *Tetrahedron Lett.*, 3683 (1964).

(15) J. W. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960), describes the ultraviolet light catalyzed reaction of alkyl iodides with N_2F_4 to give difluoraminoalkanes. W. H. Graham and C. O. Parker, *J. Org. Chem.*, **28**, 850 (1963), describe the reaction of trityl bromide with N_2F_4 to give tritydifluoramine.

XVII and the establishment of an equilibrium takes place at a faster rate than the chain-termination process. However, the relative rates of isomerization (k_2, k_{-2}, k_3, k_{-3}) compared with the rates of chain transfer (k_4) are not known. One can speculate, however, that, since the tricyclene XII is the predominant product, the most stable free-radical intermediate is XIX.[10] Similar results to those above were obtained when norbornadiene was treated under free-radical conditions with arylsulfonyl halides,[10] thiophenols,[12] and 1-iodoperfluoropropane.[11] It is difficult to correlate the chain-transfer ability of various species as judged by the ratio of products formed, since steric crowding in the final product is probably also important.[11,12]

Experimental Section[16]

General Procedure.—In Table I the results of the additions of N_2F_4 to olefins are summarized. These reactions were carried out in 80-ml or 240-ml Hastelloy-C-lined shaker tubes behind a barricade. *Caution is essential in handling N_2F_4.* Reactions should be carried out on as small a scale as possible to minimize laboratory handling hazards of the products. Adequate shielding is essential during work-up of the products as explosions may occur.[3a]

The procedure for carrying out the addition reactions was as follows: The olefin and solvent were charged into the shaker tube, and the tube was cooled (−80°) and placed in position behind the barricade. The N_2F_4 was charged into the cold tube by pressure drop from a barricaded cylinder, and the tube was heated with shaking for the required time. The reactions were followed by the pressure drop observed. The tube was cooled to 25°, and volatile products were collected in a cooled, evacuated cylinder, and any residual liquid or solid products were separated and characterized in the usual way. In a typical reaction a mixture of 16 g of 1,1-dichloro-2,2-difluoroethylene (0.12 mol) and 10.8 g of N_2F_4 (0.10 mol) was heated in an 80-ml shaker tube at 90° for 2 hr. A pressure drop from 150 to 0 psi was observed. The liquid product obtained (26 g, ~100% yield) was combined with another run and distilled to give a 65% yield of product, $F_2NCF_2CCl_2NF_2$, bp 79°, $n^{25}D$ 1.3478 (see Table I for further characterization).

1,2,2-Tribromo-1-fluorimino-2-fluoroethane (VII).—A mixture of 34.4 g (0.1 mol) of tetrabromoethylene and 9.4 g (0.09 mol) of N_2F_4 was heated at 155° for 4.5 hr with shaking. The crude product, 36 g, was "titrated" with 1-hexene to remove the bromine formed during the reaction. Gas chromatographic analysis of this product was carried out on a 2-m column of 20% tetrafluoroethylene–propylene telomer oil on firebrick at 102° with a helium carrier gas flow of 40 ml/min and showed the presence of 49% $CFBr_2C(Br)=NF$ (VII) (retention time, 24 min), 9% $CFBr(NF_2)C(Br)=NF$ (VIII) (retention time, 10 min), and 35% 1,2-dibromohexane. Fractionation of the crude product through a 10-in. Podbielniak column gave as a first fraction **1,2-dibromo-1-fluorimino-2-difluoramino-2-fluoroethane (VIII)**, a colorless liquid, bp 78° (175 mm). The infrared spectrum (liquid) showed absorption at 6.30 (C=NF) and 10.40, 10.95, 11.45, and 11.90 μ (N–F). F^{19} nmr showed peaks at −7770 cps (singlet, =NF), an AB type quartet (NF_2, ν_A −5939, ν_B −5661 cps, J_{F-F} = 446 cps), and a peak at +2080 cps (multiple, C–F) in a ratio of 1:2:1.

Anal. Calcd for $C_2Br_2F_4N_2$: N, 9.73. Found: N, 9.71.

The major product of the reaction, 1,2,2-tribromo-1-fluorimino-2-fluoroethane (VII) distilled later as a yellow liquid, bp 87° (71 mm), $n^{25}D$ 1.5167. The infrared spectrum showed bands at 6.35 (C=NF) and at 10.45 and 10.65 μ (N-F), and the F^{19} nmr analysis showed a single broad peak at −7445 cps (C=NF) and a multiple split peak at −564 cps (C–F) in approximate area ratios of 1:1.

Anal. Calcd for $C_2Br_3F_2N$: F, 12.03; N, 4.44; mol wt, 316. Found: F, 11.34; N, 4.28; mol wt, 313 (mass spectrum, Br^{79}).

2,3-Dichloro-2-difluoramino-1,1,1,3,4,4,4-heptafluorobutane (IIIf).—A mixture of 12.0 g (0.05 mol) of 2,3-dichlorohexafluoro-2-butene (Hooker Chemical Co.), 5.1 g (0.05 mol) of N_2F_4, and 1.0 g of cesium fluoride was heated with shaking at 200° for 6 hr to give a total of 10 g of liquid product. Gas chromatographic analysis of this product on a 2-m firebrick column packed with 20% of the ethyl ester of Kel-F acid 8114 (3M Co. trademark) at 50° with a helium carrier gas flow of 60 ml/min showed it to consist of 37% $CF_3C(Cl)NF_2CFClCF_3$ (retention time, 10 min) with the remainder largely starting olefin. In the absence of cesium fluoride the yield dropped to 13%. The adduct was purified by gas chromatography to give a colorless liquid, bp 95° (DTA).

The infrared spectrum showed bands at 11.25 (strong), 11.0, and 11.50 μ (NF), and F^{19} nmr showed a broad NF_2 peak at −5970 cps, two CF_3 peaks at 0 and +550 cps, and a C–F peak at +3200 cps in the correct area ratios.

Anal. Calcd for $C_4Cl_2F_9N$: C, 15.80; N, 4.61; F, 56.26; mol wt, 304. Found: C, 15.76; N, 4.81; F, 55.92; mol wt, 302 (vapor density).

The Reaction of N_2F_4 with 1,1,4,4-Tetrafluorobutadiene.[7]—A mixture of 8 g (0.06 mol) of 1,1,4,4-tetrafluorobutadiene[17] and 5.5 g (0.05 mol) of N_2F_4 was heated with shaking at 38° for 4 hr. The crude liquid product, after removal of unchanged N_2F_4, amounted to 10.9 g. Gas chromatographic separation on a 6-ft. column packed with 20% of the ethyl ester of Kel-F Acid 8114 on firebrick gave **1,2-bis(difluoramino)-1,1,4,4-tetrafluoro-3-butene** (35%) and **1,4-bis(difluoramino-1,1,4,4-tetrafluoro-2-butene** (61%).

Mass spectrometric analyses of the two isomers were quite similar, the largest *m/e* peak was 178 ($C_4F_6H_2N^+$). Infrared analysis of the 1,2 isomer showed major absorption bands at 3.2 (=CH), 3.32 (saturated CH), 5.7 ($F_2C=CH$), 7.5–8.5 region (C–F), 10.55, 10.7 (doublet, N–F), and 11.75 μ. Infrared analysis of the 1,4 isomer showed absorption at 3.2 (=CH), no band for C=C as predicted for the *trans* isomer, 7.5–9.0 (C–F), and 10.1, 10.7 μ (N–F). F^{19} nmr analysis of the isomeric mixture showed two major peaks of approximately the same area ratio, at −4828 (NF_2) and +2052 cps (CF_2).

The Reaction of N_2F_4 with Norbornadiene.—In a 240-ml tube containing 11 g (0.12 mol) of freshly distilled norbornadiene and 20 g of Halocarbon oil (Halocarbon Products Corp., Series 12-21), 13 g (0.125 mol) of N_2F_4 was condensed. The tube was sealed and heated at 50° for 1 hr. The products of three such reactions were combined and distilled to give 30 g (43%) of a mixture of 1:1 adducts as a colorless liquid, bp 60–62° (6.0 mm).

Anal. Calcd for $C_7H_8F_4N_2$: C, 42.86; H, 4.11; F, 38.75; N, 14.28. Found: C, 43.16; H, 4.34; F, 37.91; N, 15.57.

Gas chromatographic analysis on a 1-m column packed with 20% silicone 703 on firebrick at 101° with helium flow of 170 ml/min showed four peaks in approximate area ratio in order of elution of 8:7:76:9. The individual peaks were separated by preparative gas chromatography.

The first eluent (retention time, 6.2 min) was assigned as the 2,7-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (X). The F^{19} nmr spectrum (neat) showed the presence of two different NF_2 groups in 1:1 ratio, one as an AB type quadruplet, ν_A −7257, ν_B −6757 cps, (J_{F-F} = 580 cps), each peak split into doublets (J_{F-H} ~ 30 cps), and the other into a quadruplet centered at −6595 cps (J_{F-H} ~ 30 cps).[13]

Anal. Calcd for $C_7H_8F_4N_2$: F, 38.75; N, 14.28. Found: F, 38.64; N, 14.23.

The second eluent (retention time, 7.7 min) was assigned as the di-*exo*-2,3-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (XIa). The F^{19} nmr spectrum (neat) showed two relatively broad peaks in a 1:1 ratio at −6860 and −6730 cps. These peaks are the "strong" peaks of an AB-type pattern where the weak components were too broad and weak to record their position accurately, indicating that the two $-NF_2$ groups are equivalent.

(16) All melting points were taken on a Fisher-Johns block and are not corrected. Boiling points are not corrected. Infrared spectra were measured on a Perkin-Elmer recording spectrophotometer, Model 21; the listings of infrared bands include those which are relevant to the structural arguments. Fluorine nmr spectra were obtained with a high-resolution spectrometer and associated electromagnet, both manufactured by Varian Associates, operating at 56.4 Mc/sec, approximately 14,000 G. Spectra were calibrated in terms of displacements in cycles per second (cps) from the F^{19} resonance of 1,2-difluoro-1,1,2,2-tetrachloroethane (Freon-112) as an external standard. One should add +3826 cps in order to get frequencies with respect to $CFCl_3$ (Freon-11). Negative frequency displacements are for resonances at lower field than the reference. Proton nmr spectra were determined with a Varian Associates A-60 spectrometer and are calibrated in τ values. Carbon–hydrogen analyses were repeatedly found to be higher (~1%) not because of impurities but because of the combustion difficulties caused by the presence of the difluoramino groups.

(17) J. L. Anderson, R. E. Putnam, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **83**, 382 (1961).

Anal. Calcd for $C_7H_8F_4N_2$: F, 38.75; N, 14.28. Found: F, 38.60; N, 13.93.

The third and most abundant eluent (retention time, 11.5 min) showed in the F^{19} nmr spectrum (neat) three sets of quadruplets (AB type) in a ratio of about 3:1:1 indicating a mixture of two isomers. The large quadruplet, ν_A −7100, ν_B −6395 cps (J_{F-F} = 585 cps), split into doublets, $J_{H-F} \sim 30$ cps, belongs to a symmetrical isomer, assigned as the di-*exo*-3,5-bis(difluoramino)tricyclo[2.2.1.$0^{2,6}$]heptane (XIIa). The other two quadruplets, ν_A −7150, ν_B −6710 cps (J_{F-F} = 585 cps) and ν_A −7130, ν_B −6645 cps (J_{F-F} = 590 cps), both split into doublets $J_{H-F} \sim 30$ cps, belong to an isomer with two different $-NF_2$ groups assigned as the *endo-exo*-3,5-bis(difluoramino)tricyclo-[2.2.1.$0^{2,6}$]heptane (XIIb).

Anal. Calcd for $C_7H_8F_4N_2$: C, 42.86; H, 4.11; F, 38.75; N, 14.28. Found: C, 43.40; H, 4.12; F, 38.44; N, 14.56.

The fourth eluent (retention time, 14.0 min) showed in the F^{19} nmr spectrum (neat) two different NF_2 groups in 1:1 ratio, one as an AB-type quadruplet, ν_A −6935, ν_B −6530 cps (J_{F-F} = 595 cps), split in doublets (J_{F-H} = 30 cps) assigned as *endo-exo*-2,3-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (XIII). In a very small amount (<10%) there appeared another quadruplet, ν_A −7465, ν_B −6715 cps (J_{F-F} = 590 cps), split into doublets (J_{F-H} = 30 cps) belonging to a symmetrical isomer with two identical NF_2 groups, presumably the di-*endo*-2,3-bis(difluoramino)bicyclo[2.2.1]hept-5-ene (XIb).

Anal. Calcd for $C_7H_8F_4N_2$: C, 42.86; H, 4.11; F, 38.75; N, 14.28. Found: C, 43.61; H, 4.13; F, 38.32; N, 14.06.

3,5-Bis(fluorimino)tricyclo[2.2.1.$0^{2,6}$]heptane (XIV).—A mixture of 7.0 g of cesium fluoride, 20 ml of acetonitrile, and 2.0 g of 3,5-bis(difluoramino)tricyclo[2.2.1.$0^{2,6}$]heptane (mixture of XIIa and b) was heated under reflux for 2 hr. The solid was removed by filtration, the excess acetonitrile was evaporated *in vacuo*, and the residue was dissolved in carbon tetrachloride. The carbon tetrachloride solution was filtered to remove insoluble impurities, evaporated to dryness to give a semisolid residue which slowly crystallized, and after two recrystallizations from ethanol had mp 50–53°; infrared maxima (Nujol) 5.94 (C=N), 11.8–12.5 μ (=N—F, and tricyclene); only end absorption in the ultraviolet; and F^{19} nmr (CCl_4) two single peaks at −5110 (large) and −5585 cps (small peak).

Anal. Calcd for $C_7H_6F_2N_2$: N, 17.95; F, 24.34. Found: N, 17.51; F, 24.54.

2,5-Dimethyl-2,5-bis(difluoramino)dihydrofuran (IX).—In an 80-ml tube containing 6.9 g (0.07 mol) of 2,5-dimethylfuran and 11.3 g of benzene was condensed 7.5 g (0.07 mol) of N_2F_4; the tube was sealed, and the mixture heated to 78° for 1 hr. The product was distilled to give 6.0 g (43%) of 2,5-dimethyl-2,5-bis(difluoramino)dihydrofuran as a colorless liquid: bp 43–45° (4 mm); $n^{25}D$ 1.3955; infrared maxima (neat), 3.20 (=CH), 3.32 and 3.4 (CH), 6.20 (C=C), 10.25, 11.00, 11.25, 11.50, and 11.73 μ (NF_2); proton nmr spectrum (neat) in τ values at 3.74 (singlet, =CH) and at 8.3 (triplet, J_{H-F} = 2.5 cps, CH_3); and F^{19} nmr, (neat) a single broad peak at −5234 cps (NF_2).

Anal. Calcd for $C_6H_8F_4N_2O$: C, 36.00; H, 4.03; N, 14.00. Found: C, 36.02; H, 4.48; N, 14.27.

2,3-Bis(fluorimino)norbornane (XV).—A mixture of 10 g of 2,3-bis(difluoramino)norbornane (mixture of isomers), 50 g of powdered cesium fluoride, and 100 ml of acetonitrile were refluxed for 5 hr. The solids were removed by filtration, the solvent was removed *in vacuo*, and the residue was dissolved in ethanol. The solution was treated with decolorizing carbon and filtered, on cooling 6.1 g (77.5% yield) of XV was obtained as white, fluffy crystals, mp 89–90°. The infrared spectrum (KBr) showed peaks at 3.39, 3.47 (C–H), 5.97, 6.05 (C=N), 11.25, 11.55, 12.00, 12.35 μ (=NF), and no absorption was observed in the ultraviolet.

Anal. Calcd for $C_7H_8F_2N_2$: C, 53.16; H, 5.10; F, 24.03; N, 17.71. Found: C, 53.32; H, 5.03; F, 23.81; N, 17.61.

Registry No.—IIa, 1426-41-1; IIb, 16159-09-4; IId, 16159-10-7; IIe, 16159-11-8; IIg, 16063-38-0; IIh, 16203-51-3; IIi (*threo*), 16159-13-0; IIi (*erythro*), 16159-30-1; IIj,16159-14-1; $C_6H_5CF(NF_2)C(Cl)=NF$, 16203-52-4; IIIf, 16159-15-2; VII, 16159-16-3; VIII, 16159-17-4; IX, 16159-18-5; X, 16159-19-6; XIa, 16159-24-3; XIb, 16159-20-9; XIIa, 16203-53-5; XIIb, 16203-54-6; XIII, 16159-21-0; XIV, 16203-55-7; XVa, 16159-22-1; tetrafluorohydrazine, 10036-47-2; XVb, 16159-23-2; norbonene adduct, *cis-exo*, 16159-31-2; norbonene adduct, *cis-endo*, 16159-32-3; norbornene adduct, *trans-endo-exo*, 16159-33-4.

Acknowledgment.—The authors wish to acknowledge the help of the late Mr. Miller Nelson for technical assistance, members of the Physical and Analytical Division for running the gas chromatographs, infrared, nmr, and mass spectral analyses, and Dr. E. M. Atadan of the Explosives Department for generous supplies of N_2F_4.

Chemistry of Tetrafluorohydrazine. V. Synthesis of N-Difluoramino-Substituted Hydrazines

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Ultraviolet irradiation of a mixture of N_2F_4 and hexafluoroazomethane gives the N-difluoramino-substituted hydrazine, $CF_3N(NF_2)NFCF_3$. The corresponding NNF_2 compound is obtained from decafluoroazoethane. These adducts are thermally unstable, and their decomposition to starting materials was studied by infrared spectroscopy.

In reported reactions of N_2F_4 involving its dissociation into NF_2 radicals, olefins gave 1,2-bis(difluoramino)ethanes,[1] acetylenes gave vinyldifluoramines and their rearrangement products,[2] and sulfur- and oxygen-containing compounds led to the corresponding species with the difluoramino group attached to the sulfur and oxygen atoms, respectively.[3] We report here the synthesis of N-difluoramino-substituted hydrazines.

The products were obtained by reaction of N_2F_4 with perfluoroazoalkanes in the presence of ultraviolet light (eq 1).[4] Irradiation of an equimolar mixture of hexafluoroazomethane and N_2F_4 at 25° gave

$$R_fN{=}NR_f + N_2F_4 \longrightarrow R_fN(NF_2)NFR_f \quad (1)$$

Ia, $R_f = CF_3$
b, $R_f = C_2F_5$

Ia in ~50% yield. The product was purified by gas chromatography to give Ia as a colorless gas. Its physical properties are listed in Table I.

TABLE I
PHYSICAL PROPERTIES OF $CF_3N(NF_2)NFCF_3$

Bp, °C	+19° (vapor pressure)
Vapor pressure equation	Log $p_{mm} = -1267/T + 7.19$
Trouton constant	19.9
Heat of vaporization	5797 cal/mol

The F^{19} nmr spectrum of Ia was obtained at −62° (Table II).

The infrared spectrum of Ia was obtained on the vapor in a cell cooled at −46 to −80° (Figure 1b). Principal absorption bands in the N–F region are located at 10.2 and 11.3–11.5 μ with weaker absorptions at 10.8 and 11.8 μ. Figure 1a shows the infrared spectrum obtained after the cell was allowed to warm to 25° (1 hr). The bands at 7.9 and 8.35 μ are characteristic of the C–F stretching bands of hexafluoroazomethane (Figure 2), and the 9.75-μ band is characteristic of SiF_4 arising from decomposition of N_2F_4 in glass. Hence, these infrared data showed the decomposition of Ia to starting material.

TABLE II
F^{19} NMR SPECTRA OF N-DIFLUORAMINO-SUBSTITUTED HYDRAZINES

Compound	F^{19} chemical shift, cps[a-c]
$CF_3N(NF_2)NFCF_3$ (Ia)	−5325 (s, NF_2)
	+840 (s, NF)
	+3650 (d, CF_3)[d]
	+4270 (s, CF_3)
$C_2F_5N(NF_2)NFC_2F_5$ (Ib)	−5390 (m, NF_2)
	+400 (s, NF)
	+4835 (d, m, CF_3)[e]
	+6245 (t, m, CF_2)[f]

[a] All spectra were run neat using an external reference of $CFCl_3$. [b] All the resonances of the fluorine attached to nitrogen are relatively broad peaks, owing to the quadripolar relaxation of the N^{14} nucleus, and fine spin–spin couplings with other fluorines are obscured. [c] Singlets, doublets, triplets, and multiplets are denoted as s, d, t, and m, respectively. [d] The doublet splitting was not well defined. [e] The CF_3 peak was split into a doublet and an additional multiplet; the spectrum was not precisely interpreted; [f] The CF_2 peak was split into a triplet and an additional multiplet. The spectrum was not precisely interpreted.

Mass spectrometric analysis of Ia showed the positive ion fragments expected from a mixture of hexafluoroazomethane (70%) and N_2F_4 (30%), indicating the complete decomposition of Ia in the mass spectrometer.

Similarly, irradiation of a mixture of decafluoroazoethane and N_2F_4 has given the corresponding N-difluoramino-substituted hydrazine (Ib), in 36% yield. This product was also purified by gas chromatography to give Ib as a pale yellow liquid with an estimated boiling point of 77° (vapor pressure data).

The F^{19} nmr spectrum was obtained at −80° (Table II). The relative area ratios of the peaks (2:1:6:4) agree with the assigned structure.

Attempts to obtain the mass spectrum of Ib were not successful, and only cracking patterns attributable to decafluoroazoethane and N_2F_4 were observed.

The infrared spectrum of Ib was determined on the vapor in a cell cooled at −20° (Figure 3). Principal N–F absorption bands were observed at 10.2, 11.0, and 11.7 μ with weaker bands at 10.7 and 11.3 μ. The cell was warmed to 25° and allowed to stand for 30 min. The spectrum (Figure 3) now showed the characteristic C–F stretching bands of decafluoroazoethane (Figure 4) with additional bands attributable to SiF_4 (9.75 μ) and NO_2 (6.2 μ). The spectrum was unchanged after an additional 16 hr at 25°.

(1) R. C. Petry and J. P. Freeman, Abstracts of the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 46s; A. J. Dijkstra, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc., A*, 582 (1966); 105 (1967); H. Cerfontain, *ibid.*, 6602 (1965); T. E. Stevens and W. H. Graham, *J. Amer. Chem. Soc.*, **89**, 182 (1967); F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967); G. N. Sausen and A. L. Logothetis, *ibid.*, **33**, 2330 (1968); T. S. Cantrell, *ibid.*, **32**, 911 (1967); T. E. Stevens, *ibid.*, **32**, 670 (1967); S. K. Brauman and M. E. Hill, *J. Amer. Chem. Soc.*, **89**, 2127, 2131 (1967). For leading references to pertinent work, see papers I and II in this series, A. L. Logothetis, *J. Org. Chem.*, **31**, 3686 (1966); A. L. Logothetis and G. N. Sausen, *ibid.*, **31**, 3689 (1966).

(2) G. N. Sausen and A. L. Logothetis, *ibid.*, **32**, 2261 (1967); R. C. Petry, C. O. Parker, F. A. Johnson, T. E. Stevens, and J. P. Freeman, *ibid.*, **32**, 1534 (1967).

(3) For leading references to the synthesis and characterization of these compounds see paper III in this series, G. N. Sausen and A. L. Logothetis, *ibid.*, **32**, 2261 (1967).

(4) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961), describe the reaction of N_2F_4 with azoisobutane to give *t*-butyldifluoramine.

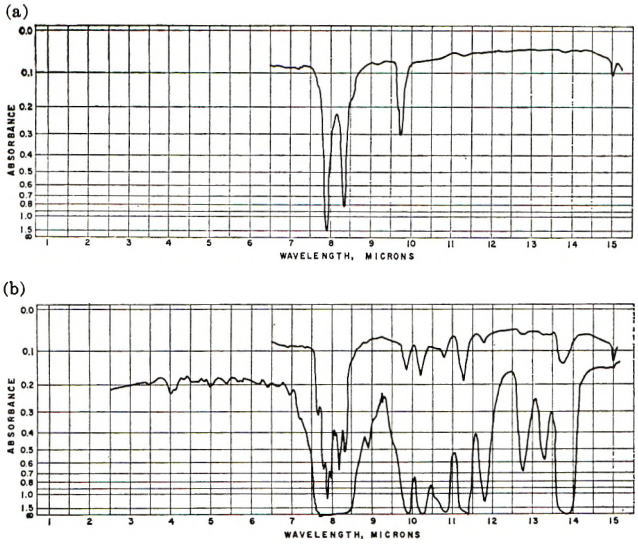

Figure 1.—Infrared spectrum of $CF_3N(NF_2)NFCF_3$: (a) 25°; (b) −46 to −80°.

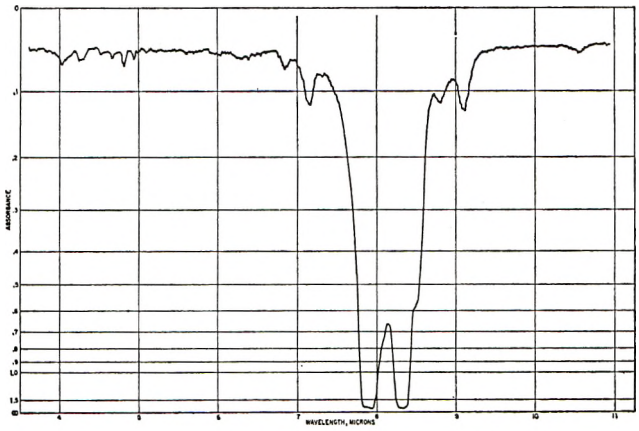

Figure 2.—Infrared spectrum of $CF_3N{=}NCF_3$.

Discussion

The mechanism of this difluoramination reaction undoubtedly involves photolytic decomposition of N_2F_4 *via* an excited difluoramino radical[5] to give a fluorine radical which subsequently adds to the azo bond (eq 2–4). No products corresponding to the

$$\cdot NF_2 \xrightarrow{h\nu} \cdot NF_2^* \rightarrow \cdot F + [NF] \quad (2)$$

$$R_fN{=}NR_f + F\cdot \longrightarrow R_fNFNR_f \quad (3)$$

$$R_fNFNR_f + N_2F_4 \longrightarrow I + \cdot NF_2 \quad (4)$$

direct addition of N_2F_4 to the azo group have been observed.

Thermal cleavage of the reaction products would lead to starting materials as observed in both mass spectrometric and infrared analyses of the products.

$$R_fN(NF_2)NFR_f \longrightarrow R_fNNFR_f + \cdot NF_2 \quad (5)$$
$$\downarrow -F \qquad \downarrow$$
$$R_fN{=}NR_f \quad 0.5N_2F_4$$

(5) This mechanism was proposed by C. L. Bumgardner, *Tetrahedron Lett.*, 3683 (1964), to explain the reaction products obtained from irradiation of 2-butene and 2-butyne with N_2F_4. The same mechanism was used to explain the formation of FSO_2NF_2 from SO_2 and N_2F_4 [C. L. Bumgardner and M. Lustig, *Inorg. Chem.*, **2**, 662 (1963), and FSO_3NF_2 from SO_3 (M. Lustig, C. L. Bumgardner, and J. K. Ruff, *ibid.*, **3**, 917 (1964)]. See also, A. L. Logothetis, G. N. Sausen, and R. J. Shozda, *ibid.*, **2**, 173 (1963), for the formation of SF_4NF_2 from the photochemical reaction of SF_4 with N_2F_4, and G. W. Fraser and J. M. Shreeve, *ibid.*, **4**, 1497 (1965), for the preparation of $F_2NC(=O)F$ by irradiation of CO and N_2F_4.

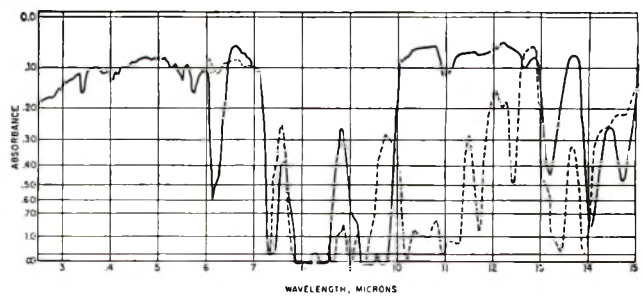

Figure 3.—Infrared spectrum of $C_2F_5N(NF_2)NFC_2F_5$: ----, −20°; ——, 25°.

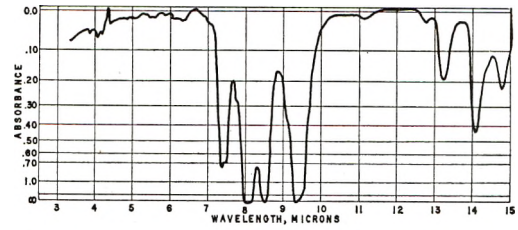

Figure 4.—Infrared spectrum of $C_2F_5N{=}NC_2F_5$.

An approximately 2:1 ratio of azo compound to N_2F_4 would be expected, and this agrees with the mass spectrometric results obtained on Ia.

The bond energy of the F_2N–N bond in I and hence its thermal stability might be expected to be low in light of the low bond dissociation energy of the N–N bond in N_2F_4 (19.8 kcal/mol)[6] and nitrosodifluoramine (10 kcal/mol).[7]

Experimental Section[8]

General Procedure.—*Caution must be exercised in the handling of N_2F_4.*[2] Irradiations were carried out behind a shield. *Remote operation during N_2F_4 reaction is imperative, and adequate shielding is essential* for work-up of the products.

2-Difluoramino-3-fluoro-2,3-diazahexafluorobutane (Ia).—A 150-ml quartz reactor was evacuated, charged with 0.47 g (2.8 mmol) of hexafluoroazomethane[9,10] and 0.30 g (2.9 mmol) of N_2F_4, and irradiated at 25° for 1.25 hr. The product gases were transferred to a cylinder cooled at −196°. Two such runs were combined, and volatile products were removed by applying vacuum at −95° (1–2 mm). The residue, 1.0 g, analyzed by gas chromatography[8] on a 6-ft column at 0°, was found to consist of 67% Ia (gc elution time, 3.0 min; 50% yield),[11] 22% unchanged hexafluoroazomethane, and small amounts of NF_3 and N_2F_4. The volatile fraction consisted mainly of *cis*- and *trans*-N_2F_2, NF_3, and N_2O, with *smaller amounts* of nitrogen, unchanged N_2F_4, $CF_3N{=}NCF_3$, and Ia. The product was further purified

(6) C. B. Colburn, *Endeavour*, **24**, 138 (1965).

(7) F. A. Johnson and C. B. Colburn, *Inorg. Chem.*, 2, 24 (1963).

(8) Infrared spectra were measured on a Perkin-Elmer recording spectrophotometer, Model 21 and Infracord Model 135. Fluorine nmr spectra were obtained with a high-resolution spectrometer and associated electromagnet (Varian Associates) operating at 56.4 Mc/sec and approximately 14,000 G. Spectra were calibrated in terms of displacements in cycles per second (cps) from the F^{19} resonance of $CFCl_3$. Negative frequency displacements are for resonances at lower field than the reference. The irradiations were carried out with a low-pressure mercury resonance lamp connected to a 60-ma, 6000-V transformer emitting mostly at 2537 Å. The gas chromatographic analyses were carried out on a 0.25-in. column, packed with 20% ethyl ester of perhalooctanoic acid (Kel-F Acid 8114, 3M Co. trademark) on firebrick. Helium carrier gas flow was 60 ml/min.

(9) W. J. Chambers, C. W. Tullock, and D. D. Coffman, *J. Amer. Chem. Soc.*, **84**, 2337 (1962).

(10) J. A. Young and R. D. Dresdner, *J. Org. Chem.*, **28**, 833 (1963), described the thermal decomposition of perfluoroazoalkanes at 350–500° in the presence of N_2F_4 to give N,N-difluoramines.

(11) G. N. Sausen, U. S. Patent 3,149,165 (1964).

by gas chromatography to give Ia as a colorless gas, which was conveniently stored in glass at −78°.

3-Difluoramino-4-fluoro-3,4-diazadecafluorohexane (Ib).—A 400-ml quartz reactor was charged with 1.63 g (6.1 mmol) of decafluoroazoethane[9] and 0.74 g (7.1 mmol) of N_2F_4, and the tube was irradiated at 25° for 1.0 hr. The reaction tube was cooled at −80°, and the volatile products were removed by applying vacuum (1–2 mm). The residual yellow liquid, analyzed by gas chromatography[8] on a 6-ft column at 25°, was found to consist of 61% unchanged decafluoroazoethane (gc retention time, 1.4 min) and 36% Ib (gc retention time, 5.2 min). The product was purified by gas chromatography on the same column to give Ib as a pale yellow liquid. The product could be stored indefinitely at −78°.

Registry No.—Ia, 1840-66-0; Ib, 3829-29-6; $CF_3N{=}NCF_3$, 372-63-4; $C_2F_5N{=}C_2H_5$, 756-00-3; tetrafluorohydrazine, 10036-47-2.

Acknowledgment.—The author is indebted to members of the Physical and Analytical Division for gas chromatography, infrared, mass spectral, and nmr analyses.

Free-Radical 1:5 Rearrangement of the Trichloromethyl Group[1,2]

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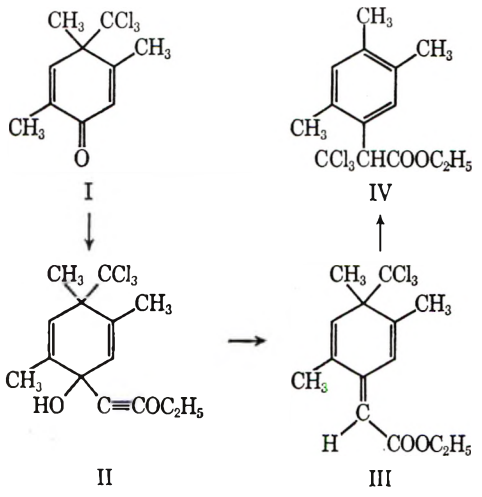
(+)-4-Trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienone (I) produces (+)-1-ethoxyethynyl-4-trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienol (II) on treatment with ethoxyethynylmagnesium bromide followed by water. Treatment of (+)-II with acid yields (−)-ethyl 4-trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienylideneacetate (III). On pyrolysis or photolysis of active III inactive ethyl α-(2,4,5-trimethylphenyl)-β,β,β-trichloropropionate (IV) is formed. Reaction of active I with ethylmagnesium bromide followed by treatment of the product with dilute acid and then heating affords inactive 2,4,5-trimethyl-β,β,β-trichloroisopropylbenzene (VIII). The free-radical nature of these rearrangements is demonstrated and discussed. Resolution of I was accomplished by reaction with active α-(isopropylidenaminooxy)propionic acid (V).

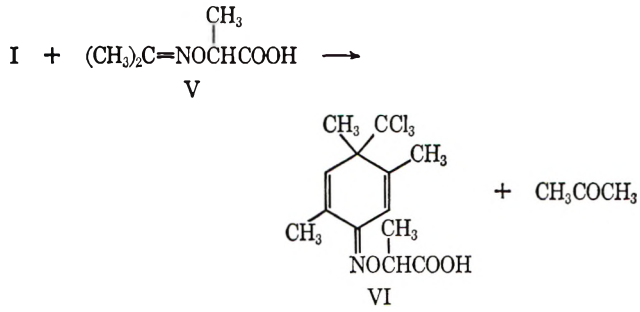
In earlier studies on the behavior of trichloromethyl groups in 4-methyl-4-trichloromethyl-2,5-cyclohexadienones, 1,5 migrations had been observed in several cases.[3] The work herein reported was initiated with the intent to find out more about the mechanism involved in the transformation of 4-trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienone (I)[4] to ethyl α-(2,4,5-trimethylphenyl)-β,β,β-trichloropropionate (IV) *via* the expected intermediate compounds, II and III (Scheme I).

SCHEME I



Since I and IV each had an asymmetric carbon (but different ones), the use of optically active I was deemed of interest. Accordingly I was resolved by reaction with active α-isopropylidenaminooxypropionic acid (V)[5] to yield a mixture of isomers of VI which was separated by fractional recrystallization. On heating with levulinic acid,[6] the pure isomer of VI was converted into active I. Thus the reagent, V, may prove of value for the resolution of other ketones (Scheme II).

SCHEME II



On treatment of active I with ethoxyethynylmagnesium bromide and work-up of the reaction mixture[3c] racemic IV was obtained. Since it was expected that active IV would be obtained, further study of the rearrangement was undertaken. By careful treatment of a similar reaction mixture with cold water, II was obtained in optically active form when active I was used. Because of experimental difficulties in handling II, no pure isomer was obtained. Hence, it is not known if a single diastereoisomer of II was present or not.[7]

On treatment with acid under mild conditions II could be transformed into III which was also active. However, on warming III to about 85° in cyclohexane

(1) This work formed part of the Ph.D. thesis (1967) of R. Layton who was the recipient of a National Institutes of Health Predoctoral Fellowship, 1966–1967. Kinetic data are listed in the thesis.

(2) Supported in part by a grant from the National Science Foundation.

(3) (a) K. von Auwers and W. Jülicher, *Chem. Ber.*, **55**, 2167 (1922); (b) M. S. Newman and R. L. Tse, *J. Org. Chem.*, **21**, 638 (1956); (c) M. S. Newman and J. A. Eberwein, *ibid.*, **29**, 2516 (1964).

(4) M. S. Newman, D. Pawellek, and S. Ramachandran, *J. Amer. Chem. Soc.*, **84**, 995 (1962).

(5) M. S. Newman and W. B. Lutz, *ibid.*, **78**, 2469 (1956).

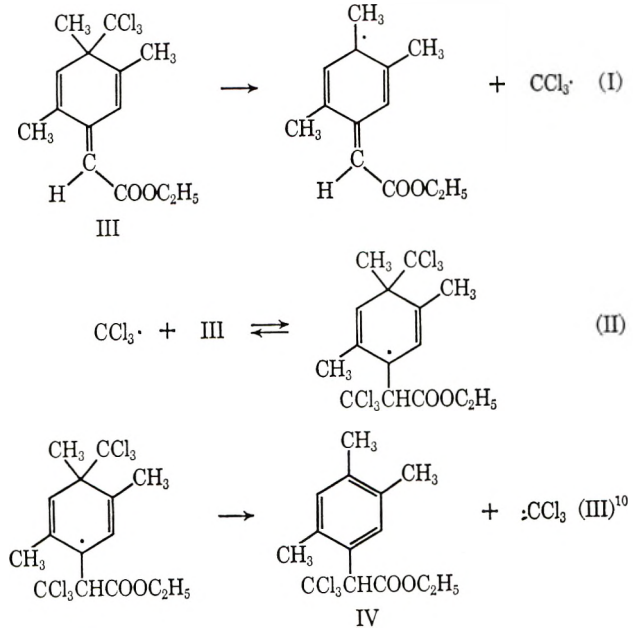
(6) C. H. DePuy and B. W. Ponder, *ibid.*, **81**, 4629 (1959).

(7) M. S. Newman, J. Eberwein, and L. L. Wood, Jr., *ibid.*, **81**, 6454 (1959), showed that only one isomer was formed on treatment of 4-methyl-4-trichloromethyl-2,5-cyclohexadienone with phenylmagnesium bromide.

or on exposure to light III rapidly rearranged to IV which was racemic.

To obtain more information about the rearrangement of III to IV, a study of the rate was undertaken. By measurement of the optical activity, the rate of the thermal rearrangement was shown to be first order with respect to III. As there was an induction period, a free-radical mechanism was suspected. This was confirmed by showing that the rearrangement at 85° could be stopped by the addition of free-radical trapping agents, such as iodine, benzoquinone, and thiophenol; and a nitrogen-purged solution of III in cyclohexane containing a small amount of α,α-diphenyl-β-picrylhydrazyl[8] was slowly decolorized on standing at room temperature. When inactive III in freshly distilled thiophenol was heated at 120 ± 5° and irradiated with 350-W unfrosted light, analysis showed that most of the III remained after 40 hr. Since ethyl 2,4,5-trimethylphenylacetate (VII) was produced in an amount approximately equivalent to the III destroyed, evidence in support of a radical produced by loss of a trichloromethyl group from III was at hand. A sample of authentic VII was prepared from authentic 2,4,5-trimethylbenzyl chloride[9] by conventional procedures.

The above results are in accordance with the reaction scheme indicated by eq III.

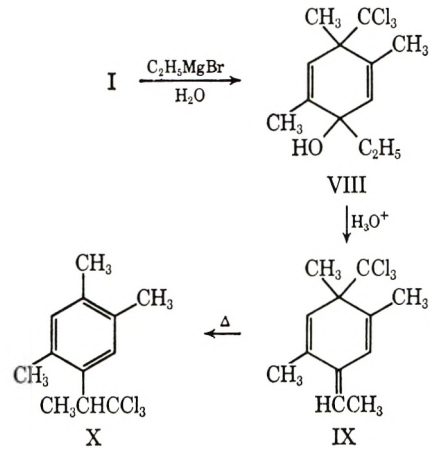


In order that the rate be first order with respect to III, one must assume a chain-terminating reaction between a trichloromethyl radical and III (see Experimental Section for the kinetic analysis). Because of the long-chain length it was not possible to isolate any product resulting from such a chain-terminating step.

Since IV is racemic, one must assume that the attack of the CCl_3 radical in eq II takes place with equal ease from either face of the plane. Models show that the trichloromethyl group in III does not interfere with approach of a CCl_3 radical from the same side. We assume that the stereochemistry of the unsaturated ester group in III is as shown because of steric factors. Although the ester II is so unstable that complete purification could not be accomplished, the nmr spectrum and thin layer chromatography of the sample used for kinetic study (see Experimental Section) indicated that III has the structure shown and was quite pure. Since III is optically active when optically active I is used as starting material, it is assumed that there is no partial racemization during the steps leading to the formation of III as there is no reason to believe in a change in stereochemistry at the 4 position in any of the steps pictured.

To rule out the argument that IV is formed in an optically active state and is racemized by enolization at a later stage, active I was treated with ethylmagnesium bromide (Scheme III). By suitable treatment the product was converted into 1,1,1-trichloro-2(2,4,5-trimethylphenyl)propane (X). As the latter was also inactive, racemization of IV by enolization seems unlikely since X would not be able to be racemized by an enolization step.

Scheme III



It had been hoped that the free acid corresponding to IV could be resolved, esterified to form active IV, and submitted to the rearrangement conditions in order to see if active IV would remain active. However, some attempts to prepare the acid failed. Hydrolysis did not occur under acidic conditions and under alkaline conditions loss of hydrogen chloride occurred along with hydrolysis.

When a solution of active III in benzene was exposed to a long-wavelength uv lamp, rearrangement to inactive IV took place. Thus the photochemical reaction occurs with racemization also. The rearrangement was zero order with respect to III. When samples of impure III were left in flasks exposed to the usual laboratory light, rearrangement slowly took place. Hence, the experiments leading to the isolation of pure III had to be done with protection from light.

Further experiments designed to elucidate the stereochemistry of certain 1,3 migrations of CCl_3 groups[11] are under study here as these may prove to be stereospecific because of increased steric factors.

(8) S. Goldschmidt and K. Renn, *Chem. Ber.*, **55**, 628 (1922).

(9) We are grateful to Lauren Dauernheim who supplied us with this material prepared by chloromethylation of 1,2,4-trimethylbenzene.

(10) Equations II and III may be substituted by one equation in which the trichloromethyl radical attacks compound III with simultaneous expulsion of a trichloromethyl radical. The rate would still be first order in compound III were this the case.

(11) M. S. Newman and F. Bayerlein, *J. Org. Chem.*, **28**, 2804 (1963).

Experimental Section[12]

Resolution of 4-Trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienone (I).—A slow current of pure nitrogen was passed through a refluxing solution of 63.4 g of I,[4] 36.3 g of V,[5] $[\alpha]^{20}D$ +31.5 ± 0.2° (*c* 8.75, H_2O), and 12 g of *p*-toluenesulfonic acid in 275 ml of 92% acetic acid for 6 hr, when a test with 2,4-DNPH solution[13] showed that acetone was no longer being evolved. The black solution was poured on ice and the organic acidic fraction isolated in the usual way. The residue was taken up in 350 ml of petroleum ether (bp 30–60°). After standing overnight 44 g of tacky crystals remained after decantation of the mother liquor. After decolorization with charcoal in ether, the product was crystallized from benzene–hexane to yield 12.8 g (15%) of colorless needles of α-(4-trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienylidenaminooxy)propionic acid (VI): mp 155.0–156.5°; $[\alpha]^{20}D$ −160 ± 1° (*c* 9.56, benzene). Three further recrystallizations from benzene–hexane changed neither the melting point nor the rotation.

Anal. Calcd for $C_{13}H_{16}Cl_3NO_3$: C, 45.8; H, 4.7; N, 4.1. Found: C, 45.9; H, 4.7; N, 4.0.

When the above preparation was repeated using (−)-V, $[\alpha]^{20}D$ −30 ± 0.2° (*c* 10, H_2O), the product was VI: mp 152.0–153.5°; $[\alpha]^{22}D$ +154 ± 1° (*c* 4.25, benzene). This was used directly for the preparation of (−)-I (see below).

A solution of 12.0 g of the above (−)-VI in 400 ml of 9:1 levulinic acid–1 *N* hydrochloric acid[6] was refluxed for 12 hr. The black solution was poured on ice and the organic product isolated as usual and distilled to yield 8.1 g (90%) of a pale yellow oil, bp 110–112° (2 mm), which soon crystallized. Recrystallization from hexane afforded colorless I, mp 57.5–59.0°, $[\alpha]^{25}D$ +26.4 ± 0.2° (*c* 8.11, benzene), with little loss. The same procedure applied to (+)-VI (see above) yielded I, mp 55.5–57.5°, $[\alpha]^{20}D$ −25.5 ± 0.2° (*c* 8.00, benzene), in high yield.

1-Ethoxyethynyl-4-trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienol (II).—To 57.9 ml of a 0.51 *M* magnetically stirred solution of ethylmagnesium bromide (0.0295 mol) in anhydrous ether was added 2.27 g (0.0325 mol) of freshly distilled ethoxyacetylene.[14] Light brown insoluble ethoxyethynylmagnesium bromide settled out. After refluxing for 20 min, a solution of 5.0 g (0.0197 mol) of inactive I in 50 ml of anhydrous ether was added over a period of 5 min. After stirring 20 min the homogeneous solution was cooled in an ice–salt mixture and decomposed with ice-cold water. The organic phase was separated and dried over anhydrous sodium carbonate, and the solvent was evaporated under reduced pressure in the cold. An ethereal solution of the brownish residue was decolorized with activated charcoal. After removal of the ether 6.3 g of a colorless oil was obtained. This was undoubtedly almost pure II as it absorbed at 2.82 (3546 cm^{-1}, m, OH) and 4.36 μ (2294 cm^{-1}, s, C≡C). There was no absorption in the carbonyl region but, on standing, carbonyl bands began to appear at the expense of the above bands.

Similar results were obtained when (+)-I was used. In a typical run (+)-I, $[\alpha]^{25}D$ +26.4, yielded II, $[\alpha]^{25}D$ +36.1 ± 1° (*c* 1.5, benzene, assuming the entire product to be II). Because of the instability of II no analytical sample was obtained, but the ir spectral determinations in this and other runs show that no I remained and, hence, essentially pure dienols (II) were present.

Ethyl 4-Trichloromethyl-2,4,5-trimethyl-2,5-cyclohexadienylideneacetate (III).—In carrying out all experiments from this point on as much work as convenient was done in the absence of light since III is light sensitive.

In a typical experiment a solution at 0° of 6.0 g of the isomers of II in 75 ml of 1:1 ether–benzene was shaken with 75 ml of iced 3 *N* hydrochloric acid, followed by a wash with 5% sodium bicarbonate. After the usual work-up an almost quantitative yield of colorless liquid which proved to be essentially pure III was obtained. No analysis was obtained for this oil, or similar oils from other reactions, as it was sensitive to heat and light. It is dangerous to keep any amount of this oil neat as when rearrangement occurs the heat rapidly builds up. Solutions of III in hydrocarbon solvents were stored below 0° for several weeks in the dark without appreciable change. The above oil (III) had no ir bands at 2.82 or 4.36 μ and did have a single carbonyl band at 5.83 μ (1715 cm^{-1}, s). The ultraviolet spectrum, λ_{max} at 292 mμ (ε 21,400) in 95% ethanol, may be compared with that of diethyl 3-carbethoxymethyl-2-cyclohexenylideneacetate,[15] λ_{max} 298 mμ (ε 21,000), as close a model compound as we could find.

The nmr spectrum of III has three singlets at τ 2.22, 3.87, and 4.37 (1 H each). We assign the 2.22 peak to the hydrogen in the 6 position of III as this would be expected to be deshielded by the carbethoxy group.[16] If this assumption is correct, the stereochemistry of the carboethoxy group as shown in III is correct. The remaining features of the nmr spectrum were as expected and confirm the structure of III. Thin layer chromatography of III on alumina using 10% ethyl acetate in benzene as developer showed that the III (R_f 0.64) prepared as described above was essentially pure as there was only a small second spot (R_f 0.68) which was undoubtedly IV since IV had the same R_f value (0.68). Similar results were obtained when (+)- and (−)-I were used as starting materials. From (+)-I (see above) there was obtained III, $[\alpha]^{20}D$ −42.0 ± 0.2° (*c* 10.4, benzene).

When the II prepared from (+)-I was converted into III as above described for inactive I, (−)-III, $[\alpha]^{20}D$ −42.0 ± 0.2° (*c* 10.4, benzene, assuming the entire product to be III), was obtained.

Ethyl α-(2,4,5-Trimethylphenyl)-β,β,β-trichloropropionate (IV).—Pure IV[3c] was obtained in every experiment starting from active or inactive I, II, or III. In all cases the product (IV) was optically inactive when measured at the sodium d line and the mercury green line. One feature of the nmr spectrum of IV is of interest. There is an octet (2 H) centered at τ 5.91. These peaks are due to the fact that the methylene hydrogens, normally a quartet (as in III), are nonequivalent because of a nonadjacent asymmetric center.[17]

Photochemical Rearrangement of III.—When 5 ml of a 10% solution of (+)-III, $[\alpha]^{19}D$ +41.2 ± 0.2° (*c* 10, benzene), in cyclohexane in a Pyrex flask was placed in direct sunlight for 6 hr there remained no optical activity at 5893 and 4960 Å. The product was essentially pure IV.

The rate of the photochemical rearrangement was studied as follows. A 3% solution of III, $[\alpha]^{20}D$ −42.0 ± 0.2° (*c* 10.4, benzene), in benzene was placed in a 1-dm Pyrex polarimeter tube and was allowed to stand in the dark at 20° for 3 hr. No change in rotation had occurred in this time. Beside the polarimeter tube was mounted a small long-wavelength uv source[18] so that readings could be taken without disturbing the photolysis. After an induction period of about 25 min after the uv light was turned on the rotation began to change. The data are listed in Table I. The observed rotation (assumed to be proportional to concentration in the range in question) was plotted against time to give a line which had a slope of about -3.5×10^{-3} deg min^{-1}. The zero-order rate constant, k_0, was calculated from eq 1 to be 2.6×10^{-4} mol $l.^{-1}$ min^{-1}.

$$k_0 = -\frac{d[III]}{dt} = \frac{-C}{[\alpha]l}\frac{\Delta\alpha\ (obsd)}{\Delta t} = \frac{-C\ (slope)}{[\alpha]l} \qquad (1)$$

(l = tube length in decimeters $[\alpha]$ = specific rotation, and C = conversion factor to change concentration units from grams per milliliter to moles per liter)

(12) Melting points of all samples were taken with a Thomas–Hoover 6406-M capillary melting point apparatus. The thermometer was corrected by comparison with the melting range of standards. Boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. Infrared absorptions are described as strong (s), medium (m) and weak (w). Ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer, using 1-cm matched cells. Nuclear magnetic resonance (nmr) spectra were determined relative to tetramethylsilane at 60 Mc with the Varian Associates high-resolution spectrophotometer, purchased in part with funds from the National Science Foundation. Carbon tetrachloride solutions were used, unless noted otherwise. An Aerograph Hy-Fi Model 600-C gas chromatograph was used for gas–liquid partition chromatographic analysis. The phrase "worked up in the usual manner" refers with minor variations to the handling of organic solutions in the following manner. The organic solution was washed successively with water and saturated sodium chloride solution and dried by filtering through a bed of anhydrous magnesium sulfate, and the solvent was removed *in vacuo*.

(13) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 111.

(14) Obtained from Chemical Samples Co., Columbus, Ohio.

(15) M. W. Cronyn and J. E. Goodrich, *J. Amer. Chem. Soc.*, **74**, 3331 (1952).

(16) L. M. Jackman, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 121.

(17) This phenomenon has been observed before, *e.g.*, J. J. Looker, *J. Org. Chem.*, **31**, 2973 (1966), and ref 8–10 therein.

(18) "Mineralight" Model SL 3660 (filter removed), Ultra-Violet Products, Inc., Pasadena, Calif.

Table I

Photochemical Rearrangement of (−)-III to IV
($k_0 = 2.55 \times 10^{-4}$ mol l.$^{-1}$ min^{-1})

Time, min[a]	$-\alpha$ (obsd)
0	1.20 ± 0.03
45	1.00
105	0.86
165	0.60
225	0.45

[a] The relative time was adjusted to compensate for an indefinite induction period.

Thermal Rearrangement of III.—Two 10% solutions of III, $[\alpha]^{19}D$ +41.2 ± 0.2° (c 10.0, benzene), in cyclohexane and benzene, respectively, were sealed into ampoules and heated in an oil bath at 95° in darkness for 1 hr. Neither solution showed any optical activity at 5893 or 4960 Å. When similar solutions were sealed and no heating was done, the rotation was essentially unchanged after 24 hr. In a similar reaction in cyclohexane in which heating was at 100° for 30 min the reaction mixture was examined by glpc with a 5 ft × 0.125 in. 5% SE-30 silicone on 60–80 mesh Chromosorb W[19] column. In addition to the solvent there was only one main product, IV: retention time, 14.3 min at 165°. There was no peak corresponding to ethyl 2,4,5-trimethylphenylacetate (VII) or hexachloroethane, but there was a small peak for chloroform.

A 10% solution of inactive III in cyclohexane was divided into three 4-ml portions in three vials covered with aluminum foil. To one was added about 3% of iodine, to another 3% of benzoquinone. The three tightly stoppered vials were heated in an oil bath at 90–95°, and aliquots were withdrawn from time to time. The pure sample was almost completely rearranged to IV in 75 min as judged by ir analysis. The other two samples showed no change from III.

A solution of 3.5 g of III in 35 ml of freshly distilled thiophenol was heated at 115–125° and irradiated with a 350-W unfrosted light. After 40 hr the reaction solution was dissolved in ether–benzene (1:1), washed with sufficient 10% sodium hydroxide to remove all of the thiophenol, and then worked up in the usual manner. The infrared spectrum of the residue indicated that a large fraction of III was still present. The residue in methylene chloride was analyzed by gas–liquid partition chromatography with a 5 ft × 0.125 in. 5% SE-30 silicone oil on Chromosorb W, analytical column at 165°. A large peak (retention time, 14.3 min) appeared which was doubtlessly the regular rearrangement product IV produced by the rearrangement of III on the chromatography column. One other major peak appeared (retention time, 3.7 min). When authentic ethyl 2,4,5-trimethylphenylacetate (VII) which had a retention time of 3.7 min was added to the solution being analyzed, the peak increased in intensity and remained symmetrical. The areas[20] under the respective peaks indicated a 7:3 ratio of IV to VII.

A magnetically stirred portion of the residue in a small sublimation apparatus at 0.2-mm pressure was heated in an oil bath at 85–90°. The small fractions that slowly condensed on the cold finger were examined by infrared analysis. Heating was interrupted while the cold finger was removed, and the cold finger was rinsed with acetone before the collection of another fraction. The infrared spectrum of the first two fractions were identical with that of VII.

The rate of the thermal rearrangement was measured in a 2-dm jacketed polarimeter tube at 85°. A 7% solution of III, $[\alpha]^{20}D$ −42.0 ± 0.2° (c 10.4, benzene), in purified *n*-decane[21] was introduced into the tube which was fitted by a rubber stopper through which a syringe needle was inserted in order to prevent compression. The needle was withdrawn after about 20 min when thermal equilibrium was established. There was an induction period of about 30 min during which the rotation did not change. The data for change in rotation with time were plotted in Figure 1 to give a straight line which had a slope of −5.40 × 10^{-3} min^{-1}. The first-order rate constant, k_1, was calculated from eq 2 above to be 1.24×10^{-2} min^{-1}.

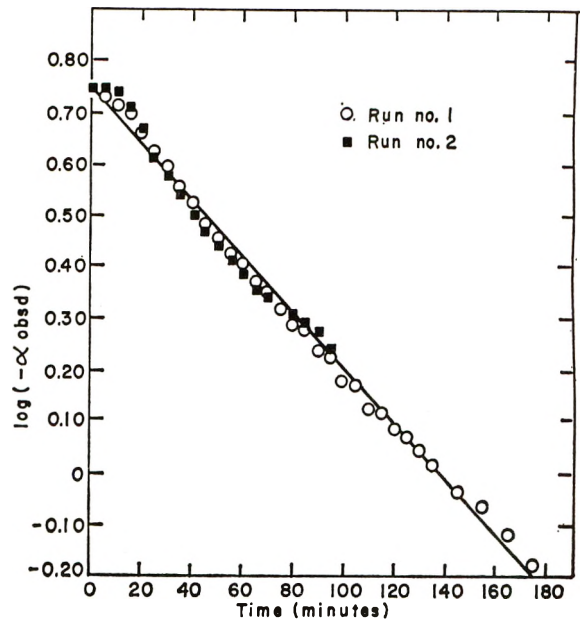


Figure 1.—A plot of log ($-\alpha_{obsd}$) *vs.* time for the thermal rearrangement of (−)-III to IV at 85°.

$$\log \alpha \text{ (obsd)} = \frac{-k_1 t}{2.30} + \text{constant} \qquad (2)$$

First-order kinetics for the thermal rearrangement of III to IV can be explained by assuming a termination reaction for CCl_3 radicals which involves III. This termination reaction could be an abstraction, abnormal addition, or disproportionation. The kinetic consequences of this type of termination reaction are derived below. The proposed chain mechanism can be represented by eq i–iii.

initiation

$$\text{III} \xrightarrow{k_1} \cdot CCl_3 + R\cdot \qquad \text{(i)}$$

propagation

$$\text{III} + \cdot CCl_3 \underset{k_3}{\overset{k_2}{\rightleftharpoons}} (\text{III-}CCl_3)\cdot \xrightarrow{k_4} \text{IV} + \cdot CCl_3 \qquad \text{(ii)}$$

termination

$$\text{III} + \cdot CCl_3 \xrightarrow{k_5} \text{unreactive radical (+ other possible reactions)} \qquad \text{(iii)}$$

Assuming the steady-state condition for the formation of $\cdot CCl_3$ and $(\text{III-}CCl_3)\cdot$ then

$$0 = k_1[\text{III}] - k_2[\text{III}][\cdot CCl_3] + k_3[(\text{III-}CCl_3)\cdot] + k_4(\text{III-}CCl_3)\cdot] - k_5[\text{III}][\cdot CCl_3]$$

$$0 = k_2[\text{III}][\cdot CCl_3] - k_3[(\text{III-}CCl_3)\cdot] - k_4[(\text{III-}CCl_3)\cdot]$$

The sum of the last two equations is

$$k_1[\text{III}] = k_5[\text{III}][\cdot CCl_3]$$

so

$$[\cdot CCl_3] = k_1/k_5$$

Assuming long chains

$$\frac{-d[\text{III}]}{dt} = k_4[(\text{III-}CCl_3)\cdot] = \frac{k_4 k_2}{k_3}[\text{III}][\cdot CCl_3]$$

therefore

$$\frac{-d[\text{III}]}{dt} = \frac{k_1 k_2 k_4}{k_3 k_5}[\text{III}]$$

Ethyl 2,4,5-Trimethylphenylacetate (VII).—A mixture of 10.0 g of 2,4,5-trimethylbenzyl chloride[9] and 21.5 g of powdered cuprous cyanide was heated at 145–150° for 30 min.[22] The cooled mixture was triturated with benzene. After removal of

(19) A Johns-Manville Products Corp. crushed firebrick product.

(20) The areas were estimated by taking the product of the height and the half-height width, assuming the peaks to be perfect triangles.

(21) *n*-Decane was purified by stirring with concentrated H_2SO_4 for 2 days followed by distillation over CaH_2.

(22) A. Modification of the procedure of S. Wawzonek, and H. Hsu, *J. Amer. Chem. Soc.*, **68**, 2741 (1946).

solvent from the filtered solution there was obtained 6.6 g (70%) of 2,4,5-trimethylbenzyl cyanide,[23] bp 105–115° (0.2 mm). Hydrolysis of 5.4 g of the cyanide in 90 ml of 60% sulfuric acid for 15 hr, followed by a conventional work-up, afforded 4.0 g (66%) of pure recrystallized 2,4,5-trimethylphenylacetic acid,[23] mp 128–129°. Esterification by treatment of the acid chloride with ethanol yielded pure VII, bp 90–92° (0.2 mm), in 75% yield.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 75.5; H, 8.9.

1,1,1-Trichloro-2-(2,4,5-trimethylphenyl)propane (X).—To a solution of 5.94 g of I in 25 ml of ether was added dropwise with stirring a solution of 0.05 mol of ethylmagnesium bromide in 50 ml of ether. After 15 min the reaction mixture was cooled and treated slowly with ice. The cold ether layer was washed with cold sodium carbonate, and the solvent was removed under reduced pressure in the cold. Infrared examination of the product (mainly VIII) showed that no I was present and OH bands in the 2.8–3.0-μ region were strong. A solution of this crude carbinol mixture[24] in 75 ml of ether was shaken with cold 3 *N* hydrochloric acid, and the ether solution was then worked up in the usual way, keeping cool and in the dark. The nmr spectrum indicated that the product contained a preponderance of one (presumably the isomer shown) isomer of IX. No elemental analyses for VIII or IX were attempted because of the sensitivity of these compounds to heat.

(23) L. I. Smith and C. W. MacMullen, *J. Amer. Chem. Soc.*, **58**, 629 (1936).

(24) We assume that a mixture of stereoisomeric carbinols was present because of the complexity of the nmr spectrum. In another case[7] only one isomer was formed.

The nmr spectrum of IX (which was undoubtedly quite pure) had two multiplets for the vinyl hydrogens, one centered at τ 3.63 (1 H) and one centered at τ 4.40 (2 H). The 4-methyl group appeared as a singlet at τ 8.42 (3 H) and the remaining methyl groups as multiplets centerd at τ 7.90, 8.15, and 8.72 (9 H).

A solution of the above semibenzene IX in 5 ml of hexane was exposed to sunlight for several hours. The solvent was then removed under reduced pressure and the residue distilled to yield 4.35 g (70%) of yellow oil, bp 81–83° (0.1 mm).

A careful fractionation afforded a pure colorless sample of X which had nmr peaks as follows: τ 2.79, 3.20 (1 H each, aromatic), a quartet centered at τ 5.92 (1 H, benzylic); a doublet centered at τ 8.39 (3 H, aliphatic CH_3); a singlet at τ 7.91 (3 H aromatic CH_3); and a partly resolved doublet at τ 7.81 (6 H, aromatic CH_3).

The structure of X was further substantiated by mass spectrophotometry. Molecular ions of weights 264–270 were obtained, the variations being attributable to the chlorine isotopes. No satisfactory elemental analyses for X were obtained owing to the lack of stability. The analyses for C, H, and Cl added to 100%, but the chlorine values were lower than required by the formula $C_{12}H_{15}Cl_3$ owing to loss of HCl.

Registry No.—(+)-I, 16214-72-5; (−)-I, 16214-73-6; (+)-II, 16214-74-7; (−)-III, 16214-75-8; (±)-IV, 16214-76-9; (+)-VI, 16214-77-0; (−)-VI, 16214-78-1; VIII, 16214-79-2; (±)-IX, 16214-80-5; (±)-X, 16214-81-6.

Studies on the Bromination of Isoprene

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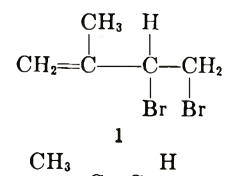
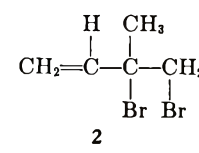
A study of the bromination of isoprene under various conditions is reported. Although previous reports stated that bromination of isoprene gave exclusively *trans*-1,4-dibromo-2-methyl-2-butene (**4**), it has been shown that, depending on the conditions, varying amounts of the following dibromides are also formed: *cis*-1,4-dibromo-2-methyl-2-butene (**3**), 3,4-dibromo-3-methyl-1-butene (**2**), and 3,4-dibromo-2-methyl-1-butene (**1**). The formation of **1**, **3**, and **4** was confirmed by comparison with authentic isomers, using infrared and vpc analysis. The unambiguous syntheses of **3** and **4** are reported. The presence of **2** was based on infrared and vpc studies, and on its rearrangement to **3** and **4**. The equilibration mechanism probably involves a covalent transition state in which the rearranging bromine atom is attached to carbon atoms at both ends of the allylic system, as proposed by Hatch, *et al.*, for the equilibration of 3,4-dibromo-1-butene and *trans*-1,4-dibromo-2-butene. In the addition of bromine to isoprene, in nonpolar solvents, it is suggested that π complexes (four of them are possible from attack of bromine on either end of the *s-cis* and *s-trans* forms of the isoprene molecule) are initially formed that break down to give bromonium ions in which the charge is highly dispersed across the whole allylic system. The bromonium ions from the *s-cis* and *s-trans* forms of isoprene would give **3** and **4**, respectively, by attack of tribromide ion on the terminal, vinyl carbon atom. Dibromide **2** (or **1**, depending on which end of the isoprene molecule was originally attacked) could be formed by opening of the three-membered ring.

Several researchers have reported that the product obtained from the bromination of isoprene is exclusively 1,4-dibromo-2-methyl-2-butene,[1] and that it has the *trans* configuration.[2,3] While studying the allylic diazide, prepared from isoprene dibromide, we became suspicious that this dibromide was not exclusively the *trans* isomer.[4] In order to establish the composition of the dibromide product from isoprene and to begin a mechanistic investigation of diene bromination, of which little is known, we undertook a study of the bromination of isoprene. Theoretically four dibromides, whose structures are shown below, are possible from the addition of bromine to isoprene. The formation of tetrabromide would be expected to be minimal since butadiene is reported to give no tetrabromide[5] and 2,3-dimethyl-1,3-butadiene in only small amounts.[6]



1



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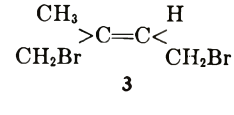

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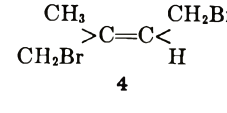


4

Results and Discussion

The results of our study on the bromination of isoprene under various conditions are shown in Table I. The percentages of the dibromides were determined by

(1) H. Staudinger, O. Muntwyler, and O. Kupfer, *Helv. Chim. Acta*, **5**, 756 (1922).

(2) A. A. Petrov, *J. Gen. Chem. USSR*, **13**, 741 (1943).

(3) Y. M. Slobodin, *ibid.*, **24**, 444 (1954).

(4) C. A. VanderWerf and V. L. Heasley, *J. Org. Chem.*, **31**, 3534 (1966).

(5) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1959).

(6) O. J. Sweeting and J. R. Johnson, *ibid.*, **68**, 1057 (1946).

vpc analysis. The identity of each isomer, with the exception of **2**, was based on comparison of retention times and infrared spectra with those of authentic samples. The structure of **2** was confirmed by its infrared spectrum and by the fact that it rearranged to give **3** and **4**. The synthesis of **1** has already been reported.[2] The unambiguous syntheses of **3** and **4**, reported here for the first time, are discussed in the Experimental Section.

TABLE I
ADDITION OF BROMINE TO ISOPRENE UNDER VARIOUS CONDITIONS

Solvent	Temp, °C	Dibromides, % 1	2	3	4
Chloroform	25	5	14	8	73
Chloroform	0	3	21	5	71
Chloroform	−45	1	20	3	76
n-Pentane	25	12	4	10	74
n-Pentane	0	6	9	7	78
n-Pentane	−45	3	14	3	80
Carbon tetrachloride	25	8	5	10	77
1,2-Dichloroethane	25	5	6	11	78

The rearrangement of **4** at 25° was studied in various solvents. The percentages of the dibromides at equilibrium are indicated in Table II.

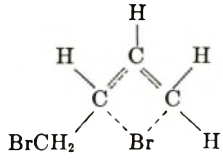
TABLE II
EQUILIBRATION OF *trans*-1,4-DIBROMO-2-METHYL-2-BUTENE[a] AT 25°

Solvent	Dibromides, % 1	2	3	4
Carbon tetrachloride	7	Trace	23	70
Chloroform	3	Trace	4	93
n-Pentane	10	Trace	21	69
1,2-Dichloroethane	5	Trace	21	74
Neat	5	Trace	21	74

[a] Although only the equilibration of **4** was studied, all of the other dibromides (**1**, **2**, and **3**) were observed to rearrange under somewhat different conditions, and undoubtedly would have given the same percentages of dibromides at 25°. The rearrangements of **1**, **2**, and **3** are discussed in greater detail in the Experimental Section.

One observation that can be made from the data in in Tables I and II is that the *trans*-1,4-dibromo-2-methyl-2-butene mentioned in previous reports contained significant quantities of other isomers, the percentages of which depended on the method of synthesis and isolation, and how long the dibromide was allowed to stand.

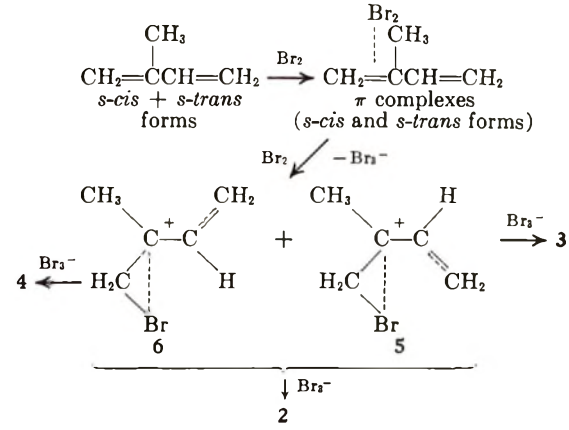
The results of the bromination of butadiene, reported by Hatch and coworkers,[5] and our results on the bromination of isoprene differ mainly in that butadiene gives no *cis*-1,4-dibromide, neither during bromination nor equilibration, and much larger quantities of vicinal dibromide. Hatch, *et al.*,[5] in discussing the mechanism of the addition of bromine to butadiene suggested that the transition states for addition of bromine to the diene and equilibration of the dibromide isomers are probably identical, and can be represented



It seems reasonable to assume that the transition state involved in the rearrangements of **1**, **2**, **3**, and **4** is essentially identical with that reported by Hatch, *et al.*[5] (shown above) for the butadiene dibromides. However, we would like to suggest that an entirely different mechanism is involved in the addition of bromine to isoprene (and perhaps other dienes). In order to discuss this mechanism, the recent studies by Buckles and coworkers[7] on the addition of bromine to an olefin (specifically *cis*- and *trans*-stilbene) must be considered. These authors have shown that the initial step in the addition of bromine to an olefin in a nonpolar solvent involves initial formation of a π complex that breaks down to give a bromonium ion, which is subsequently opened to give a dibromide. They[7] also state that, in a solvent with a low dielectric constant, the system is most stable when the charge is dispersed over a large area (a three-membered bromonium ion), rather than when it is localized on a single carbon atom (a carbonium ion). Hence, *cis*-stilbene undergoes a reaction with bromine to give exclusively *dl*-α,α^1-dibromobibenzyl. Formation of *meso*-α,α^1-dibromobibenzyl would have indicated the presence of a carbonium ion.

Perhaps isoprene (*s-cis* and *s-trans* forms), as does a monoolefin, undergoes reaction with bromine in a nonpolar solvent (*n*-pentane) to form π complexes (Scheme I). The resulting bromonium ions (**5** and **6**) should be

SCHEME I



most stable if the charges were dispersed over the whole allylic system. The extended π bonding in the bromonium ions would prevent rotation around the 2,3-carbon bond. Dibromide **2** could be formed from both **5** and **6**, by opening of the three-membered ring; **3** and **4** would result from attack of the tribromide ion on the terminal vinyl carbon atom of **5** and **6**, respectively.[8] If the equations in Scheme I correctly represent the mechanism for addition of bromine to isoprene, then the amount of **3** and **4** formed on bromination may reflect the ratio of *s-cis* and *s-trans* forms of isoprene existing at a particular temperature. The results in Table

(7) (a) R. E. Buckles, J. M. Bader, and R. J. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962); (b) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *ibid.*, **32**, 888 (1967).

(8) It seems doubtful that **3** and **4** are formed by rearrangement of **2** since it is reasonably stable under the reaction conditions. For example, after refluxing in carbon tetrachloride for 16 hr, **2** had rearranged only 60%. Since a typical bromination experiment requires about 1 hr, often at low temperatures, little rearrangement should have occurred. Small amounts of bromine or hydrogen bromide did not seem to significantly increase the rate of rearrangement.

I seem to indicate this relationship inasmuch as the increase in formation of **3** from lower to higher temperatures is in line with an increase in concentration of the less stable form of the diene (*s-cis*) at higher temperatures. The work by Buckles, *et al.*,[7] indicates that the charge should become more localized as the polarity of the solvent increases (*n*-pentane to chloroform). Again, the results in Table I confirm this, since the percentage of **2** is significantly higher in chloroform than *n*-pentane at all temperatures.[9]

Additional evidence for this mechanism comes from studies on the reaction of N-bromosuccinimide with isoprene in water. We have determined that the product from this reaction is exclusively 1-bromo-2-methyl-1-buten-2-ol.[10] No 4-bromo-2-methyl-2 buten-1-ol was detected. N-bromosuccinimide probably functions as a source of bromine, in low concentration, which attacks isoprene to give the π complex. In the polar solvent (H_2O) the π complex breaks down to give the localized carbonium ion (tertiary carbon atom) which subsequently bonds with water to give the bromohydrin. Bromonium ion formation seems doubtful since it would be opened mainly at the primary carbon atom to give 2-bromo-2-methyl-3-buten-1-ol, which undoubtedly would rearrange slowly to 4-bromo-2-methyl-2-buten-1-ol.

Attack by bromine at the opposite end of the isoprene molecule, *via* the same type of mechanism, would lead to **1** and also **3** and **4**. Attack seems to occur mainly on the double bond with the methyl group.[10]

Experimental Section[11]

Materials.—Unless otherwise indicated the solvents and reagents were obtained commercially in high purity. The isoprene, furnished by Phillips Petroleum, polymerization grade, was shaken with sodium bisulfite to remove peroxides, distilled immediately prior to use, and carefully isolated from oxygen.[12]

Bromination of Isoprene. General Procedure.—To 6.8 g (0.10 mol) of isoprene in 100 ml of solvent in a nitrogen atmosphere at the selected temperature was added dropwise with stirring 16.0 g (0.10 mol) of bromine. The solvent was removed at low pressure with no heat applied. The dibromides were analyzed without distillation. It was confirmed that the dibromides were not lost during solvent removal. Although the total yield of dibromides was not determined, it is probably quite good since little residue was observed on a few samples that were distilled.

Procedure for Analysis of the Dibromides.—The vpc analysis of the dibromides was done with an Aerograph 90 P-3 chromatograph under the following conditions: flow rate (He), 495 cc/min; column length and diameter, 6 ft × 0.25 in.; column temperature, 60°; column composition, 2.5% SE-30 on 60–80 mesh DMCS Chromosorb W. Under these conditions the retention times of **1**, **2**, **3**, and **4** are, respectively, 100, 83, 204, and 260 sec. A 10% solution of the dibromides in *n*-pentane gave the best analysis.

As nearly as could be determined, none of the dibromides rearranged on the column. However, **2** rearranged approximately 5% while passing through the considerably warmer detector.

The percentages of dibromides were based on their adjusted areas in the chromatograms. The adjustments were based on the following determinations: ratio of A_3/A_4 divided by W_3/W_4 is equal to 1,[13] and the ratio A_1/A_4 divided by W_1/W_4 is equal to 0.84. The area/weight ratio for dibromides **1** and **2** was assumed to be unity on the basis of their similar molecular structures.

Owing to the baseline drift, resulting from the high flow rate, the extreme sensitivity and other factors, the accuracy of the experimental results probably does not exceed ±(percentage of dibromide × 0.05).

The Authentic Isomers.—*trans*-1,4-Dibromo-2-methyl-2-butene (**4**) and *cis*-1,4-dibromo-2-methyl-2-butene (**3**) were synthesized from *trans*- and *cis*-2-methyl-2-butene-1,4-diol by a reaction with PBr_3 according to the method of Valette.[14] The boiling points for **3** and **4** are approximately 48–50° (0.1–0.2 mm). The boiling point of the dibromide mixture from isoprene is essentially identical with this. The infrared spectra of authentic **3** and **4** were nearly identical. Both showed a powerful absorption band at 1200 and the C–Br absorption bands at 550 and 628 cm^{-1}, respectively.[15] The structures of **3** and **4** were confirmed by the fact that, when they were heated at 100° in a sealed tube, each rearranged to give a mixture of approximately 26% **3** and 74% **4**, with small amounts of **1** and **2**.

trans-2-Methyl-2-butene-1,4-diol was prepared by the reduction of diethyl mesaconate[16] with aluminum hydride[17] in the following manner. Diethyl mesaconate (24.1 g, 0.129 mol) in tetrahydrofuran (130 ml) was added to 300 ml of 0.863 *M* aluminum hydride. Methanol was added to destroy the excess hydride, and a 60% potassium sodium tartrate solution was used to decompose the addition complex. After removal of the solvent, distillation of the remaining liquid resulted in three fractions, the highest boiling of which, bp 96–98° (0.10 mm), showed a powerful OH absorption band[15] from 3300 to 3400 cm^{-1} with essentially no carbonyl absorption. The yield was approximately 15%. Treatment of this compound with PBr_3 as indicated above, resulted in pure **4**.

cis-2-Methyl-2-butene-1,4-diol was prepared from citraconic anhydride and aluminum hydride with the same ratio of reagents as described in the preparation of the *trans* diol. The *cis* diol, which was obtained when the addition complex was destroyed with potassium sodium tartrate, contained some impurities since the infrared spectrum showed, in addition to the OH absorption band, a carbonyl band which could not be removed by distillation. Vpc analysis on a Polypak column confirmed these impurities. However, when this impure *cis* diol was treated with PBr_3, **3** was obtained without contamination.

The *cis* diol was obtained in much higher purity, but in very low yield, by decomposing the addition complex with 50% sodium hydroxide. The infrared spectrum of this diol showed no carbonyl absorption band, and was strikingly similar to the spectrum of the *trans* diol. The boiling point of the *cis* diol is approximately the same as for the *trans* diol.

Dibromides **3** and **4** and *cis*- and *trans*-2-methyl-2-butene-1,4-diol showed weak C=C absorption bands in the neighborhood of 1675 cm^{-1}. In addition to the similar OH and C=C absorption bands, the *cis* and *trans* diol showed the following principal bands (cm^{-1}), respectively: 2940, 2875, 1460, 1380, 1040, and 1009 and 2930, 2875, 1450, 1380, 1065, and 1000.

Identification of the Dibromides Isomers Formed on the Bromination of Isoprene.—The chromatogram of the appro-

(9) Other factors may be involved in the increase of **2** in chloroform, since bromination in dichloroethane, which has a higher dielectric constant than chloroform, does not lead to a significant increase in **2**. Also, **1** does not show the same increase in going from *n*-pentane to chloroform.

(10) E. J. Reist, I. G. Junga, and B. R. Baker [*J. Org. Chem.*, **25**, 1673 (1960)] confirmed that the epoxide from this bromohydrin product is primarily 3,4-epoxy-3-methyl-1-butene (91%); they did not identify the impurity, although it was likely 3,4-epoxy-2-methyl-1-butene. A. A. Petrov [*J. Gen. Chem. USSR*, **13**, 481 (1943)], in a very similar reaction (using N-bromoacetamide instead of N-bromosuccinimide), established that the bromohydrin product is 1-bromo-2-methyl-3-buten-2-ol. Nmr studies by us on the product from isoprene, water, and N-bromosuccinimide confirm the exclusive formation of 1-bromo-2-methyl-3-buten-2-ol.

(11) Boiling points are uncorrected.

(12) If this procedure was not followed rigorously, drastically different results were obtained, probably owing to radical reactions, caused by peroxides.

(13) This ratio was determined early in the study under identical conditions except the column did not contain dichlorodimethylsilane. The slight column change should not effect this ratio.

(14) A. Valette, *Ann. Chim.*, **3**, 644 (1948).

(15) For a discussion of the positions of absorption bonds in the infrared, see L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1957.

(16) The diethyl mesaconate was prepared from highly purified mesaconic acid, ethyl alcohol, and sulfuric acid. Under these acidic conditions, rearrangement around the olefinic bond could occur. However, vpc analysis of the diethyl mesaconate indicated only one compound, presumably diethyl mesaconate.

(17) For the preparation of aluminum hydride, see H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966). Lithium aluminum hydride was employed, under various conditions, for the reduction of diethyl mesaconate, but without success.

priate bromination product (example *n*-pentane, 25°) showed four peaks. The second, third, and fourth peaks were identified as **1**, **3**, and **4**, respectively, on the basis that the retention time and infrared spectrum[18] of each was identical with that of the appropriate authentic isomer. The second and third peaks were further confirmed as **1** and **3** by heating samples of them at 100° and observing that they rearranged to essentially the same mixtures as reported for authentic **3** and **4**.

The dibromide corresponding to the first peak in the chromatogram and assigned structure **2** was isolated from the dibromide mixture (*n*-pentane, 25°) by low temperature fractional distillation. It was assigned structure **2** on the basis that its infrared spectrum showed the terminal vinyl absorption bands[15] at 930 and 990 cm^{-1}, and that it rearranged[8] on refluxing to **3** and **4**.

The Equilibration Studies.—Solutions of approximately 15% **4** in the solvents listed in Table II were allowed to stand at room temperature (approximately 25°) for about 6 months. Analyses at the end of 3- and 6-month periods were essentially the same. As indicated, the equilibration of **4** without a solvent was studied. The essentially pure **4** used in the equilibration study was prepared by recrystallization of the product obtained from the bromination of isoprene at −45°. The recrystallization was carried out in *n*-pentane at Dry Ice temperatures. Vpc analysis indicated that only traces of the other dibromides remained. The **4** prepared in this manner was used in the equilibration studies without distillation since distillation sometimes resulted in rearrangement. We are unable to account for the fact that distillation of **4**, purified by recrystallization, did not always result in rearrangement. However, equilibration studies in $CHCl_3$ on a sample of **4**, prepared in this way and distilled without rearrangement, gave identical results with that of undistilled **4**.

(18) A small sample of each isomer was isolated from the gas chromatograph. These samples were used to make the infrared spectra. The spectra were identical with the spectra of the authentic isomers, except for some very minor impurity peaks in the latter.

Registry No.—Isoprene, 78-79-5; **3**, 16526-18-4; **4**, 16526-19-5.

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The Chlorination of Olefins with Cupric Chloride. A Comparative Study of *trans*-Ethylene-d_2 and *cis*- and *trans*-2-Butene

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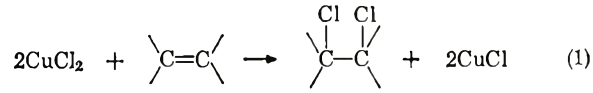
The chlorination of olefins at 320° with cupric chloride does not always proceed with a high degree of *trans* addition. Although both *cis*- and *trans*-2-butene chlorinate by largely *trans* addition, the chlorination of *trans*-ethylene-d_2 is nearly random. The order of stereoselectivity is *cis*-2-butene > *trans*-2-butene ≫ *trans*-ethylene-d_2. The random chlorination of *trans*-ethylene-d_2 occurs during the product-forming step. Neither ethylene-d_2 nor product isomerization is responsible. However, most of the randomly chlorinated product from *cis*- and *trans*-2-butene can be explained by 2-butene isomerization and the interconversion of the 2,3-dichlorobutane diastereomers. The greater stereoselectivity in the chlorination of *cis*- over *trans*-2-butene is mainly due to the isomerization of *meso*- into *dl*-2,3-dichlorobutane. At 320°, this isomerization occurs approximately 1.4 times faster than the isomerization of *dl*- into *meso*-2,3-dichlorobutane. Evidence is also presented which shows that cupric chloride and not chlorine is the chlorinating agent. The mechanism of this reaction is discussed in terms of chloronium ion and radical intermediates.

The literature contains several examples of the use of cupric chloride as a versatile chlorinating agent for a variety of organic molecules.[1-4] Undoubtedly, the most extensive industrial application of this chemistry of cupric chloride is in so-called "oxychlorination" reactions. This is a vapor phase reaction normally carried out at temperatures of 220–330°.[5] In this process, cupric chloride chlorinates the double bond of the olefin and in turn is reduced to cuprous chloride. Cuprous chloride is then reoxidized with hydrogen chloride and oxygen, and the process is repeated many times.



$$2CuCl_2 + \text{>C=C<} \longrightarrow \text{>C(Cl)–C(Cl)<} + 2CuCl \quad (1)$$

$$2CuCl + 2HCl + \tfrac{1}{2}O_2 \longrightarrow 2CuCl_2 + H_2O \quad (2)$$

This paper deals with the mechanism of the olefin chlorination step (eq 1). Arganbright and Yates recently reported on the chlorination of *cis*- and *trans*-2-butene with cupric chloride supported on pumice.[1] They found that at 290° this reaction proceeds with a high degree of *trans* addition. In this present work, we have extended the study of olefin chlorination with cupric chloride with the objective of answering the following questions. (1) Do olefin substituents greatly influence the stereochemistry of this reaction? Specifically, is the chlorination of the simplest olefin, ethylene, also highly stereoselective? (2) Why is the chlorination of *cis*-2-butene more stereoselective than *trans*-2-butene? (3) Is elemental chlorine involved in this reaction?

Results

Both *cis*- and *trans*-ethylene-d_2 were required for this study. They are conveniently synthesized by the stereospecific reduction of acetylene-d_2.[6] We confirmed the stereochemistry of these reductions by infrared spectroscopy. The characteristic bands for *cis*- and *trans*-ethylene-d_2 appear at 842 and 987 cm^{-1}, respectively.[7,8]

(1) R. P. Arganbright and W. F. Yates, *J. Org. Chem.*, **27**, 1205 (1962).
(2) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **30**, 587 (1965).
(3) J. K. Kochi and D. M. Mog, *J. Amer. Chem. Soc.*, **87**, 522 (1965).
(4) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).
(5) G. W. Hearne, U. S. Patent 2,399,488 (1946); A. J. Johnson and A. J. Cherniavsky, U. S. Patent 2,746,844 (1956).
(6) R. Spector, Ph.D. Thesis, University of Pennsylvania, Philadelphia, Pa., 1965.
(7) R. L. Arnett and B. L. Crawford, *J. Chem. Phys.*, **18**, 118 (1950).
(8) W. M. Schubert, B. S. Rabinovitch, N. R. Larson, and V. A. Sims, *J. Amer. Chem. Soc.*, **74**, 4590 (1952).

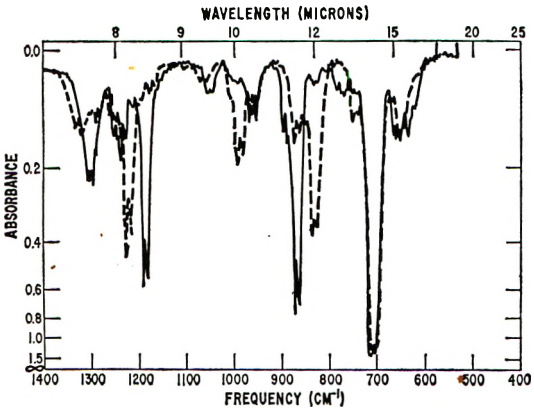
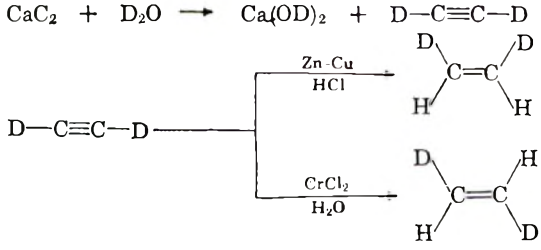
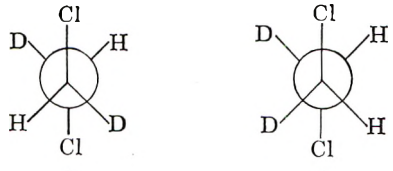


Figure 1.—Gas cell infrared spectrum: ———, 90% *meso*-1,2-dichloroethane-1,2-d_2, 6% $C_2H_3DCl_2$, 4% $C_2H_4Cl_2$; — —, 81% *dl*-1,2-dichloroethane-1,2-d_2, 15% $C_2H_3DCl_2$, 4% $C_2H_4Cl_2$.



The addition chlorination of either ethylene-d_2 can produce two diastereomers, *meso*-1,2-dichloroethane-1,-2-d_2 (**1**) and *dl*-1,2-dichloroethane-1,2-d_2 (**2**). We



1 **2**

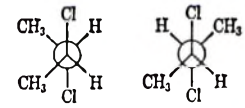
prepared these two reference compounds by the chlorination of *cis*- and *trans*-ethylene-d_2 in acetic acid. Under these conditions, exclusively *trans* addition is expected.[9] The fact that this reaction is indeed stereospecific is evident from the infrared spectra. The spectrum of either compound has intense bands which are absent in the other. The reference bands chosen for calibration are located at 1183 cm^{-1} for the *meso* isomer and 838 cm^{-1} for the *dl* isomer (Figure 1). Mass spectrometry gave the following deuterium distribution: *meso* dichloride **1**, 90% $C_2H_2D_2Cl_2$, 6% $C_2H_3DCl_2$, 4% $C_2H_4Cl_2$; *dl* dichloride **2**, 81% $C_2H_2D_2Cl_2$, 15% $C_2H_3DCl_2$, 4% $C_2H_4Cl_2$. Hydrogen–deuterium exchange likely occurs during the acetylene-d_2 synthesis or the acetylene reduction step or both. A large excess of fresh calcium carbide was used in all acetylene-d_2 syntheses. Small amounts of calcium hydroxide in the carbide could result in exchange with deuterium oxide to give some hydrogen in the acetylene-d_2. Significant amounts of hydrogen in acetylene-d_2 prepared in this way has been reported (3 mol % or as much as 6% C_2H D).[10] However, the infrared spectra clearly show that this exchange, wherever it occurs, is not accompanied by the isomerization of *cis*- and *trans*-ethylene-d_2 or the *meso* and *dl* dichlorides **1** and **2**. For the purposes of this study, 81 and 90% $C_2H_2D_2Cl_2$ is sufficient. It is only important that the isomers are not contaminated with one another.

Now that the dichlorides **1** and **2** have been characterized, the stereochemistry of the chlorination of *trans*-ethylene-d_2 with cupric chloride can be established. This reaction was conducted in an externally heated Vycor tube at 320° with 10% cupric chloride impregnated on a 8–10 mesh pumice support. The infrared spectrum of the purified 1,2-dichloroethane-1,2-d_2 mixture (preparative vpc) indicated that the product comprised 58% *meso*- and 42% *dl*-1,2-dichloroethane-1,2-d_2. The randomly chlorinated product is not due to the isomerization of *trans*-ethylene-d_2 under the reaction conditions. The unreacted ethylene-d_2 contained only 4% of the *cis* isomer. Neither do the products isomerize significantly. Under these conditions, a mixture of 90% of the dichloride **1** and 10% of the dichloride **2** gave a product whose isomer ratio changed only slightly to 84 and 16% of the dichlorides **1** and **2**, respectively. In this later experiment, the copper chloride is first partially reduced with ethylene to make certain that both copper(I) and -(II) are present. Nitrogen is then passed through the mixture of the chlorides **1** and **2**. This nitrogen stream, now containing dichloride vapor is passed through the reactor at the same temperature and contact time used in the chlorination of *trans*-ethylene-d_2.

The chlorination of *cis*- and *trans*-2-butene is much more stereoselective under the conditions used in the chlorination of *trans*-ethylene-d_2 (Table I). Table I

TABLE I
THE CHLORINATION OF *cis*- AND *trans*-2-BUTENE WITH $CuCl_2$ AT 320°. PRODUCT COMPOSITION

2,3-Dichlorobutanes, %



			2-Butenes, %	
Reactants	*dl*	*meso*	*cis*	*trans*
cis-2-Butene	82.5	17.5	90.1	9.9
trans-2-Butene	23.3	76.7	6.3	93.7

also shows that the interconversion of isomeric 2-butenes occurs somewhat more extensively than the isomerization of *trans*-ethylene-d_2, and, as one might expect, *cis*-2-butene isomerizes faster than *trans*-2-butene. The extent of 2-butene isomerization is quite significant compared to the amount of random chlorination.

The stability of *dl*-2,3-dichlorobutane (**3**) and *meso*-2,3-dichlorobutane (**4**) was also examined under the reaction conditions using partially reduced cupric chloride. The isomerization of these compounds is also significant compared to the amount of random chlorination of the 2-butenes. Moreover, the *meso* dichloride **4** isomerizes about 1.4 times faster than the *dl* isomer **3**. The dichloride **4** gave a product comprising 86.8% of **4** and 13.2% of **3** whereas the dichloride **3** gave 90.9% of **3** and 9.3% of **4**.

The last objective of this study was to determine if elemental chlorine is involved in these reactions. To resolve this question, we chose to measure the rate of chlorine production from our cupric chloride–pumice system at 320°. We then compared this to (1) the rate expected for a rapid equilibrium among cupric

(9) R. Fahey and C. Shubert, *J. Amer. Chem. Soc.*, **87**, 5172 (1965).
(10) L. C. Leitch and A. T. Morse, *Can. J. Chem.*, **30**, 924 (1952).

chloride, cuprous chloride, and chlorine and (2) the rate of 1,2-dichloroethane production. Chlorine is, indeed, produced when the olefin is replaced by nitrogen and can be conveniently measured iodometrically. Using a nitrogen flow rate of 9.89 mmol/min, the rate of chlorine production is 0.018 ± 0.001 mequiv every 2 hr over three successive 2-hr runs. This is far short of that expected if the following reaction were in rapid equilibrium.

$$2CuCl_2(s) \rightleftharpoons 2CuCl(s) + Cl_2(g)$$

The equilibrium partial pressure of chlorine at 600°K is 4.6×10^{-4} atm.[11] Considering the nitrogen flow through our reactor the expected rate of chlorine production is about 57 times greater than that observed. Replacing part of the nitrogen with ethylene (2.11 mmol/min) but under otherwise identical conditions, 1,2-dichloroethane is produced at 0.45 ± 0.04 mmol/min (three successive measurements) over an 8-min period. This reaction was carried to 24% completion based on cupric chloride. The zero-order dependence on cupric chloride is not surprising. Arganbright and Yates reported that the chlorination of olefins with cupric chloride on pumice appeared to take place at a constant rate.[1]

Discussion

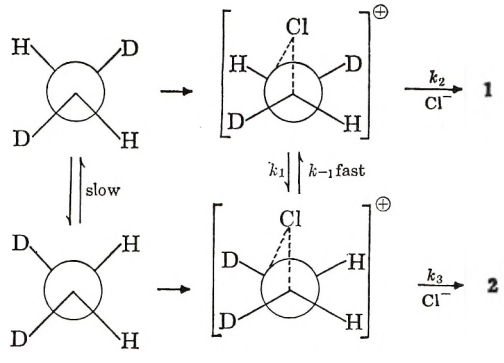
Arganbright and Yates reported that the chlorination of *cis*- and *trans*-2-butene with cupric chloride at 290° proceeds with a high degree of *trans* addition.[1] They proposed a chloronium ion intermediate to account for this. In general, we concur with their observation of the high stereoselectivity with the 2-butenes. But our results also show that the chlorination of olefins with cupric chloride is not always a highly stereoselective reaction. It is strongly influenced by the degree and geometry of olefin substitution.

The chlorination of *trans*-ethylene-d_2 with cupric chloride on pumice occurs with little stereoselectivity. Only 16% of the reaction proceeds by a stereospecific *trans* addition while 84% is random. Our data clearly shows that neither olefin nor product isomerization is responsible. The random chlorination must occur during the product-forming step.

In sharp contrast with *trans*-ethylene-d_2, the chlorination of both *cis*- and *trans*-2-butene is highly stereoselective under the same conditions (Table I). In this system, however, the extent of olefin isomerization and interconversion of the 2,3-dichlorobutane diasteriomers is large compared to the relatively small amount of random chlorination. In fact, the 17.5% of the *meso* dichloride **4** obtained from *cis*-2-butene can be conveniently accounted for in terms of olefin and product isomerization. The unreacted 2-butene contained 9.9% of the *trans* isomer, and under the reaction conditions, the *dl*-dichloride **3** isomerized to 9.1% of the *meso* isomer **4**. The same interpretation can be made to account for the 23.3% of *dl* dichloride **3** obtained from the chlorination of *trans*-2-butene. Although *cis*-2-butene isomerizes faster than *trans*-2-butene it, nevertheless, chlorinates with greater stereoselectivity. The explanation lies in the relative rates for the interconversion of products. The *meso* dichloride isomerizes approximately 1.4 times faster than the dichloride **3**.

The proposal of a chlorinium ion by Arganbright and Yates to account for the stereochemistry of the chlorination of the 2-butenes is a reasonable one. There is strong evidence for the existence of such intermediates. Among the most convincing is a recent report by Fahey on the dramatic stereospecific *trans* addition of chlorine to *cis*-di-*t*-butylethylene.[12] Fahey also observed rearranged products resulting from a stereospecific *trans*-methide shift from the *t*-butyl substituent. If the chloronium ion is the only intermediate in the chlorination of *trans*-ethylene-d_2, then the interconversion of rotamers, steps k_1 and k_{-1}, must be faster than product formation, steps k_2 and k_3 (Scheme I). If one considers the same mechanism for the chlorination of the 2-butenes, then the relative rates for the two steps must be reversed. Product formation must be faster than the interconversion of rotamers.

SCHEME I



However, the interconversion of chloronium ions must go through open-chain transition states. One would then expect the more highly substituted ones to isomerize more rapidly. If this ionic scheme is to be consistent with our observed order of stereoselectivity, the conversion of the chloronium ion into product must be much faster for the 2-butenes than for *trans*-ethylene-d_2. A mechanism which more consistently accounts for our results is one in which the reaction partitions between a radical and bridged ion pathway. Poutsma has observed such a dual mechanism for the dark chlorination of several olefins with chlorine under nitrogen.[13] He has shown that the radical route is much less stereoselective. Competition between the two routes is influenced by olefin substitution, the ionic route being somewhat favored with increasing number of alkyl substituents, particularly at low olefin concentrations.

Since cupric chloride is the chlorinating agent in our system, a cupric chloride–olefin complex must form during the reaction. Partitioning between the radical and ionic pathway might occur by either chlorine atom or (Cl^+) transfer from copper. This is similar to the scheme suggested by Poutsma where the two routes evolved from an olefin–chlorine π complex.[13] Although some chlorine can be produced in our system, it is only 6×10^{-3} times the rate of 1,2-dichloroethane production. Substantial involvement of chlorine through a rapid equilibrium disproportionation of cupric chloride

(11) J. A. Allen, *J. Appl. Chem.*, **12**, 406 (1962).

(12) R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966).

(13) M. Poutsma, *ibid.*, **87**, 2172 (1965).

is unreasonable. The rate of chlorine production is kinetically controlled and only 1.8% of that expected for a rapid equilibrium.

Experimental Section

Acetylene-d_2.—A three-necked, 50-ml flask fitted with an addition funnel and a water-cooled condenser was flame dried while being purged with a stream of nitrogen. The nitrogen purge was continued as the apparatus cooled to room temperature. Calcium carbide (25 g) was transferred to the three-necked flask from a freshly opened container. Then 10 ml of deuterium oxide was added to the addition funnel. Another apparatus was now assembled. A 1-gal. glass bottle was filled with water and fitted with a rubber stopper containing two pieces of glass tubing. One piece extended only 1 in. into the bottle and the other extended to the very bottom. Both pieces of tubing contained a two-way stopcock. The nitrogen flow through the three-necked flask was stopped and these two apparatus were connected with Tygon tubing extending from the top of the condenser in the first apparatus to the short piece of tubing in the second. As deuterium oxide was slowly added to the calcium carbide, the water in the 1-gal. bottle was displaced by acetylene-d_2. The addition of deuterium oxide was continued until only 500 ml of water remained. At this point, the stopcocks were closed and the two apparatus disconnected.

trans-Ethylene-d_2.—The following is a modification of the procedure described by Spector.[6] Zinc amalgam was prepared by adding granulated zinc (50 g) to 10 ml of mercury followed by 5 ml of 1 *N* sulfuric acid. The mixture was heated on a steam bath for 20 min. The amalgam was then washed several times with distilled water and placed in a 500-ml, glass-stoppered flask. A solution of 120 g of chromic chloride hexahydrate (0.45 mol) and 75 ml of concentrated hydrochloric acid in 150 ml of water was added. The mixture was stoppered and shaken vigorously until the color turned from green to deep blue, characteristic of the hydrated chromous ion. The stopper was removed periodically to permit small amounts of hydrogen to escape.

The long section of tubing on the 1-gal. bottle containing acetylene-d_2 was connected to an aspirator. The stopcock to the aspirator was opened and the remaining 500 ml of water was removed. The stopcock was then immediately closed. This created a partial vacuum in the bottle. This section of tubing was then inserted into the chromous chloride solution and the stopcock opened. The solution was transferred into the bottle by suction, and the mixture was shaken on a mechanical shaker for 2.5 hr. This reaction was repeated, and the vapor contents of the two bottles were transferred into a steel lecture bottle. The lecture bottle was cooled in liquid nitrogen. Air and hydrogen were then removed with a vacuum pump. The infrared spectrum showed an intense band at 987 cm^{-1}, characteristic of *trans*-ethylene-d_2. There was no band at 843 cm^{-1} for *cis*-ethylene-d_2.[7,8]

cis-Ethylene-d_2.—The following is a modification of the procedure described by Spector.[6] Copper-activated zinc was prepared by adding 150 g of zinc dust to a rapidly stirred solution of 36 g of cupric sulfate pentahydrate in 600 ml of water. Some heat was evolved in this reaction, and the blue solution was decolorized. The mixture was stirred for approximately 15 min and then filtered. The resulting copper-activated zinc was washed several times with water and transferred to a 1-gal. bottle. The bottle was filled with water, and all but 300 ml of water was displaced with acetylene-d_2 according to the procedure described earlier. The final 300 ml of water was removed with an aspirator and replaced with a solution of 24 ml of concentrated hydrochloric acid in 90 ml of water. This mixture was vigorously shaken for 18 hr on a mechanical vibrator. After this time, the copper-activated zinc was coated with zinc chloride and had caked. Gas chromatography also showed that all of the acetylene-d_2 had not yet been reduced. Therefore, the vapor contents were displaced by water into a liquid nitrogen trap where the hydrogen was removed with a vacuum pump. The gas was then transferred into a 1-gal. bottle containing fresh copper-activated zinc and the mixture was shaken for an additional 8 hr. The product, now essentially free of acetylene-d_2, was transferred to a steel lecture bottle. The infrared spectrum had an intense band at 842 cm^{-1} for *cis*-ethylene-d_2 and no band at 987 cm^{-1} for *trans*-ethylene-d_2.[7,8]

***meso*-2,3-Dichloroethane-1,2-d_2 (1).**—A three-necked, 100-ml, round-bottom flask was painted black then fitted with a Dry Ice condenser, magnetic stirring bar, and a sintered-glass, gas-saturating tube. Glacial acetic acid (50 ml) was added followed by 8.6 g (0.121 mol) of chlorine. While the solution was rapidly stirred, 2 l. of *trans*-ethylene-d_2 (0.089 mol) was passed through the gas-saturating tube. It was introduced at such a rate that very little passed through the system unreacted. After the addition was completed, the Dry Ice–acetone mixture was removed from the condenser, and the contents frozen to the base of the condenser were allowed to melt and return to the reaction mixture. The contents were then added to 125 ml of water. The organic phase was removed and washed twice with 10 ml of water. Gas chromatography showed that except for some high boiling products, nearly 100% of this material had the same retention time as 1,2-dichloroethane. The product was further purified by preparative gas chromatography using a 4 ft × 0.25 in. column packed with 20% LB 550X Ucon on Chromosorb R at 90°. A total of 0.34 g (4%) of pure product was obtained. Mass spectroscopy gave the following percentages: 90% $C_2H_2D_2Cl_2$, 6% $C_2H_3DCl_2$, and 4% $C_2H_4Cl_2$. For infrared data, see Figure 1.

***dl*-1,2-Dichloroethane-1,2-d_2 (2).**—This procedure is identical with that used in the synthesis of the *meso* isomer except *cis*- rather than *trans*-ethylene-d_2 was used. A total yield of 0.39 g (4%) of pure product was obtained. Mass spectroscopy gave the following percentages: 81% $C_2H_2D_2Cl_2$, 15% $C_2H_3DCl_2$, and 4% $C_2H_4Cl_2$. For infrared data, see Figure 1.

The Chlorination of *cis*- and *trans*-2-Butene with Cupric Chloride on Pumice.—Cupric Chloride impregnated on pumice was prepared by adding 107 g of 8–10 mesh pumice to a solution of 16.1 g of cupric chloride dihydrate in 60 ml of water. This mixture was constantly stirred over a steam bath to remove the water.

The chlorination of olefins was carried out in a reactor consisting of a vertically mounted (24 × 330 mm) Vycor tube containing a coarse, sintered glass disk at its base. The tube was externally heated, and contained a thermocouple well which extended vertically through the center such that the temperature could be measured at any point along its length. The pumice supported cupric chloride (40 g) was then introduced and gradually heated in a stream of nitrogen fed through the base of the reactor. The temperature along most of the reactor length was adjusted to 320° with a distribution ranging between 300 and 320°. A feed comprising 2.11 mmol of 2-butene/min and 7.18 mmol of nitrogen/min passed through the reactor. The product was collected in a Dry Ice–acetone trap over a 12-min period. An evacuated gas sampling bottle was then connected to the trap, and the unreacted butenes were collected as the product warmed to room temperature. The butenes were then analyzed by gas chromatography at 48° using an 8 ft × 0.25 in. column packed with silver nitrate–benzyl cyanide on 60/80 mesh Chromosorb R. The ratio of *meso*- to *dl*-2,3-dichlorobutanes in the liquid product was also determined by gas chromatography. A 4 ft × 0.25 in. column packed with 20% LB 550X Ucon on Chromasorb R was used with a temperature program from 30 to 200° at 10°/min. Better resolution can be achieved with a 20 ft × 0.25 in. column operated isothermally at 140°. The by-products in this reaction are *cis*- and *trans*-2-chloro-2-butene (5–7%).

Chlorination of *trans*-Ethylene-d_2 with Cupric Chloride on Pumice.—This reaction was identical with that described for the 2-butenes except that the unreacted ethylene-d_2 was collected in a liquid nitrogen trap connected in series with the Dry Ice–acetone trap. A gas-sampling bottle was connected to the liquid nitrogen trap and both were evacuated. The unreacted ethylene-d_2 was then transferred to the gas-sampling bottle as it gradually warmed to room temperature. The unreacted ethylene-d_2 was analyzed by infrared using the calibrated absorption for *cis*- and *trans*-ethylene-d_2 at 842 and 987 cm^{-1}, respectively.[7,8]

The chlorinated product in the Dry Ice–acetone trap was allowed to warm to room temperature, and was washed with 4 ml of water. The organic phase was separated and the 1,2-dichloroethane-1,2-d_2 mixture was isolated pure by preparative gas chromatography using those conditions described earlier. The ratio of *meso*- to *dl*-1,2-dichloroethane-1,2-d_2 was determined by infrared spectroscopy (gas cell) using the calibrated absorption for the *meso* and *dl* isomers at 1183 and 838 cm^{-1}, respectively.

Isomerization of the Dichlorides with Cu(I) and Cu(II) Chlorides on Pumice.—The reactor containing cupric chloride

on pumice was assembled as described earlier and heated to 320°. At this temperature, a feed comprising 2.11 mmol of ethylene/min and 7.18 mmol of nitrogen/min was passed through the reactor for 3 min. This reduced part of the cupric chloride so that both Cu(I) and Cu(II) chlorides were present. The system was purged with nitrogen for 30 min. A micro gas scrubbing bottle, containing 120 μl of the appropriate dichloride was connected between the nitrogen line and the reactor. Nitrogen was then passed through the scrubbing bottle at 9.29 mmol/min. The nitrogen, now containing dichloride vapor, passed through the reactor with the same contact time as the olefins described previously. The product was trapped in a Dry Ice–acetone bath and analyzed by gas chromatography or infrared spectroscopy in the usual way.

Rate of 1,2-Dichloroethane Formation from Ethylene and Cupric Chloride.—Ethylene was chlorinated by cupric chloride impregnated on pumice according to the procedures described earlier. Helium was introduced at the end of the reaction zone at 9.29 mmol/min. This diluted the product stream such that 1,2-dichloroethane remained in the vapor phase. The product was collected in gas-sampling bottles over one 2-min and two 3-min time intervals. The product was then analyzed by gas chromatography using calibrated response factors relative to nitrogen. Nitrogen is used as the internal standard because it is metered into the reactor at a known rate which does not change during the reaction. Therefore, the rate of product formation, the rate of ethylene consumption, and the material balance can be determine from the integrated band areas.

Rate of Chlorine Production from Cupric Chloride on Pumice.—The pumice to be used in this experiment was heated in air at 550° for 20 hr to oxidize any organic matter which might be present. It was then impregnated with cupric chloride in the usual way. It was then heated to 320 in the reactor described earlier in a stream of nitrogen (9.89 mmol/min). The effluent was directed into two gas scrubbers containing aqueous potassium iodide solution. This was done for three successive 2-hr runs. After each run, the liberated iodine was titrated with standard sodium thiosulfate solution. The rate of chlorine evolution was nearly constant (0.018 ± 0.001 mequiv/2 hr).

Registry No.—Cupric chloride, 7447-39-4; *trans*-ethylene-d_2, 1517-53-9; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; **1**, 16622-55-2; **2**, 16622-56-3.

Acknowledgment.—Our thanks to Dr. P. Zakriski for performing the mass spectrometric analyses, to Dr. J. Burr for his help with the infrared spectra, and to Professor P. Bartlett for his helpful discussions.

Synthesis and Hydrolysis Kinetics of Lincomycin Acetals

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A series of *para*-substituted O-benzylidene acetals at the 3,4 position of the antibiotic lincomycin was synthesized in search of an easily cleaved acetal. The hydrolysis reactions of these acetals follow pseudo-first-order kinetics and appear to follow the generally accepted mechanism for simple acetal hydrolysis. The pH-rate profile for the acetal containing a *p*-phenolic substituent indicates that the hydronium ion catalysis of the phenolate ion form as well as the phenol form of the derivative has to be considered. The second-order rate constants of hydrolysis for the series of arylidene derivatives at 70° gave a correlation coefficient of 0.996 in a modified Hammett σ^+ plot with a ρ value of -1.85. From this correlation a σ^+ value of -3 is estimated for the *p*-phenolic oxy anion. The use of arylidene derivatives as protective groups is discussed.

Benzylidene acetals of polyfunctional molecules are commonly used as protective groups.[1] In search of an easily cleaved acetal of lincomycin, the effect of substituents on the rate of hydrolysis of arylidene acetals was studied since Kreevoy and Taft[2] only quantitated the substituent effect for numerous aliphatic acetals and ketals. While the study was being completed, an article by Fife and Jao[3] was published in which the effect of substituents on the rates of hydrolysis of cyclic and acyclic arylidene acetals were found to give plots of log k *vs.* σ or σ^+ with curvature for *para*-substituted compounds. In the present study with *para*-substituted 3,4-O-benzylidene acetals of lincomycin, a correlation coefficient of 0.996 was obtained in a modified Hammett σ^+ plot. This type of correlation is useful in the selection of acetals to use as protective groups.

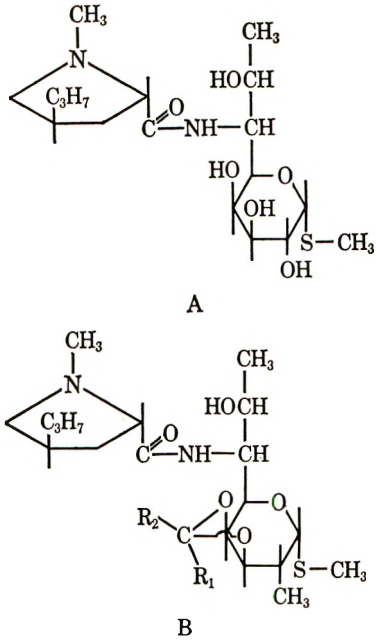
The antibiotic lincomycin proved to be an ideal molecule in which to study the effect of substituents on the rates of acetal hydrolysis, since acetals are easily formed with the *cis* hydroxyls on C_3 and C_4 of lincomycin (see Figure 1). In addition, the analytical problem was simplified by the lack of an intense uv chromophore in lincomycin. A range of hydrolysis rates is provided by the following substituents in the *para* position of 3,4-O-benzylidenelincomycin: chloro, hydrogen, methyl, methoxy, and hydroxyl.

(1) J. F. W. McOmie, *Advan. Org. Chem.*, 191 (1963).
(2) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).
(3) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

Results

Synthesis and Structure Determination of the Lincomycin Acetals.—Acetals are commonly prepared by catalysis with strong acids, dehydrating agents ($ZnCl_2$, etc.), and in some cases with neutral amine salts of strong acids (NH_4Cl, etc.). Since lincomycin is somewhat unstable in strong acid media, acetal formation was attempted using lincomycin–HCl with excess aldehyde without any additional acid. Acetal formation was found to occur readily under these conditions in virtually quantitative yield when benzene was used to remove the water azeotropically.

The lincomycin acetals were initially isolated as the hydrochloride salts, but only the *p*-chloro-, -hydrogen-, and -methyl-substituted 3,4-O-benzylidene derivatives could be recrystallized as the hydrochloride salts. The less stable acetals, such as the 3,4-O-(*p*-hydroxybenzylidene) and the 3,4-O-anisylidene derivatives, decomposed rapidly on attempted recrystallization from hydroxylic solvents, yielding lincomycin–HCl. Recrystallization of the hydrochloride salts from nonhydroxylic solvents was difficult since the lincomycin acetals are very insoluble in most of these solvents. Consequently, the 3,4-O-anisylidene and 3,4-O-(*p*-



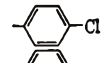
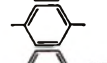
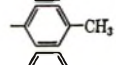
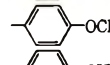
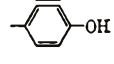
	R_1	R_2
I, 3,4-O-isopropylidenelincomycin	$-CH_3$	$-CH_3$
II, 3,4-O-(*p*-chlorobenzylidene)-lincomycin		-H
III, 3,4-O-benzylidenelincomycin		-H
IV, 3,4-O-*p*-toluylidenelincomycin		-H
V, 3,4-O-anisylidenelinocmycin		-H
VI, 3,4-O-(*p*-hydroxybenzylidene)-lincomycin		-H

Figure 1.—Lincomycin (A) and lincomycin acetal (B) structures.

hydroxybenzylidene) acetals were purified by crystallization after conversion to the free base form.

Nmr and chemical studies were previously used to establish the structure of lincomycin and 3,4-O-isopropylidenelincomycin (see Figure 1).[4] The lincomycin bis(N-ethylcarbamate) prepared from anisylidenelincomycin and ethyl isocyanate was identical with the lincomycin 2,7-bis(N-ethylcarbamate)[5] prepared from 3,4-O-isopropylidenelincomycin and ethyl isocyanate as shown by identical ir spectra, melting points, and tlc R_f values. The location of the anisylidene moiety is thus at the 3,4 position of lincomycin (see Figure 1).

The asymmetric benzylic carbon introduces the possibility of forming two diastereoisomeric acetal derivatives. The quasi-equatorial phenyl isomer (relative to the sugar ring), as shown in Figure 1, is considered to be the preferred structure of the derivative, and this is in accord with predictions of greater thermodynamic stability for equatorial phenyl-1,3-dioxan derivatives of cyclic sugars.[6] Dreiding models of the quasi-axial phenyl isomer show a 1,3-diaxial interaction and a generally greater steric hindrance than does the quasi-equatorial phenyl isomer.

Four out of the five *para*-substituted O-benzylidene derivatives (II, III, IV, and V) reported herein have

(4) H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Amer. Chem. Soc.*, **86**, 4223 (1964).

(5) D. G. Martin, U. S. Patent 3,271,385 (Sept 6, 1966).

(6) A. B. Foster, A. H. Haines, J. Homer, J. Lehmann, and L. F. Thomas, *J. Chem. Soc.*, 5005 (1961).

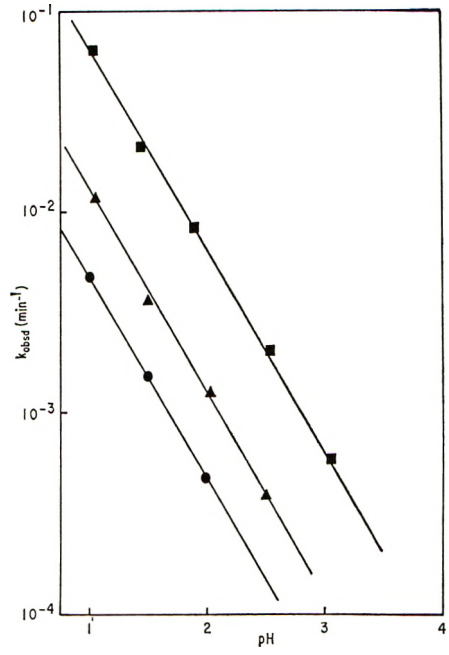


Figure 2.—Plots of log k (min^{-1}) *vs.* pH at 37° and μ = 0.1 for ■, 3,4-O-*p*-toluylidenelincomycin; ●, 3,4-O-(*p*-chlorobenzylidene)lincomycin; ▲, 3,4-O-benzylidenelincomycin.

only one signal in the nmr spectrum at 367 cps for the benzylic proton. Since the acetal moiety of V is at the 3,4 position of lincomycin and has a single benzylic proton signal at 367 cps, II, III, and IV are also at the 3,4 position of lincomycin and have the same stereochemistry about the benzylic carbon. The last compound, *p*-hydroxybenzylidenelincomycin acetal, has a benzylic proton signal at 367 cps and at 352 cps besides additional division of other peaks, which indicates a two-component mixture. One component appears to be the same type of isomer as II, III, IV, and V. The second component could be a diastereoisomer, a positional isomer, or a degradation product.

Differential kinetic analysis[7] of the mixed isomers of *p*-hydroxybenzylidenelincomycin showed the ratio of fast to slow hydrolyzing isomers to be 3:2. Using this ratio 3:2 and the areas under the nmr benzylic proton signals, the slow and fast hydrolyzing isomers can be assigned to the signals at 367 and 352 cps, respectively. Since the 3,4-lincomycin acetals II, III, IV, and V have a benzylic proton signal at 367 cps, it is implied that the slowly hydrolyzing isomer is 3,4-O-(*p*-hydroxybenzylidene)lincomycin. This is also in agreement with the kinetic data (to be shown later) where the second-order rate constant for the slowly hydrolyzing isomer fits the modified Hammett σ^+ correlation, whereas the fast hydrolyzing isomer does not.

Hydrolysis Kinetics of Lincomycin Acetals.—The second-order rate constants for hydrolysis at 37° are given in Table I and the pH-rate profiles in Figures 2 and 3. The pseudo-first-order plots for the acetals II–V were linear for 95% of the reaction. For VI (*p*-hydroxybenzylidenelincomycins) the initial portion of the kinetic plot is curved, but the plot for the last 25% of the reaction is linear. This type of kinetic plot is resolved by the method of residuals[7] (see Figure 4).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, pp 162–164.

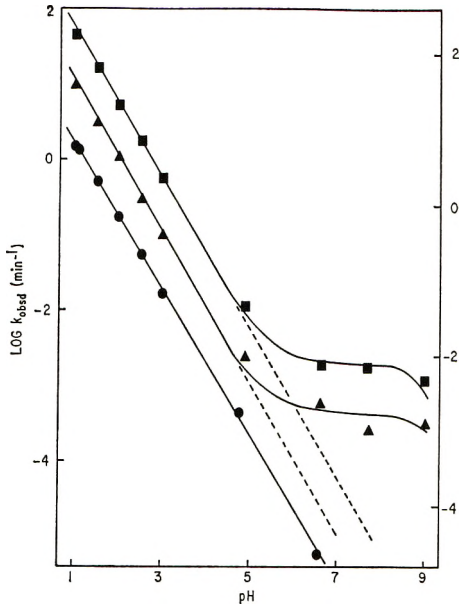


Figure 3.—Plots of log k (min^{-1}) *vs.* pH at 70° and μ = 0.1 for ●, 3,4-O-anisylidenelincomycin (right-hand ordinate scale); ▲, 3,4-O-(*p*-hydroxybenzylidene)lincomycin (left-hand ordinate scale; ■, fast hydrolyzing isomer of *p*-hydroxybenzylidenelincomycin (left-hand ordinate scale).

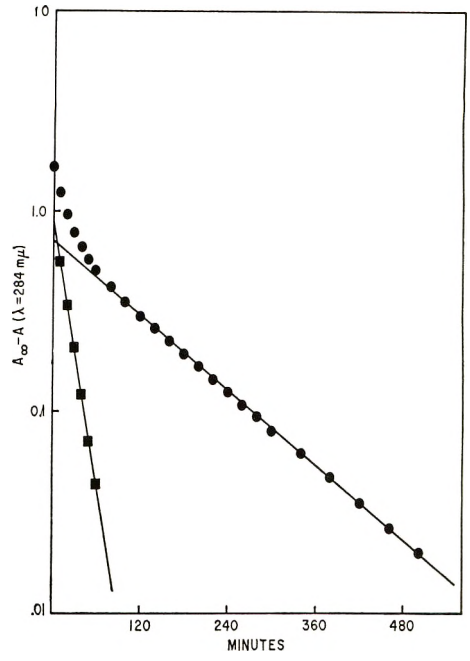


Figure 4.—First-order plot for the hydrolysis of *p*-hydroxybenzylidenelincomycin acetal at 37°, pH = 3.03, and μ = 0.1. The curve is resolved into a two-component system by the method of residuals.

TABLE I

HYDROLYSIS RATE CONSTANTS AT 37° AND μ = 0.1

Compound	Slope of pH-rate profile	Second-order rate constant, sec^{-1} M^{-1}
3,4-O-(*p*-Chlorobenzylidene)lincomycin (II)	−1.04	0.00093
3,4-O-Benzylidenelincomycin (III)	−1.03	0.0024
3,4-O-*p*-Toluylidenelincomycin (IV)	−1.02	0.0120
3,4-O-Anisylidenelincomycin (V)	−0.98	0.0732
p-Hydroxybenzylidenelincomycin (VI)		
3,4-O-Acetal	−1.00	0.127
Fast acetal (isomer of VI)	−0.98	0.813

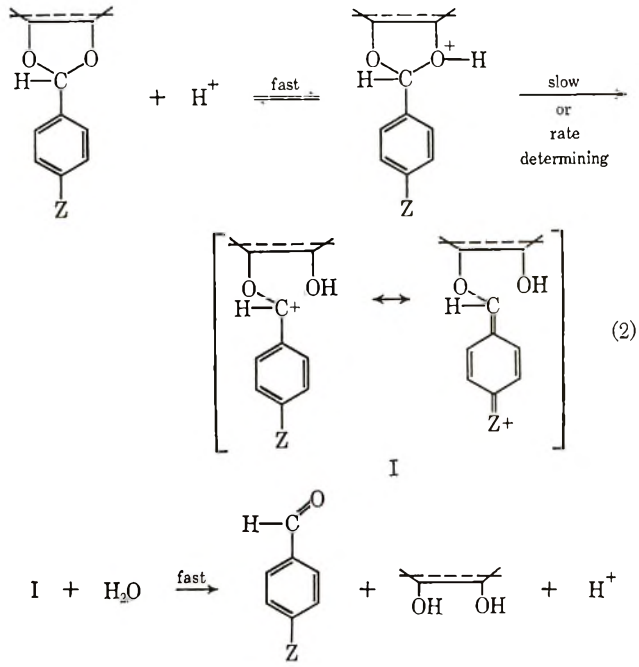
Because of the decreased rate of reaction, the rate constants for 3,4-O-(*p*-hydroxybenzylidene)lincomycin and 3,4-O-anisylidenelincomycin were determined at 70° instead of 37° in the pH range 7–9. To obtain a log k *vs.* pH plot over the whole pH range 1–9, the 37° rate constants were extrapolated to 70° by using linear graphs of ln k vs. $1/T$ for 37, 42, 47, and 55°.

Discussion

Mechanism of Lincomycin Acetal Hydrolysis.—The pH profiles for all the acetals are straight lines with slopes approximately equal to −1 in the pH range 1.0–3.5 at 37° and μ = 0.1 (Figures 2 and 3). In Figure 3 the pH profile is linear over the pH range 1–7 for 3,4-O-anisylidenelincomycin, but for the *p*-hydroxybenzylidenelincomycins the pH profiles deviate from linearity at pH 6, indicating a change in reaction mechanism. The data in the pH range 1–3.5 for the hydrolysis of all the acetals are in agreement with the rate law

$$\text{rate} = \frac{d[\text{acetal}]}{dt} = k[H^+][\text{acetal}] \qquad (1)$$

The generally accepted mechanism for hydrolysis of alkylidene derivatives[8,9] is a rapid, reversible protonation of an acetal oxygen followed by a rate-determining heterolysis to a carbonium ion and an alcohol molecule with rapid decomposition of the carbonium ion to products. A similar mechanism, eq 2, can be written for arylidene acetals. The important difference is that the charge on the carbonium ion is stabilized by resonance with the aryl groups in addition to charge stabilization by the alkoxy group.



(2)

Both the preequilibrium and the rate-determining step in the acetal hydrolysis mechanism 2 should be greatly aided by electron-releasing groups in the alde-

(8) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 3146 (1953).

(9) F. Stasiuk, N. A. Sheppard, and A. N. Bourns, *Can. J. Chem.*, **34**, 123 (1956).

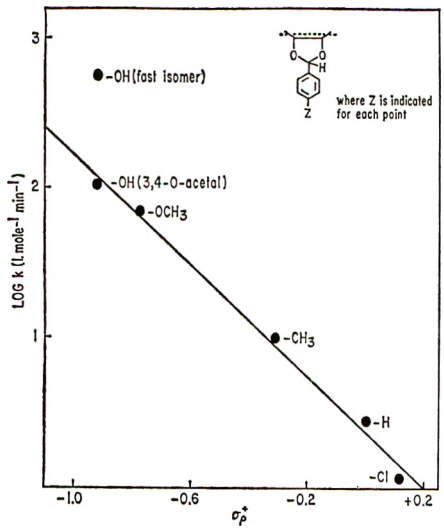
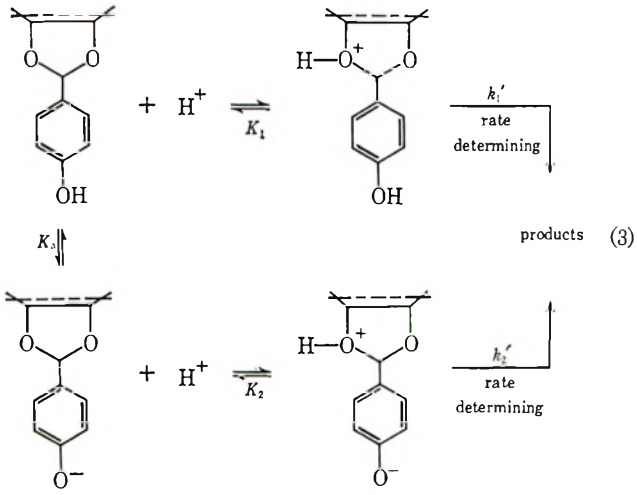


Figure 5.—Semilogarithmic plot of pH-independent rate constants at 70° *vs.* σ_p^+ values for the hydrolysis of lincomycin acetals.

hyde portion of the acetal, which serve to increase the basicity of the acetal and stabilize the carbonium ion intermediate. Since the hydrolysis of the phenolate anion form of *p*-hydroxybenzylidenelincomycin acetal should be extremely rapid, it offers a simple explanation for the deviation from linearity in the pH-rate profiles. Mechanism 3 illustrates the reactions under consider-



ation. If [A] = concentration of acetal, [AH] = concentration of acetal in undissociated form, [A⁻] = [A] − [AH] = concentration of acetal as phenolate anion, K_a, K_1, and K_2 are defined as dissociation constants, and $k_1 = k_1'/K_1$ and $k_2 = k_2'/K_2$, then k_{obsd} is given by eq 4. Since the reversible protonations K_1 or

$$k_{obsd} = \frac{k_1[H^+]}{1 + \frac{K_a}{[H^+]}} + \frac{k_2[H^+]}{1 + \frac{[H^+]}{K_a}} \quad (4)$$

K_2 and the rate-determining heterolysis steps k_1 or k_2 are not presently separable, only rate constants k_1 or k_2, which are functions of both steps, can be determined. Equation 4 fully describes the pH-rate profile for *p*-hydroxybenzylidenelincomycin shown in Figure 3. A similar mechanism was used by Bender and Silver[10] to explain the pH-rate profile for the hydrolysis of 2-*p*-hydroxyphenyl-1,3-dioxanes.

(10) M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **85**, 3006 (1963).

The phenolic ionization constant (K_a) for 3,4-O-*p*-hydroxybenzylidenelincomycin was determined at 70°. in a thermostated Cary cell from spectrophotometric data.[11] The values of k_1 and k_2 for *p*-hydroxybenzylidenelincomycin were calculated using eq 4 and the apparent K_a. They are listed in Table II. In Figure 3 the points for the *p*-hydroxybenzylidenelincomycin acetals are experimental, and the solid line is the calculated curve for eq 4 using the parameters in Table II. In the case of the 3,4-O-anisylidene derivative, the pH-rate profile continues to exhibit linearity as the pH is increased and can be completely described by rate eq 1 as expected for the *p*-methoxy group.

TABLE II

KINETIC CONSTANTS ($sec^{-1}\ M^{-1}$) FOR *p*-HYDROXYBENZYLIDENELINCOMYCINS AT 70° AND μ = 0.1

pK_a = 9.11, 9.01, 8.99; average = 9.04

k_1 (3,4-O-acetal) = 1.72 $sec^{-1}\ M^{-1}$

k_1 (fast acetal) = 9.17 $sec^{-1}\ M^{-1}$

Calculated k_2 using eq 5	pH 6.61	pH 7.69	pH 9.00	Average
k_2 (3,4-O-acetal)	1.01×10^4	4.6×10^3	1.11×10^4	8.6×10^3
k_2 (fast acetal)	3.17×10^4	3.22×10^4	4.90×10^4	3.8×10^4

Modified Hammett σ^+ Correlation.—As mentioned previously, acetal hydrolysis mechanisms 2 and 3 should be greatly aided by electron-releasing groups in the aryl portion of the acetal. To quantitate the effect of electron-donating substituents and support mechanisms 2 and 3, plots of log k *vs* σ^+ values were constructed according to the modified Hammett equation, eq 5. The σ^+ values were taken from ref 12

$$\log k - \log k_0 = \rho\sigma^+ \quad (5)$$

and are given in Table III, along with the second-order rate constants at 70°.

TABLE III

ACTIVATION PARAMETERS, σ_p^+ VALUES AND pH-INDEPENDENT RATE CONSTANTS FOR LINCOMYCIN ACETAL HYDROLYSIS

Compd no.	Phenyl substituent	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu	σ_p^+	k, sec^{-1} M^{-1} at 70°
II	*p*-Cl	19.3	−14.0	+0.114	0.0192
III	*p*-H	18.9	−13.6	0	0.046
IV	*p*-CH_3	16.6	−17.3	−0.311	0.164
V	*p*-OCH_3	17.6	−11.0	−0.778	1.14
VI	*p*-OH (fast acetal)	15.5	−12.9	−0.92	9.17
	p-OH (3,4-O-acetal)	16.4	−12.8	−0.92	1.72
	p-O^- (fast acetal)				3.8×10^4
	p-O^- (3,4-O-acetal)				8.6×10^3

[a] Calculated at 37° with rate constant units of $sec^{-1}\ M^{-1}$.

The pH-independent rate constant for the hydrolysis of the *p*-phenolate anion acetal was estimated at 70°, but its temperature dependence was not determined. Therefore, the pH-independent rate constants for the other *para*-substituent acetals were extrapolated to 70° and used in the modified Hammett σ^+ correlation in Figure 5. The Hammett plot at 70° has the constants $\rho = -1.85$ and $\log k_0 = 0.367$. With these parameters and the rate constant at 70°, a σ_p^+ value of −3.0 can be estimated for the phenolic oxyanion, which reflects its very large electron-donating ability.

The pH-independent rate constants at 70° have correlation coefficients of 0.962 and 0.996 for σ and σ^+

(11) D. H. Rosenblatt, *J. Phys. Chem.*, **58**, 40 (1954).

(12) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 90.

values, respectively. At 37° the correlation coefficients are 0.971 and 0.994 for σ and σ^+, respectively. The higher correlation coefficient for σ^+ indicates a direct resonance interaction between the substituent and the reaction center and that the transition state has carbonium ion character.

The activation parameters are listed in Table III and were calculated by applying eq 6. The adherence of the data to eq 6 is shown in Figure 6. The activation enthalpies are within the range obtained for other acetals.[3] The activation entropies are negative values for the hydrolysis of lincomycin acetals, but comparing the structural effects on the entropy of activation in Table IV one would expect $\Delta S^{\ddagger}$ to be negative and utilize the A-1 reaction.[3,13]

$$k = \frac{\kappa kT}{h} e^{\Delta S^{\ddagger}/R} e^{-\Delta H^{\ddagger}/RT} \qquad (6)$$

TABLE IV
ACTIVATION ENTROPIES FOR HYDROLYSIS OF VARIOUS ACETALS

Compound	$\Delta S^{\ddagger}$,[a] eu
Dimethyl acetal	+13.1[b]
Dimethyl formal	+6.8[b]
Diethyl formal	+6.9[b]
Benzaldehyde diethyl acetal	+1.0[c]
2,2-Dimethyl-1,3-dioxolane	+7.9[d]
2-Methyl-1,3-dioxolane	+5.6[d]
1,3-Dioxolane	−0.6[d]
2,4,4,5,5-Pentamethyl-1,3-dioxolane	−3.8[d]
2-Phenyl-1,3-dioxolane	−8.9[c]
3,4-O-Benzylidenelincomycin	−13.6

[a] Entropies calculated at 25, 30, or 37°. [b] J. Koshikallio and E. Whalley, *Trans. Faraday Soc*, **55**, 809 (1959). [c] See ref 3. [d] P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.* **15**, 871 (1961).

Aryl Acetals as Protective Groups.—Unsubstituted benzylidene acetals are occasionally unsuitable as protective groups owing to acid-catalyzed migration of esters under the conditions required to remove the acetal.[14] The $t_{1/2}$ of the 3,4-O-(*p*-hydroxybenzylidene)lincomycin acetal (VI) is approximately 50 times less than the unsubstituted benzylidene acetal III (Table V). Other workers have shown that certain substituted benzylidene acetals hydrolyze faster than the corresponding unsubstituted benzylidene acetal.[15,16] The present observation, that σ^+ values are directly related to the rates of hydrolysis of the acetals, may facilitate the choice of the proper substituted benzylidene acetal and extend their utility as protective groups.

TABLE V
HALF-LIVES ($t_{1/2}$) OF *para*-SUBSTITUTED 3,4-BENZYLIDENELINCOMYCIN ACETALS AT pH 1.0 AND 37°

Compd no.	$t_{1/2}$, min	σ^+
II	124	+0.114
III	48.1	0.0
IV	9.64	−0.311
V	1.58	−0.778
VI	0.91	−0.92

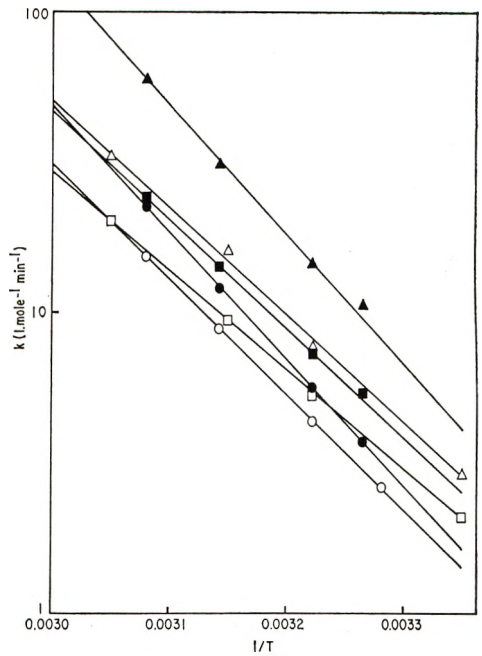


Figure 6.—Arrhenius plots of the second-order pH-independent rate constants for the acidic hydrolysis of ▲, 3,4-O-benzylidenelincomycin (0.01); ●, 3,4-O-(*p*-chlorobenzylidene)lincomycin (0.01); ■, 3,4-O-*p*-toluylidenelincomyin (0.1); ○, 3,4-O-anisylidenelincomycin (1.0); △, 3,4-O-(*p*-hydroxybenzylidene)lincomycin (1.0); □, fast hydrolyzing isomer of *p*-hydroxybenzylidenelincomycin (10.0) (multiply ordinate scale by the numbers in parentheses).

Experimental Section

Table VI records the analytical properties of the lincomycin acetals. The acetals were synthesized by essentially the same procedure as described below in the synthesis of V. Acetals II, III, and IV were isolated as the hydrochloride salts and recrystallized from methyl cellosolve by rapidly cooling a saturated solution of the acetal prepared from hot Methyl Cellosolve. The acetal IV was converted into the free base and chromatographed on a column of Florisil followed by elution with methyl ethyl ketone. The solvent was removed and the compound recrystallized as described below.

For the pK_a determination and the kinetic studies at the alkaline pH's, the two components of *p*-hydroxybenzylidenelincomycin acetal were partially separated by chromatography on a column of carboxymethylcellulose resin with a linear gradient of triethylamine acetate (pH 8) from 0.05 to 0.10 *M*.

3,4-*O*-Anisylidenelincomycin Base (V).—A solution of 47.0 g of lincomycin hydrochloride hemihydrate dissolved in mixture of 125 ml of dimethylformamide, 75 ml of anisaldehyde, and 160 ml of benzene was heated in a bath at 140°. The benzene–water azeotrope was allowed to distil at 105–110° and, upon collecting each 50 ml of distillate, an additional 50 ml of dry benzene was added. Crystallization slowly occurred after 100 ml of distillate was collected and, after an additional 250 ml of distillate was collected, the reaction flask was allowed to cool to room temperature. The pale brown reaction mixture was treated with 200 ml of ether, and the solids were isolated by filtration and washed with ether. The yield of crude white 3,4-O-anisylidenelincomycin–HCl, after drying at 40° under vacuum, was 43.0 g (82% of theory). Tlc (silica gel, acetone–ether 8:2) showed one major spot with trace contaminants of lincomycin and anisaldehyde.

A suspension of 21.0 g of 3,4-O-anisylidenelincomycin–HCl in 150 ml of water was shaken with 15 ml of 2 *N* sodium hydroxide in a separatory funnel. The product was extracted with four 400-ml portions of ether. The ether extracts were combined, dried well with sodium sulfate, and concentrated to 100 ml by

(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(14) M. Smith, O. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Amer. Chem. Soc.*, **84**, 430 (1962).
(15) S. Chladek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).
(16) F. Cramer, W. Saenger, K. H. Scheit, and J. Tennigkeit, *Ann. Chem.*, **679**, 156 (1964).

Table VI

Properties of the *para*-Substituted Benzylidene Derivatives of Lincomycin

Compd no.	Substituent	Formula	Equiv wt Calcd	Equiv wt Found	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % S	Found, % Cl
II	*p*-Cl[a]	$C_{25}H_{38}N_2O_6SCl_2$	567.6	567	53.09	6.77	4.95	5.67	12.54	52.24	7.10	4.65	5.63	11.79
III	*p*-H[a]	$C_{25}H_{39}N_2O_6SCl$	531.1	532	56.53	7.40				55.66	7.59			
IV	*p*-CH_3[a]	$C_{26}H_{41}N_2O_6SCl$	545.1	541	57.28	7.58	5.56	5.88	6.50	56.03	7.76	5.58	5.95	6.31
V	*p*-OCH_3	$C_{26}H_{40}N_2O_7S$	524.6	524	59.53	7.69	5.34	6.10		59.77	7.66	5.34	6.17	
VI	*p*-OH	$C_{25}H_{38}N_2O_7S$	510.7	498	58.80	7.50	5.49	6.28		58.11	7.76	5.42	6.16	

[a] Hydrochloride salts.

distillation. Crystallization was induced with seed crystals. After standing in the refrigerator overnight, the white needlelike crystals were removed by filtration and washed with ether–hexane 1:1. The recovery was 13.2 g after drying at 65° under high vacuum. An additional 4.7 g of product was obtained by adding hexane to the mother liquor giving a total recovery of 17.9 g. Tlc on silica gel G (acetone–ether, 8:2) showed a single compound with R_f 0.8. The compound was recrystallized by dilution of an acetone–ether solution of the compound with hexane.

Kinetic Measurements.—The hydrolysis of lincomycin acetals was followed by observing the appearance of aldehyde in the ultraviolet region of the Cary Model 11 or 15 spectrophotometers. Table VII shows that the progress of the hydrolysis reactions can be followed by observing the appearance of the product spectrophotometrically, since the molar absorptivity of reactant is small compared to that of the product.

In the acidic pH region the rates were fast enough to allow following the complete reaction on the Cary recording spectrophotometer. The Cary 5-cm cell was thermostated to the required temperature within ±0.5°. In the pH region 7–9 the reaction solutions were sealed in ampoules and thermostated in a 70° oil bath for the required times and then assayed on the Cary. The A_∞ values for the 70° runs were calculated from the initial concentration of acetal. The buffers used were chloride for pH 1–3, acetate for pH 3–7, and phosphate for pH 7–9. Potassium chloride was used to adjust the ionic strength to 0.1.

Table VII

Molar Absorptivties of Lincomycin Acetals and Corresponding Aldehydes at the Wavelength of Maximum Absorbance of the Aldehyde

Product	Product, λ_{max}, mμ	a_M (product)	a_M[a] (reactant)
Benzaldehyde	249	11,200	186
p-Chlorobenzaldehyde	260	16,100	247
p-Methoxybenzaldehyde	285	16,800	236
p-Tolualdehyde	262	16,100	275
p-Hydroxybenzaldehyde	284 (pH 1–5)	15,800	500 (pH 1–5)
p-Hydroxybenzaldehyde	330 (pH 9–10)	27,000	400 (pH 9–10)

[a] Molar absorptivity of the lincomycin acetal at λ_{max} of the corresponding aldehyde.

Registry No.—II HCl, 16315-42-7; III HCl, 16315-43-8; IV HCl, 16394-31-3; V, 16315-44-9; VI, 16315-45-0.

Some Structural and Acidity Relationships in Olefinic Carboxylic Acids

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In an attempt to resolve some contradictions between reported experimental data and arguments which relate acidity and structure in β-substituted acrylic acids, the *cis–trans* isomer pairs of β-methyl-, β-ethyl-, β-isopropyl-, β-*t*-butyl-, and β-phenylaerylic acids, and *cis*- and *trans*-2-methylcyclopropanecarboxylic acids were prepared and their dissociation constants were determined by potentiometric titration. The results are shown in Table II. In contrast with earlier reports, the *cis*- and *trans*-β-methylacrylic acids (crotonic acids) have essentially the same dissociation constants. The results remove an inconsistency as to the effect of a *cis*-β-methyl group on the acidity of α,β-olefinic acids, and it is suggested that replacement of a *cis*-β hydrogen by a methyl group results in a decrease in acidity of 0.43–0.44 pK. The general trend in difference of acidity between *cis* and *trans* isomers with increasing size of β substituent is consistent with steric interaction between the *cis*-β substituent and the carboxyl group resulting in an increasing twisting of the carboxyl group out of the olefinic plane.

Attempts to correlate structural features and acidity in carboxylic acids and then interpret the correlations have fascinated chemists over the years. One such correlation, that *cis* isomers of α,β-olefinic carboxylic acids are more acidic than the corresponding *trans* isomers, has been explained by Ingold[2] in terms of steric inhibition of resonance. Thus, "On account of size only we expect a methyl, or a phenyl, or a chlorine substituent, if *cis*-related to the carboxyl group, to cause a twisting of the latter out of the ethylenic plane, and thus to strengthen the acid."[2] That is, the noncoplanarity of the ethylenic and carboxyl groups interferes with the conjugation between these groups which results in destabilization of the acid relative to the corresponding anion, and consequently an increase of acidity. Some doubts about the completeness of this explanation have been raised.[3] Specifically, using published values of acidity constants,[4] it is difficult to see why replacement of a *cis*-β hydrogen by a methyl group should result in ΔpK values of +0.15, +0.43, −0.37, and +0.43 in acrylic acid, *trans*-crotonic acid, methacrylic acid, and *trans*-β-ethylacrylic acid. That is, steric inhibition of resonance, a *cis*-β-methyl group interacting with a carboxyl group, seems to be inadequate to explain acidity changes of different size and even different sign brought about by a constant change in structure. The present work was carried out in order to examine systematically acidity relationships in *cis–trans* pairs of α,β-olefinic carboxylic acids and to use the

(1) Based on the M.S. Thesis of E. A. McCoy.

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 744.

(3) L. L. McCoy and G. W. Nachtigall, *J. Amer. Chem. Soc.*, **85**, 1321 (1963).

(4) Taken from the values compiled in Table II by McCoy and Nachtigall.[3]

results, if possible, to clarify the difficulties indicated for the "steric inhibition of resonance" explanation.

Experimental Section

Materials.—*trans*-Cinnamic acid and *trans*-crotonic acid were commercial materials recrystallized to constant melting point. *cis*-2-Methylcyclopropanecarboxamide which was converted into the corresponding acid by treatment with nitrous acid was supplied by Dr. D. Applequist. All of the other acids were prepared by methods described in the literature. The melting points and boiling points of the acids and references for their preparation are given in Table I. These physical constants were used only to characterize the acids. Purity and isomeric identity were established for the olefinic acids by nuclear magnetic resonance spectra, and for the cyclopropane acids by infrared spectra.[5] The spectra indicated that all of the acids were isomerically pure (<1% isomeric impurity); for the *cis*-alkyl substituted olefinic acids this is in agreement with observations by Rappe and Adestrom[6]. Less than 1% impurity was present in all acids except the *cis*-β-ethyl-, *cis*-β-isopropyl-, and *cis*-β-*t*-butylacrylic acids which were not distilled so as to minimize possibility of isomerization, but in these cases the only impurity (about 4–6%) appeared to be residual amounts of the solvent ether used in their isolation.[6] These spectral results with regard to impurities were confirmed by the titration results.

TABLE I

PHYSICAL PROPERTIES OF SEVERAL α,β-OLEFINIC ACIDS

Acid	Mp, °C	Bp, °C (mm)
cis-$CH_3CH{=}CHCOOH$[a]		42–42.5 (1.9) [80–81 (26)][b]
trans-$CH_3CH{=}CHCOOH$	71.4–71.8 (71.6)[c]	
trans-$CH_3CH_2CH{=}CHCOOH$[d]		64–65 (1.3) [105 (19)][d]
trans-$(CH_3)_2CHCH{=}CHCOOH$[d]		71–73 (1.3–1.4) [113 (20)][d]
trans-$(CH_3)_3CCH{=}CHCOOH$[e]	61–63.5 (62–63°)[e]	
cis-$C_6H_5CH{=}CHCOOH$[f]	64–67.4 (42, 58, 68)[g]	
trans-$C_6H_5CH{=}CHCOOH$	134–134.6 (132.5–133.5)[h]	
cis-1-COOH[i], 2-CH_3		93–95° (22) [91.0–91.5° (14)][i]
trans-1-COOH[i], 2-CH_3		84–85 (8) [90–91 (11)][i]

[a] Reference 6. [b] A. Dadieu, A. Pongratz, and K. W. F. Kohlrausch, *Monatsh. Chem.*, **60**, 211 (1932). [c] "The Merck Index," 6th ed, Merck and Co., Inc., Rahway, N. J., 1952, p 285. [d] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, **130**, 2343 (1928). [e] R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, **72**, 4359 (1950). [f] A solution of *trans*-cinnamic acid in benzene was irradiated with uv light and the resulting *cis–trans* mixture was separated by Faseeh's method [*Pakistan J. Sci. Res.*, **3**, 63 (1951)]. [g] H. Stobbe, *Ann.*, **402**, 187 (1914). [h] C. Paul and W. Hartman, *Ber.*, **42**, 3930 (1909). [i] Reference 5.

Titrations.—Except for minor modifications, *e.g.*, change in volume of acid solution titrated to 10 ml and use of a smaller syringe buret, the titrations were carried out at 25.0° essentially as described in earlier work.[3] Data from these titrations were used to calculate thermodynamic acidity constants[3] which are reported as pK values in Table II.

Discussion

The values shown in Table II lead to a number of conclusions and suggestions. Thus, the pK value for *cis*-crotonic acid determined here is appreciably different from that reported in the literature, but its use removes one of the difficulties which initiated this work. That is, the replacement of the *cis*-β hydrogen in acrylic acid (pK 4.26[4]) by a methyl group to give *cis*-crotonic acid (pK 4.70, this work) gives a ΔpK of +0.44, a value consistent with two of the other cases cited earlier. The reason for the discrepancy between the value reported for *cis*-crotonic acid (pK 4.41[4,7]) and the value determined in this work is not clear. The acid used in the previous work was converted into its sodium salt which was purified; the free acid was liberated from the sodium salt in solution by treatment with hydrochloric acid to obtain the *cis*-crotonic acid free from isomerism in solution.[7] Neither the method of preparation nor the means of determining the purity of the acid, prior to or following purification, are indicated by Larsson and Adell.[7] In the absence of such information, it is suggested that the relatively low pK value reported could be attributed to the presence of a slight excess of hydrochloric acid used in treating the sodium salt or the presence of β-chlorocrotonic acid, a possible precursor of the *cis*-crotonic acid used. We suggest that the reported pK value for angelic acid, also determined by Larsson and Adell,[7] may be incorrect. On the basis that in these compounds under consideration replacement of a *cis*-β hydrogen by a methyl group should produce a constant ΔpK (0.43–0.44), we suggest that the pK for angelic acid should be approximately 5.09.[8]

The pK value for *cis*-crotonic acid observed in this work brings into question the earlier correlation that *cis* acids are stronger than the corresponding *trans* acids. The pK values for the *cis* isomers of both crotonic and β-ethylacrylic acid are, within experimental error, the same as those for the *trans* isomers and it is only with the β-isopropylacrylic acid that a significant difference in pK is apparent. This suggests that in terms of steric effects, the *cis*-β-methyl and *cis*-β-ethyl groups have no more effect on acidity than a *cis*-β hydrogen. It should be noted that the present results for *cis*-crotonic acid remove (invalidate) one of the most frequently cited examples of *cis* acids being stronger than the isomeric *trans* acids.

In spite of this correction, the ΔpK values in Table II clearly show the trend that as the size of the *cis*-β substituent increases the *cis* isomer becomes increasingly more acidic than the *trans* isomer. The ΔpK values differ in a manner similar to the conformational free-energy differences between axial and equatorial orientation for these substituents attached to cyclohexane. This suggests that the substituent interaction with the carboxyl group in the acids is essentially the same as it

(5) Reproductions of the infrared spectra of the cyclopropane compounds were sent to us by Dr. Applequist. A method of isomeric analysis using the infrared spectra has been reported: D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **82**, 2372 (1960).

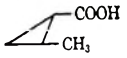
(6) C. Rappe and R. Adestrom, *Acta Chem. Scand.*, **19**, 383 (1965).

(7) E. Larsson and B. Adell, *Z. Phys. Chem.* (Leipzig), **A159**, 315 (1932).

(8) (a) We believe this constant ΔpK value for a *cis*-β-methyl group will hold only so long as there is no appreciable steric interaction between ethylenic substituents located *trans* to the carboxyl group. However, where such interaction does occur, a buttressing effect may result which in turn may cause the *cis*-β-methyl group to interact more strongly with the carboxyl group. Thus, ΔpK for the tiglic acid–trimethylacrylic acid pair may be appreciably less than the 0.43–0.44 range indicated by the acid pairs considered in this work. (b) The value 5.09 is our suggested value only if the methacrylic acid pK value of 4.66 is correct. This value, determined also by Larsson and Adell,[7] used acid for which no data concerning preparation or purity was cited. For reference purposes, we feel the pK of methacrylic acid also should be redetermined. (c) This value of 0.43–0.44 is the same as that suggested by Branch and Calvin ("The Theory of Organic Chemistry," Prentice-Hall Co., Inc., New York, N. Y., 1946, pp 237–238) for the effect of β-alkyl groups (*cis* or *trans*) on acidity constants.

Table II

The Acid Dissociation Constants (pK) of Several α,β-Olefinic Carboxylic Acids at 25.0°

No.[h]	Acid	pK_{trans}	pK_{cis}	ΔpK
1	$CH_3CH{=}CHCOOH$	4.74 ± 0.02 (4.69,[a] 4.71,[b] 4.71,[c] 4.69,[d] 4.71[e])	4.70 ± 0.01 (4.41[f])	0.04
2	$CH_3CH_2CH{=}CHCOOH$	4.74 ± 0.02 (4.69[a])	4.70 ± 0.02	0.04
3	$(CH_3)_2CHCH{=}CHCOOH$	4.75 ± 0.02 (4.70[a])	4.63 ± 0.03	0.12
4	$(CH_3)_3CCH{=}CHCOOH$	4.88 ± 0.02	4.12 ± 0.02	0.76
5	$C_6H_5CH{=}CHCOOH$	4.50 ± 0.01 (4.44[g])	3.93 ± 0.02 (3.88[g])	0.57
6		5.00 ± 0.02	5.02 ± 0.01	−0.02

[a] D. J. G. Ives, R. P. Linstead, and H. L. Riley, *J. Chem. Soc.*, 561 (1933). [b] B. Saxton and G. W. Waters, *J. Amer. Chem. Soc.*, **59**, 1048 (1937). [c] E. Larsson and B. Adell, *Z. Phys. Chem.* (Leipzig), **A157**, 342 (1931). [d] W. L. German, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [e] L. Otvos and F. Sirokman, *Acta Univ. Szeged., Acta Phys. Chem.*, **2**, 118 (1956); pK determined at 18°. [f] Reference 7. [g] F. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.*, 1008 (1937). [h] Registry no.: 1 (*trans*), 107-93-7, (*cis*), 503-64-0; 2 (*trans*), 13991-37-2, (*cis*), 16666-42-5; 3 (*trans*), 16666-43-6, (*cis*), 1775-44-6; 4 (*trans*), 16666-45-8, (*cis*), 1577-94-2; 5 (*trans*), 140-10-3, (*cis*), 102-94-3; 6 (*trans*), 6202-94-4, (*cis*), 6142-57-0.

is with the axial hydrogens in cyclohexane, *i.e.*, their steric effectiveness is a function of their conformational orientation and not their gross size.[9] An increased twisting of the carboxyl group relative to the ethylenic bond as the effective size of the substituent increases and a consequent increase in "steric inhibition of resonance" is consistent with the ΔpK values observed.[10]

In the sense that, at a maximum, the carboxyl group can be twisted perpendicular to the ethylenic plane, we expect that the effect of substituents on the relative acidity of *cis* and *trans* pairs should reach a maximum with increasing effective size of the *cis*-β substituent. With further increases in size, the *cis*-β substituent should begin to hinder solvation of the carboxyl group,[11] and we would expect a gradual decrease in the difference of acidity between *cis* and *trans* isomers.

The cyclopropane compounds were examined with the initial thought that a *cis*-2 substituent would restrict the carboxyl group to an orientation approaching perpendicular to the cyclopropane ring; such an orientation should enhance the conjugation of the cyclopropane ring and the carboxyl group, and thus *decrease* the acidity of the *cis* isomer relative to the *trans*. Unfortunately, the results do not permit any definite conclusion, *i.e.*, the methyl group might be of inadequate size to restrict the carboxyl group (see discussion of the crotonic acids), or the carboxyl group might already be restricted by conjugation in the *trans* case.

Acknowledgment.—We wish to thank the National Science Foundation for support of part of this work. We also want to thank Mr. Bruce Smart for purifying the *trans* isomers of crotonic and cinnamic acids.

(9) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 44, 45.

(10) Recently [J. Steigman and D. Sussman, *J. Amer. Chem. Soc.*, **89**, 6406 (1967)], an alternative to the "steric inhibition of resonance" explanation for the increased acidity of *ortho*-substituted benzoic acids relative to benzoic acid has been presented. This alternate "solvent structure" explanation also has as its starting point the twisting of the carboxyl group out of the plane of the benzene ring. To the extent that the π system of an olefin can affect solvent structure analogously to the π system of a benzene ring, this explanation would be applicable to the present compounds.

(11) G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).

Reaction of Certain Electrophiles with Some Imines Derived from Cyclohexanone and Isobutyraldehyde[1]

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Acid chlorides and alkyl and aryl isocyanates and isothiocyanates were allowed to react with imines derived from cyclohexanone and isobutyraldehyde. A variety of N-(1-alkenyl)amides (**2**, **8**), N-(1-alkenyl)ureas and thioureas (**3**, **5**, **12**), 2-enaminocarbamides (**4**, **6**), and triazinones (**11**) were formed and isolated as reaction products, depending upon the nature of the imine, type of electrophile, and reaction conditions. The results are compared with the reported work on the reaction of these reagents with N,N-disubstituted enamines from the same carbonyl compounds. The products can be rationalized as arising from three possible modes of attack by the electrophile on the imine: (1) nitrogen attack, with α-hydrogen elimination; (2) α-carbon attack, and (3) C=N attack followed by ring formation.

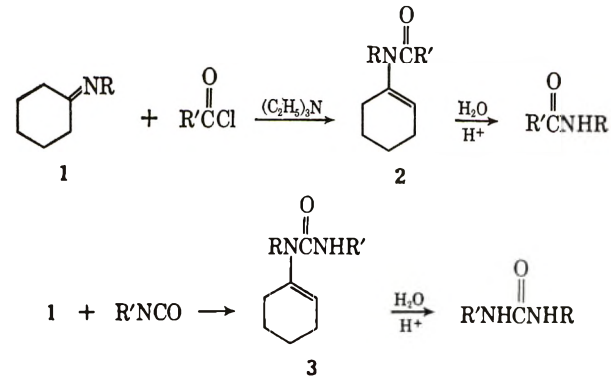
The imines of cyclohexanone and isobutyraldehyde are for the most part easily prepared[2] and, unlike many aliphatic imines, not subject to rapid polymerization and condensation reactions. We wished therefore to compare the behavior of the imines of these two carbonyl compounds toward certain electrophiles with those reported for the corresponding enamines. In the latter instance, it was shown that final substitution products with various acid chlorides,[3] isocyanates,[4] and the like involved electrophilic substitution on the olefinic carbon α to the carbon bearing the enamino nitrogen.

It would be anticipated that the imines could react by at least three possible modes. Imines, having a reactive carbon bearing a labile hydrogen (enolizable imines), such as those derived from cyclohexanone and isobutyraldehyde, could be expected to form products arising from acid chloride or isocyanate attack at the α position in exact analogy to results reported for the enamines. Alternatively, these electrophilic reagents could irreversibly react at the imino nitrogen and through loss of α hydrogen give stable enamides or enureas. Finally, the imines could react at the C=N bond to form cyclic products in analogy to reaction of isocyanates with aromatic Schiff bases or methylene imines.[4b,5]

The literature contains some work relative to reaction of these electrophiles with imines containing enolizable hydrogen. Thus, N-alkyl-N-alkenylamides are formed by the action of certain acid halides on aldimines.[6] On the other hand, it is reported that ketimines (from cyclohexanone) give carbon acylated products.[7] Studies on the effect of isothiocyanates and isocyanates on acetophenone anil indicate that only α-carbon attack occurs. Anils of benzoylthioacetanilide and benzoylmalonanilides, respectively, were isolated.[8]

It was found that when N-alkyl-N-cyclohexylidenamines were allowed to react with various acid chlorides or isocyanates, neutral N-acylated enamides (**2**) and enureas (**3**) could be isolated in fair yields (Scheme I).

SCHEME I



(See Table I for compilation and structure of compounds.) Anils of cyclohexanone showed no evidence of giving enureas with isocyanates but, rather, α-carbon attack occurred with formation of the 3′,4′-dichloro-2-(*p*-chloroanilino)-1-cyclohexene-1-carboxanilide (**4**). Structures were confirmed by elemental and spectral analysis with further confirmation by hydrolysis to known amides or ureas.[9]

Reaction of **1** with isothiocyanates was more complicated. Alkyl isothiocyanates gave cyclohexenylthioureas which on attempted distillation reverted to **1** and isothiocyanate. Certain arylisothiocyanates initially form **5**, but on heating rearrange to the vinylogous thiourea **6**, perhaps as a result of reversible thermal dis-

(1) Presented before the Division of Organic Chemistry at the First Midwest Regional Meeting, American Chemical Society, Kansas City, Mo., Nov 5, 1965, Abstract No. 440.

(2) (a) W. F. Bruce and R. N. Blomberg, U. S. Patents 2,700,681 and 2,700,682 (1955); (b) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967); (c) K. L. Campbell, A. G. Sommers, and B. K. Campbell, *J. Amer. Chem. Soc.*, **66**, 82 (1944).

(3) (a) A. Stork and H. K. Landesmann, *ibid.*, **78**, 5128 (1956); (b) S. Hunig, *Chem. Ber.*, **90**, 2833 (1957), and succeeding papers.

(4) (a) S. Hunig, *Angew. Chem.*, **71**, 312 (1959); (b) D. Clemens and W. Emmons, *J. Org. Chem.*, **26**, 767 (1961); (c) G. Berchtold, *ibid.*, **26**, 3043 (1961); (d) M. Perelman and S. A. Mizak, *J. Amer. Chem. Soc.*, **84**, 4988 (1962).

(5) (a) R. Huisgen, K. Herbig, and M. Morikgwa, *Chem. Ber.*, **100**, 1107 (1967); (b) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press Inc., New York, N. Y., Chapters 4 and 5.

(6) H. Breederveld, *Rec. Trav. Chim.*, **79**, 401 (1960).

(7) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963); see also V. E. Harvey, El Cerrito, and S. A. Ballard, U. S. Patent 2,418,173 (1947), and British Patent 638,091 (1950) [*Chem. Abstr.*, **41**, 4510 (1947); **44**, 9476 (1950)]. However, at least some N acylation apparently occurs because N-cyclohexylhexanamide was obtained after hydrolysis of the reaction mixture from N-cyclohexylidenecyclohexylamine and caproyl chloride. The intermediate acyl enamide was not fully characterized. A. A. Brizzolara, Jr., "An Investigation of Some Reactions of Enamines," Columbia University, Ph.D. Thesis, 1960.

(8) J. Moszew, A. Inasinski, K. Kubiczek, and J. Zawrzykraj, *Rocz. Chem.*, **34**, 1169 (1960); *Chem. Abstr.*, **55**, 1533a (1961).

(9) Thus, the possibility that the isocyanate–imine adducts are 4-amino-2-azetidinones[4d] rather than enureas (**3**, **12**) is ruled out by consideration of the ir 6.0 μ (C=O), nmr δ 5.8 (C=C**H**), and facile hydrolysis to 3-alkylureas. The β-lactams display ir 5.7 μ (C=O), nmr, δ 4.4–5.3 (Cβ-**H**), and hydrolyze to carboxamides similar to **10**. Spectral evidence, especially ir 6.0 μ (C=N, C=O), and nmr, δ 7.5–7.8 (C**H**=N), also serve to differentiate iminoanilide (**9**) from the alternate β-lactam structure.

TABLE I

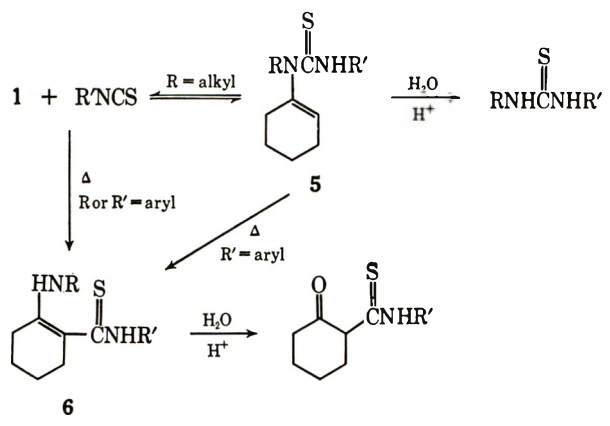
REACTION OF ELECTROPHILES WITH IMINES FROM CYCLOHEXANONE AND ISOBUTYRALDEHYDE

Compd	R	R′	X	Yield, %	Mp or bp (mm), °C	Calcd, % C	H	Cl	N	S	Mol wt	Found, % C	H	Cl	N	S	Mol wt	Pertinent nmr (CCl_4), δ
2a	CH_3	$2,4\text{-}Cl_2C_6H_3OCH_2$	O	61	107–108	57.33	5.45	22.57	4.46			57.21	5.55	22.64	4.39			5.7 (m, =CH) 3.0 (s, NCH_3)
2b	$(CH_3)_2CH$	$ClCH_2$	O	32	50–51			16.44	6.49					16.54	6.34			5.7 (m, =CH)
3a	CH_3	CH_3	O	95	65 120–130 (1)	64.25	9.59		16.65		168	64.14	9.53		16.56		160	5.6 (m, =CH, NH) 2.6 (d, $NHCH_3$) 2.9 (s, NCH_3)
3b	CH_3	$3,4\text{-}Cl_2C_6H_3$	O	74	Oil	56.19	5.39		9.36			55.57	5.41		9.36			5.9 (m, =CH) 2.9 (s, NCH_3)
3c	CH_3	$2\text{-}(NO_2)C_6H_4$	O	90	120.5–122	61.07	6.22		15.26			60.87	6.24		15.61			5.9 (m, =CH) 3.0 (s, NCH_3)
4				70	147–150	57.66	4.33	26.88	7.08			58.01	4.18	26.85	7.05			11.8 (m, $4\text{-}ClC_6H_4NH$)
5a	CH_3	C_2H_5	S	86	43–44				14.13	16.17					14.15	15.86		6.0 (m, NH) 5.7 (m, =CH) 3.3 (s, NCH_3)
5b	CH_3	$3,4\text{-}Cl_2C_6H_3$	S	85	107–108	55.33	5.12	22.49	8.89	10.17	315	53.30	5.06	22.50	8.87	10.04	297	5.9 (m, =CH) 3.4 (s, NCH_3)
5c	$n\text{-}C_4H_9$	$3,4\text{-}Cl_2C_6H_3$	S	92	95–96	57.13	6.20		7.84	8.97	357	56.50	6.12		7.89	9.16	363	5.8 (m, =CH)
6a	CH_3	$3,4\text{-}Cl_2C_6H_3$	S	57	160–161	53.33	5.12	22.49	8.89	10.17	315	53.37	5.13	22.47	8.83	10.14	323	12.8 (m, CH_3NH) 2.9 (d, NCH_3)
6b	$n\text{-}C_4H_9$	$3,4\text{-}Cl_2C_6H_3$	S		140–141	57.13	6.20		7.80	8.97		57.32	6.21		7.80	8.97		12.9 (m, C_4H_9NH)
6c	$4(CH_3)C_6H_4$	$3,4\text{-}Cl_2C_6H_3$	S	67	153–154	61.38	5.15	18.12	7.16	8.19		61.42	5.21	17.98	6.99	8.15		13.6 (m, *p*-tolyl-NH)
8				48	50–51.5	59.54	7.99	17.58	6.94			59.41	7.88	17.73	7.03			*a*
9a	$(CH_3)_2C{=}CH$	$3,4\text{-}Cl_2C_6H_3$	O	91	90–95	57.52	5.79	22.64	8.94			57.53	5.80	22.64	8.94			*a*
9b	$(CH_3)_2C$	$3,4\text{-}Cl_2C_6H_3$	O	78	62–64	57.15	6.39	22.49	8.89			57.22	6.46	22.53	8.90			11.1 (s, NH) 7.6 (s, CH=N) 1.28 [s, $C(CH_3)_2$]
11a	CH_3	$4\text{-}ClC_6H_4$	O	80	Oil	63.04	8.09		12.97		324	62.68	8.05		12.81		321	*a*
11b	C_2H_5	$3,4\text{-}Cl_2C_6H_3$	O	93	110–113	59.1	7.52	18.4	10.9		386	58.90	7.37	18.53	10.6		393	*a*
12a	CH_3	$4\text{-}ClC_6H_4$	O	96	78–82	60.37	6.33	14.85	11.74		239	60.56	6.14	14.58	11.57		240	5.8 (m, =CH) 2.9 (s, NCH_3) 1.7, 1.8 [$=C(CH_3)_2$]
12b	$(CH_3)_2CH$	$3,4\text{-}Cl_2C_6H_3$	O		80–81	55.82	6.02	23.54	9.30		301	55.91	5.63	23.55	9.15		305	5.8 (m, =CH) 1.7, 1.9 [$=C(CH_3)_2$] 1.1 [d, $CH(CH_3)_2$]
12c	$(CH_3)_2CH$	$3,4\text{-}Cl_2C_6H_3$	S	80	115			22.35	8.83		317			22.21	8.56		333	5.9 (m, =CH) 1.7, 1.9 [$=C(CH_3)_2$]

[a] See Experimental Section.

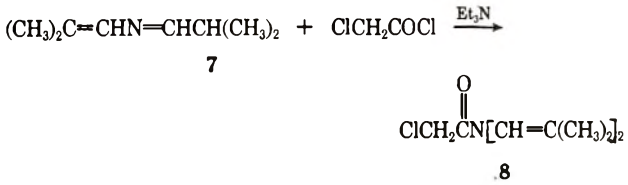
sociation to starting isothiocyanate and imine, followed by irreversible formation of **6** (Scheme II).[10]

SCHEME II

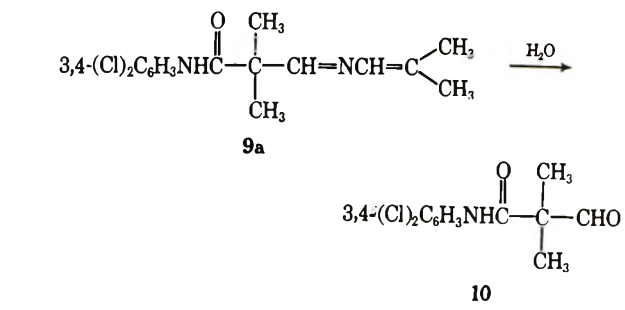


In contrast to **1**, anils of cyclohexanone with isothiocyanates gave only 2-anilino-1-cyclohexenthiocarboxamides (**6**). The anils thus behave similarly to those described in ref 8.

The structure of the imine from isobutyraldehyde largely determined the mode of attack of the various electrophiles. **7** is both an imine and enamine and its reaction with chloroacetyl chloride gave **8**. This reaction represents an extension of Brederveld's method[6]



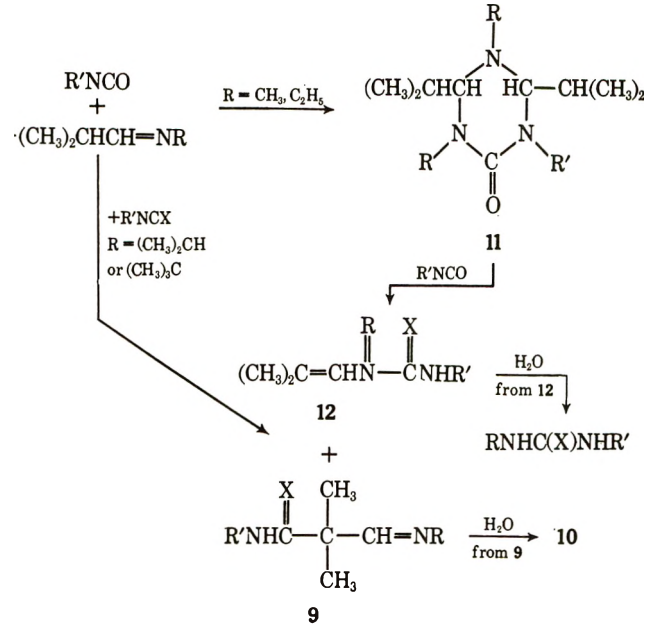
for the preparation of N,N-dialkenylamides. Reaction of isocyanate with **7** does not give dialkenylurea, but rather reaction occurs at the α carbon to produce **9a**.



The amidic proton is seemingly hydrogen bonded with the imino nitrogen as evidenced by the unusually low absorption of this proton in the nmr, δ 10.3–10.6 (see NH, **9a**, **9b**).

N-Isobutylidene-N-methylamine reacts with isocyanates at room temperature to form triazinones (**11**), in analogous fashion to that found for certain imines possessing no α hydrogen.[4a,5] However, further reaction of **11** with isocyanate gives alkenylureas (**12**), possibly through electrophilic attack of isocyanate on the basic ring nitrogen, followed by ring opening *via* α-hydrogen elimination. N-Ethyl-N-isobutylidenamine behaves similarly, although anilide (**9**) is found to some extent [determined by nmr measurement of the ratio $(CH_3)_2C{=}C$ (from **12**) to $-C(CH_3)_2-$ (from **9**)]. N-Isopropylisobutylidenamine with greater bulk than the N-methyl or -ethyl homologs gives, with isocyanates on heating, a mixture of alkenylurea (**12**) and anilide (**9**) in a ratio of approximately 3:2. No apparent triazinone formation was observed. Curiously, 3,4-dichlorophenyl isothiocyanate on heating with N-isopropylisobutylidenamine gave only **12** and no **9**. Finally, N-*t*-butylisobutylidenamine gave only **9** with isocyanate (Scheme III).

SCHEME III



Experimental Section

All melting points were taken on a Fisher-Johns block. All microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tenn. Ir spectra were determined on a Beckman IR-Va and nmr spectra on a Varian Model A-60 spectrometer with chemical shifts reported in parts per million from tetramethylsilane as an internal standard.

Imines Derived from Cyclohexanone and Isobutyraldehyde.—The preparation of these materials have been previously described.[2a,b,11]

Materials 2a,b.—The preparation of these materials from the respective N-alkylcyclohexylidenamine[3a] and acid chloride can be illustrated by the preparation of **2a**.

N-(1-Cyclohexen-1-yl)-2-(2,4-dichlorophenoxy)-N-methylacetamide (2a).—2,4-Dichlorophenoxyacetyl chloride (35.0 g, 0.146 mol) was placed in 200 ml of benzene, cooled to 0–5°, and N-methylcyclohexylidenamine (16.7 g, 0.15 mol) contained in 100 ml of benzene was added dropwise, with cooling. After addition the mixture was stirred for 15 min; then triethylamine (15 g, 0.15 mol) was added dropwise at 0–5°. After addition, the reaction mixture was refluxed for 1 hr. The reaction mixture was filtered, the salt cake was washed with benzene, and the combined filtrate and washings were washed twice with *ca.* 200 ml of water. After drying over anhydrous magnesium sulfate and subsequent removal of solvent under vacuum, the residue was recrystallized twice (charcoal) from hexane.

1-(1-Cyclohexen-1-yl)-1,3-dimethylurea (3a).—N-Methylcyclohexylidenamine (15.7 g, 0.14 mol) was dissolved in 200 ml of toluene, and to this solution methyl isocyanate (8.4 g,

(10) Thermal dissociation has also been observed in certain enureas derived from 2-phenylpyrroline by S. J. Love and J. A. Moore, *J. Org. Chem.*, **33**, 2361 (1968).

(11) R. H. Hasek, E. U. Elam, and J. C. Martin, *ibid.*, **26**, 1822 (1961).

0.14 mol) was added at room temperature. The reaction was exothermic, with the temperature rising to 35°. After standing for 2 hr at ambient temperature, solvent was removed and the oily residue distilled at 120–130° (1 mm) to give 7 g of oil, which later solidified. This material was recrystallized from cold hexane. A second preparation afforded a 95% yield of oil, which solidified on seeding.

1-(Cyclohexen-1-yl)-3-(3,4-dichlorophenyl)-1-methylurea (3b).—N-Methylcyclohexylidenamine and 3,4-dichlorophenyl isocyanate (0.1 mol each) reacted exothermally in toluene at room temperature to give, upon removal of solvent, 22 g of light yellow oil which did not crystallize.

1-(1-Cyclohexen-1-yl)-3-(2-nitrophenyl-1)methylurea (3c).—In similar manner to the preparation of **3a** and **3b**, 2-nitrophenyl isocyanate with N-methylcyclohexylidenamine gave yellow crystals from ethanol.

Materials 5a–c.—The reactions of isothiocyanates with N-alkylcyclohexylidenamines, carried out in toluene or benzene at room temperature, were mildly exothermic. Several hours were usually required for complete disappearance of isothiocyanate as monitored by ir. Upon removal of solvent, the residue was purified by suitable recrystallization. However, care was taken with products arising from aryl isothiocyanates not to expose them to heat; recrystallization from cold (−10°) concentrated toluene or ether solution was found necessary to prevent rearrangement. The preparation of **5a** and **5b** are representative of the procedures used to make these materials.

1-(1-Cyclohexen-1-yl)-3-ethyl-1-methyl-2-thiourea (5a).—N-Methylcyclohexylidenamine (11.1 g, 0.1 mol) and ethyl isothiocyanate (8.7 g, 0.1 mol) reacted at room temperature to give, after removal of solvent, 17 g of an oil which later crystallized, mp 43–44°. On distillation of some of the oil, fractions were collected at 45–55° (10 mm) which was shown by ir to contain isothiocyanate and imine. Upon standing, **5a** was again formed from the distillate.

1-(1-Cyclohexen-1-yl)-3-(3,4-dichlorophenyl)-1-methyl-2-thiourea (5b).—N-Methylcyclohexylidenamine (10.3 g, 0.094 mol) was dissolved in 100 ml of toluene and at room temperature 3,4-dichlorophenyl isothiocyanate (19.1 g, 0.094 mol) was added dropwise. After standing several hours crystals formed, mp 107–108°. By partial evaporation of the toluene in the cold (−10°), 24.5 g of crystals, mp 107°, was obtained. **5b**, upon melting at 107°, resolidified and melted again at 135–140°.

Materials 6a,b.—These materials could be prepared directly from the appropriate aryl isothiocyanate and N-alkyl-N-cyclohexylidenamine by reacting equimolar amounts of these reagents in refluxing toluene or alcohol for several hours, followed by removal of solvent and recrystallization of the solid residue from hot alcohol. A small amount of 1-aryl-3-alkyl-2-thiourea derived from the respective aryl isothiocyanate was found as by-product. Alternatively, **5** (R′ = aryl) was dissolved in anhydrous ethanol, heated for several minutes at reflux, and **6** collected as crystals upon cooling.

3′,4′-Dichlorothio-2-*p*-toluidino-1-cyclohexene-1-carboxanilide (6c).—To 12 g of 3,4-dichlorophenyl isothiocyanate dissolved in tetrachloroethylene was added dropwise an equimolar amount of N-cyclohexylidene-*p*-toluidine. No appreciable exotherm was noticed, and, to cause the isothiocyanate to react, the material was heated to 70° for 3 hr. Crystals formed, and upon cooling 15.7 g of solid was isolated by filtration. Recrystallization from ethanol afforded product.

3′,4′-Dichloro-2-(*p*-chloroanilino)-1-cyclohexene-1-carboxanilide (4).—To 10.3 g of N-cyclohexylidene-*p*-chloroaniline contained in toluene was added an equimolar amount of 3,4-dichlorophenyl isocyanate dissolved in toluene. To cause disappearance of isocyanate (as monitored by ir), the material was refluxed for several hours, and after removal of toluene the solid remaining recrystallized from ethanol.

2-Chloro-N,N-bis(2-methylpropenyl)acetamide (8).—The procedure given above describing the preparation of **2a** was used. Upon distillation the product was collected at 97–108° (1 mm). The oil was recrystallized from hexane three times to give 47.5% yield of crystals: nmr (CCl_4), δ 1.57 (s, 6, $=CCH_3$), 1.74 (d, 6, J = 1 Hz, CCH_3), 3.95 (s, 2, $ClCH_2$), and 5.95 (m, 2, $=CH$).

[2-(3,4-Dichlorocarbaniloyl)-2-methylpropylidene]-(2-methylpropenyl)amine (9a).—3,4-Dichlorophenyl isocyanate (18.8 g, 0.1 mol) and 0.1 mol of N-isobutylidene-N-(2-methyl-1-propenyl)amine (**7**) were both dissolved in 100 ml of toluene; 0.25 ml of triethylamine was added. The mixture was refluxed for 8 hr, after which no isocyanate remained in the mixture. Upon removal of solvent, the residue recrystallized from hexane twice (charcoal), afforded white crystals: ir (CCl_4) 6.0 μ (C=O); nmr (CCl_4), δ 1.45 [s, 6, $C(CH_3)_2$], 1.83, 2.06 [2 s, 6, $=C(CH_3)_2$], 7.6 (s, 1, CH=N), and 10.3 [s (broad), 1, C(O)NH].

1-(*p*-Chlorophenyl)tetrahydro-4,6-diisopropyl-3,5-methyl-*s*-triazin-2(1H)-one (11a).—This material was prepared by reacting in benzene at room temperature a 2:1 mole ratio of N-isobutylidene-N-methylamine[12] with *p*-chlorophenyl isocyanate. Vacuum removal of solvent gave an oil: ir (CCl_4) 6.0 μ (C=O); nmr (CCl_4), δ 0.56–1.11 [4 d, 12, J = 7 Hz, $CH(CH_3)_2$], 2.32 (s, 3, C_2NCH_3), 2.90 (s, 3, $CNCH_3$ C=O), 3.70 (d, 1, J = 7 Hz, CHCHN), and 4.18 (d, 1, J = 7 Hz, CH–CHN).

1-(3,4-Dichlorophenyl)tetrahydro-4,6-diisopropyl-3,5-diethyl-*s*-triazin-2(1H)one (11b).—This material was prepared by adding 0.2 mol of N-isobutylidene-N-ethylamine in ether to 0.1 mol of 3,4-dichlorophenyl isocyanate, dissolved in ether. After standing at room temperature several hours, the material was vacuum treated at room temperature to give 36.1 g of viscous oil which solidified on standing. Recrystallization was effected at room temperature from ether–pentane to give **11b**: ir (CCl_4) 6.0 μ (C=O); nmr (CCl_4), δ 3.7 (d, 1, J = 7 Hz, CHCHN), 4.3 (d, 1, J = 7 Hz, CH–CHN), 1.7–3.5 [m, 4, CH_3CH_2N and m, 2 $CH(CH_3)_2$], and 0.5–1.3 [d and t, 18, J = 7 Hz, $(CH_3)_2CH$ and CH_3CH_2].

3-(*p*-Chlorophenyl)-1-methyl-1-(2-methylpropenyl)urea (12a).—N-Isobutylidene-N-methylamine (10.3 g, 0.12 mol) was heated for *ca.* 1 hr in refluxing chlorobenzene with an equimolar amount of *p*-chlorophenyl isocyanate until no isocyanate remained in the mixture (as measured by ir). The material isolated after evaporation of solvent was an amber oil which was further purified by recrystallization from cold hexane to give pure **12a**: ir (CCl_4) 6.0 μ (C=O).

3-(3,4-Dichlorophenyl)-1-isopropyl-1-(2-methylpropenyl)urea (12b).—N-Isobutylidene-N-isopropylamine and 3,4-dichlorophenyl isocyanate (0.1 mol each) were mixed together and refluxed in 100 ml of tetrachloroethylene for 1 hr. After evaporation of the solvent, residual oil remaining was shown by nmr spectroscopy to have, in addition to spectral assignments for **12b** (see Table I), the following additional peaks for groups in compound [2-(carbaniloyl)-2-methylpropylidene]isopropylamine (**9**): nmr (CCl_4), δ 1.30 [d, 6, J = 7 Hz, $CH(CH_3)_2$] and 1.43 [s, 6, $C(CH_3)_2$]. The crude oil contained a ratio of **12b**:**9** as determined by nmr of *ca.* 3:2. Hydrolysis of a portion of the crude oil with hot 18% HCl gave a solid which upon recrystallization from methylcyclohexane gave **10** (identified by mixture melting point and ir). The solid remaining undissolved in hot methylcyclohexane was shown after recrystallization from aqueous ethanol to be 3-isopropyl-1-(3,4-dichlorophenyl)urea, mp 205°, as determined by mixture melting point and identical ir with those of an authentic sample. Elution of the bulk of the crude oil through a silicic acid column with carbon tetrachloride followed by recrystallization from cold hexane gave pure **12b**: ir (CCl_4) 6.0 μ (C=O).

3-(3,4-Dichlorophenyl-1-isopropyl-1-(2-methylpropenyl)-2-thiourea (12c).—This material was obtained in analogous fashion to that for **12a**. There was no gross contamination of the crude as measured by nmr, and the crude oil solidified and was easily recrystallized from ethanol.

[2-(3,4-Dichlorocarbaniloyl)-2-methylpropylidene]-*t*-butylamine (9b).—3,4-Dichlorophenyl isocyanate (37.6 g, 0.2 mol), dissolved in *ca.* 50 ml of chlorobenzene was added to N-(2-methylpropylidene)-N-*t*-butylamine (25.4 g, 0.2 mol) contained in 100 ml of chlorobenzene. Reflux for *ca.* 30 min was necessary to cause complete reaction of the isocyanate. Upon removal of solvent, the residue (essentially all **9b** as indicated by nmr spectra) solidified and was recrystallized from cold pentane to give 48.9-g yield of white crystals **9b**: ir (CCl_4) 6.0 μ (C=O), CH=N).

Hydrolysis of Initial Reaction Products. Hydrolysis of 2-(2,4-Dichlorophenoxy)-N-(1-cyclohexen-1-yl)N-methylacetamide (2a).—**2a** (*ca.* 1.0 g) was placed in 5 ml of concentrated hydrochloric acid, heated momentarily. Solid began to dissolve, whereupon suddenly more solid precipitated. The mixture was diluted with once its volume of water and filtered and the solid washed with more water and dried, mp 112–114°. The material proved to be 2-(2,4-dichlorophenoxy)-N-methylacetamide as determined by ir and mixture melting point with an authentic sample.

(12) R. Tiollais, *Bull. Soc. Chim. Fr.*, 708 (1947).

Hydrolysis of 1-(1-Cyclohexen-1-yl)-3-(3,4-dichlorophenyl)-1-methylurea (3b).—**3b** (5 g) was placed in 20 ml of water and 20 ml of 10% hydrochloric acid added. The material was permitted to stand overnight with occasional stirring. The solid which formed was filtered off, washed with water, and recrystallized from benzene, mp 157–159°. The material proved to be 1-(3,4-dichlorophenyl)-3-methylurea as determined by ir and mixture melting point with an authentic sample.

Hydrolysis of 3′,4′-Dichloro-2-(*p*-chloroanilino)-1-cyclohexene-1-carboxanilide (4).—Approximately 2 g of **4** was heated on a steam bath with 20 ml of 18% hydrochloric acid for 2–3 hr, cooled, filtered, washed with water, and recrystallized from aqueous ethanol, followed by a second recrystallization from methylcyclohexane, mp 138–140°. The structure of 3′,4′-dichloro-2-oxocyclohexanecarboxanilide was assigned to this material from consideration of the following data: ir (CCl_4) 3.0 (NH), 5.9 (ketone C=O), and 6.0 μ (amide C=O).

Anal. Calcd for $C_{13}H_{13}Cl_2NO_2$: Cl, 24.8; N, 4.9. Found: Cl, 24.6; N, 4.9.

Hydrolysis of 1-(Cyclohexen-1-yl)-3-(3,4-dichlorophenyl)-1-methyl-2-thiourea (5b).—**5b** (*ca.* 2 g) was placed in 30 ml of 10% hydrochloric acid, and the mixture was allowed to stand overnight with occasional stirring. Upon filtering, the resulting solid was recrystallized from chloroform, mp 150–152°. The material proved to be 1-(3,4-dichlorophenyl)-3-methyl-2-thiourea as determined by ir and mixture melting point comparison with an authentic sample.

Hydrolysis of 3′,4′-Dichloro-2-(methylamino)thio-1-cyclohexene-1-carboxanilide (6a).—**6a** (*ca.* 1 g) was placed in 20 ml of 18% hydrochloric acid and heated gently on a steam bath for 10–15 min. The aqueous portion was decanted, and the residual tacky solid recrystallized from aqueous ethanol to give crystals, mp 112–114°. The structure of 3′,4′-dichloro-2-oxothiocyclohexanecarboxanilide was assigned this material from consideration of the following data: ir (CCl_4) 3.0 (NH), and 5.95 μ (C=O); nmr showed nine aliphatic hydrogens, one NH, and three aromatic hydrogens.

Anal. Calcd for $C_{13}H_{13}Cl_2NOS$: Cl, 23.60; N, 4.63; S, 10.6. Found: Cl, 23.97; N, 4.70; S, 10.6.

Hydrolysis of [2-(3,4-Dichlorocarbaniloyl)-2-methylpropylidene](2-methylpropenyl)amine (9a).—**9a** (*ca.* 5 g) was placed in 20 ml of 18% hydrochloric acid and heated on a steam bath for 15 min. The acid was decanted, and the residue heated further with water on the steam bath. The mixture was decanted again and the residual solid air dried, then recrystallized from methylcyclohexane, mp 102–104°. The structure of 3′,4′-dichloro-2,2-dimethylmalonaldehydanilide (**10**) was assigned to this material from consideration of the following data: ir (CCl_4) 3.0 (N–H), 5.85 (aldehyde C=O), and 5.96 μ (amide C=O); nmr spectra were consistent, showing six identical methyl protons, one aldehydic proton, one NH, and three aromatic protons.

Anal. Calcd for $C_{11}H_{11}Cl_2NO_2$: Cl, 27.4; N, 5.4. Found: Cl, 27.7; N, 5.5.

Hydrolysis of 2-(*p*-Chlorophenyl)-1-methyl-1-(2-methylpropenyl)urea (12a).—**12a** (*ca.* 1 g) was placed in 20 ml of 20% hydrochloric acid solution, and the mixture was refluxed for 15 min. The cooled solution was decanted and diluted with water. The resulting precipitate was separated and recrystallized from aqueous methanol to give 0.5 g of *p*-chlorophenyl-3-methylurea as identified by ir spectra and mixture melting point.

Registry No.—**2a**, 16241-20-6; **2b**, 16241-21-7; **3a**, 16240-17-8; **3b**, 16240-18-9; **3c**, 16240-19-0; **4**, 16286-17-2; **5a**, 16240-20-3; **5b**, 16240-21-4; **5c**, 16240-22-5; **6a**, 16240-23-6; **6b**, 16240-24-7; **6c**, 16240-25-8; **8**, 16240-26-9; **9a**, 16240-27-0; **9b**, 16240-28-1; **10**, 16240-29-2; **11a**, 16240-30-5; **11b**, 16240-31-6; **12a**, 2572-41-0; **12b**, 16240-33-8; **12c**, 16240-34-9; 3′,4′-dichloro-2-oxocyclohexanecarboxanilide, 16240-35-0; 3′,4′-dichloro-2-oxothiocyclohexanecarboxanilide, 16240-36-1; cyclohexanone, 108-94-1; isobutyraldehyde, 78-84-2.

The Reaction of 2-Phenyl-1-pyrroline with Phenyl Isocyanate

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The reaction of phenyl isocyanate with 2-phenyl-1-pyrroline at 25° leads to 2-phenyl-1-phenylcarbamoyl-2-pyrroline (**2**). At higher temperatures the 3-substituted 2-pyrroline **4** is formed, and loss of isocyanate from **4** gives the 1-pyrroline-3-carboxanilide **5**. The 1-carbamoylpyrroline **2** undergoes rapid thermal elimination of phenyl isocyanate at 40°.

Although 2 + 2 cycloaddition reactions of isocyanates and olefins or of ketenes and azomethines are well-established preparative methods for azetidinones,[2] the cycloaddition of isocyanates and azomethines to form uretidinones have been reported on only a few occasions,[3,4] and the structural evidence for these products was extremely limited by contemporary standards. With a view to the possibility of obtaining a 1,6-diazabicyclo[3.2.0]heptane derivative by this cycloaddition process, we have studied the reaction of phenyl isocyanate with 2-phenyl-1-pyrroline (**1**). In previous work, a "well-defined" product was reported from the reaction of 2,5-dimethyl-1-pyrroline with phenyl isocyanate,[5] but the composition and structure of the compound were not specified.

The reaction of equimolar amounts of 2-phenyl-1-pyrroline and phenyl isocyanate at room temperature in hydrocarbon solution gave an unstable 1:1 product in 75% yield. The 1-phenylcarbamoyl-Δ^2-pyrroline structure **2** was indicated by the shift in the ultraviolet maximum from 243 mμ in **1** to 255 mμ **2**, a triplet nmr peak due to H-3 at δ 5.31, and acid hydrolysis to the ureido ketone **3**. Hydrolysis of **2** resulted in a significant amount of the original pyrroline as well.

At 110°, equimolar condensation led to a different 1:1 product and a compound containing one pyrroline and two isocyanate units, together with unreacted pyrroline and a trace of the hydrolysis product, **3**. The 1:1 and 1:2 products were obtained in a combined yield of about 40% (based on phenyl isocyanate), with the latter predominating in a ratio of about 3:1.

The minor (1:1) product was a base with ultraviolet absorption very similar to that of the pyrroline **1**; the pK_a' was 1.8 units lower than that of **2**. Schotten–Baumann benzoylation of the compound gave a product whose properties were consistent with the benzamido ketone **6**. These data suggest the Δ^1-pyrroline-3-carboxanilide structure **5** for the condensation product. Dickinson and Lang quite recently reported the

(1) National Science Foundation Predoctoral Fellow, 1965–1967.

(2) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press Inc., New York, N. Y., 1967.

(3) A. Seiner and F. G. Shepheard, *J. Chem. Soc.*, 494 (1909).

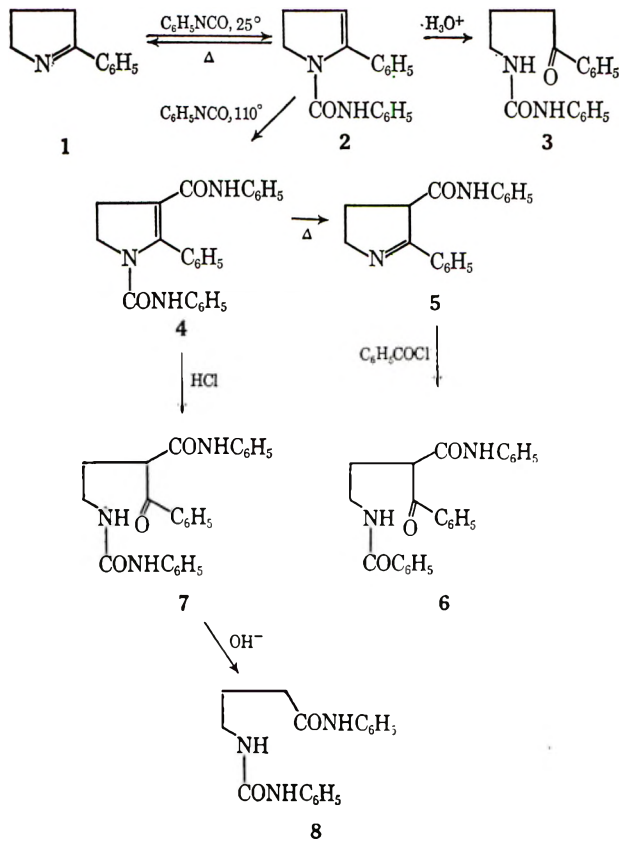
(4) W. J. Hale and N. A. Lange, *J. Amer. Chem. Soc.*, **41**, 379 (1919).

(5) G. G. Evans, *ibid.*, **73**, 5230 (1951).

formation of another 2-substituted Δ^1-pyrroline-3-carboxamide and commented on the point that the nonconjugated tautomer is the stable form.[6]

The 1:2 adduct, formed in larger amount at 110°, was a neutral compound with λ_{max} 316 mμ, indicative of a conjugated system. It was shown to be the 1-carbamoyl-2-pyrroline-3-carboxanilide **4** by acid hydrolysis to the ureido ketoanilide **7** and cleavage of the β-keto anilide system in **7** with base to benzoic acid and the anilide **8** (Scheme I). An authentic sample of **8** was prepared for comparison from γ-aminobutyric acid.

SCHEME I



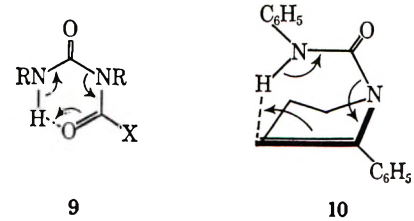
At 170°, the Δ^1-3-carboxanilide (**5**) was the only product isolated from the reaction of **1** and isocyanate. The product distribution at various temperatures indicates that the initial attack of phenyl isocyanate on **1** occurs at N-1, and that the 3-substituted products **4** and **5** arise sequentially at higher temperatures. The conversion of **4** to **5** occurred in low yield on heating the former at 180° under reduced pressure; a more practical procedure is the treatment of **4** with aniline, which led cleanly to an easily separable mixture of **5** and diphenylurea.

Conversion of the primary 2-pyrroline **2** or the 3-carboxanilide **5** to the disubstituted product **4** with excess phenyl isocyanate could be demonstrated, but these reactions did not provide an improved preparation of **4** because the presence of excess isocyanate seriously complicated the product isolation. In the reaction of **5** with isocyanate, it appeared from thin layer chromatography that the amount of the disubstitution product increased on cooling the reaction solution from 80° to room temperature.

(6) W. B. Dickinson and P. C. Lang, *Tetrahedron Lett.*, 3035 (1967).

Perhaps the most significant point among these transformations is the exceptional facility with which the 1-carbamoylpyrroline **2** undergoes loss of phenyl isocyanate. This reaction was followed by measurement of the characteristic isocyanate band in the infrared at 2250 cm^{-1}. The dissociation of a 0.017 *M* solution of **2** in chloroform at 40° is shown in Figure 1; under these conditions about 20% of the compound dissociated in 3 hr. On longer standing the isocyanate concentration eventually dropped, presumably owing to further reaction with **1** and/or oligomerization. The acceleration in rate of isocyanate release evidently reflects catalysis of the reaction by the product pyrroline.

The pyrroline **2** is a vinylurea, a system which seems not to have been described heretofore.[7] The thermal decomposition of ureas normally requires temperatures above 200°, although biurets and allophanates dissociate smoothly at 130°,[8] presumably to a cyclic elimination (**9**) similar to the decarboxylation of a β-keto acid. The dissociation of **2** can also be envisioned as a cyclic process (**10**), recalling the facile decarboxylation of β,γ-unsaturated acids.[9,10] The only isocyanate elimination comparable with that of **2** of which we are aware is the dissociation of 1-phenylcarbamoylimidazole and -benzimidazole reported by Staab and others.[11,12]



9 **10**

The second stage in the reactions of **1** with phenyl isocyanate at higher temperatures is evidently electrophilic attack on the vinylurea system of **2** by another mole of isocyanate, and subsequent loss of the 1-carbamoyl group by elimination as in the case of **2**. The dissociation of **4** was not studied in detail. The compound does not decompose at a detectable rate at moderate temperatures, but, from the appearance of **5** at 110°, dissociation must become appreciable at 80–100°. The greater stability of **4**, compared with **2**, is consistent with the conjugated enamide system.

Since the present work was completed, the reaction of phenyl isocyanate with cyclic azomethine systems has been reported by Huisgen and coworkers in connection with the general phenomenon of "1,4-dipolar cycloaddition."[13] With dihydroisoquinoline, a dipolar intermediate is obtained which combines with a second mole of the azomethine to given an oxotriazine; combination of the dipolar intermediate with a second mole of isocyanate was not observed, nor were uretidinones reported. In another recent related study, attack of phenyl isocyanate on 2-methyl-2-oxazoline has been

(7) Compounds of this type have also been obtained by J. P. Chupp and E. R. Weiss, *J. Org. Chem.*, **33**, 2357 (1968).

(8) I. C. Kogon, *ibid.*, **23**, 1594 (1958).

(9) R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, **72**, 4359 (1950).

(10) R. B. Woodward and E. C. Kornfeld, *ibid.*, **70**, 2508 (1948).

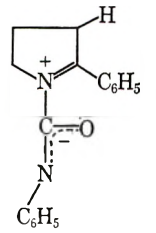
(11) H. A. Staab and W. Benz, *Angew. Chem.*, **73**, 66 (1961); H. A. Staab and G. Seel, *Ann. Chim.*, **612**, 187 (1958).

(12) J. Derkosch, K. Schlogl, and H. Woidich, *Monatsh. Chem.*, **88**, 35 (1957).

(13) R. Huisgen, K. Herbig, and M. Morikawa, *Chem. Ber.*, **100**, 1107 (1967).

reported to occur at the exocyclic methyl group rather than at the annular nitrogen,[14] a result which presents an interesting contrast to the behavior of the pyrroline **1**. 2-Phenyl-2-oxazoline was unreactive. In the present work, an attempt was made to bring about reaction of 2-phenyl-1-*p*-toluenesulfonyl-2-imidazoline with phenyl isocyanate; again, no reaction occurred.

The dipolar adduct **11**, corresponding to that proposed in 1,4-dipolar cycloadditions,[13] is assumed to be the intermediate in the formation of the carbamoylpyrroline 2. Unlike the previous cases studied, further addition of a second pyrroline molecule can be interdicted by deprotonation. The steric effect of the phenyl group may also be an interfering factor in the 1,4-dipolar addition reaction of **1** and the 2-phenylimidazoline or -oxazoline.



11

Experimental Section[15]

2-Phenyl-1-pyrroline (**1**) was prepared by the procedure of Starr:[16] bp 95–97° (0.5 mm); mp ~30°; nmr, δ^{CCl_4} 1.85 (apparent quintet of triplets, 2, J = ~7.5 and ~2 Hz; H_4), 2.77 (triplet of quintets, 2, J = 8 and ~2 Hz; H_3), 3.92 (triplet of triplets, 2, J = 7 and 2 Hz; H_5), 7.24 (m, 3 H; H_{meta} and H_{para}), 7.73 ppm (m, 2 H; H_{ortho}).[17]

2-Phenyl-1-phenylcarbamoyl-2-pyrroline (**2**).—A solution of 1.14 g (7.9 mmol) of 2-phenyl-1-pyrroline and 0.94 g (7.9 mmol) of phenyl isocyanate in 10 ml of *n*-decane was allowed to stand at 25°. A white solid began to separate after 1 hr; after 24 hr, the mixture was diluted with hexane and the solid was collected; 1.55 g (75%) of white crystals, mp 98–102° and 102–108°, was obtained in two crops. After recrystallization from methanol, the melting point was 116–117°, but analytical data were unsatisfactory. In a subsequent preparation, polar solvents were avoided; several recrystallizations from methylene chloride–hexane gave **2** as white needle clusters: mp 116–118°; λ_{max}^{MeOH} 255 mμ (ε 23,000); ν_{Nujol} 3300 (w), 1650 (s), 1625 (w), 1600 (s), 1540 (s), cm^{-1}; δ^{CDCl_3} 2.3–3.1 (m, 2; H_4), 4.22 (t, 2, J = 9 Hz; H_5), 5.31 (t, 1, J = 3 Hz; H_3), 6.20 (s, br; NH), 7.0–7.4 ppm (m, 9–10; aryl).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.87; H, 5.99; N, 10.51.

Hydrolysis of **2** was carried out by warming a solution of 100 mg of **2** in 1.5 ml of dioxane and 1.5 ml of 6 *N* HCl for 1 hr. After addition of water and chilling, a pale tan solid, 25 mg, mp 136–138°, separated. The infrared spectrum corresponded in all peaks with that of a specimen of the urea **3** characterized as described below. The acidic filtrate was basified, and the ether-soluble base was converted into the picrate of 2-phenyl-1-pyrroline, 69 mg, mp 202° dec.

Dissociation of 2-Phenyl-1-phenylcarbamoyl-2-pyrroline (**2**).—The infrared measurements were recorded on a Perkin-Elmer Model 337 spectrophotometer using a 2.5-mm cavity cell. The integrated absorption intensity of the isocyanate band was obtained by cutting out and weighing the peak. A calibration curve with known concentrations of phenyl isocyanate (0.5–5.0 × 10^{-3} *M*) was used to obtain concentrations; this curve was not linear (negative slope).

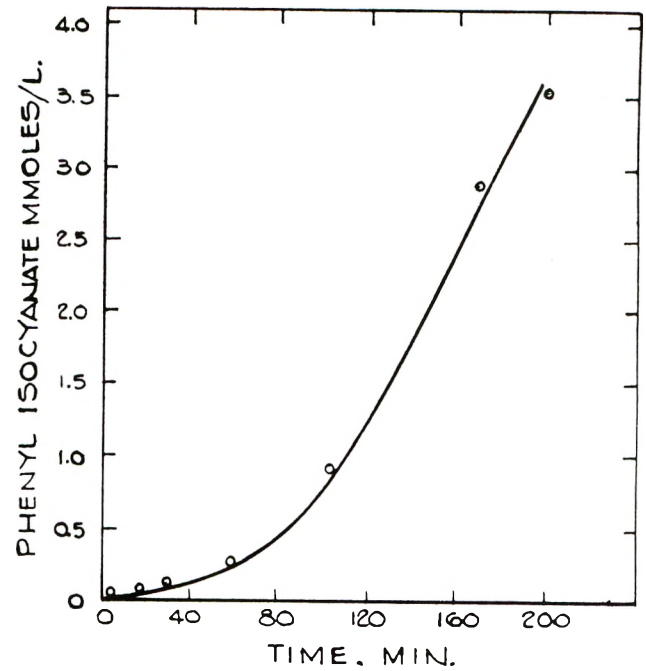


Figure 1.—Loss of phenyl isocyanate from **2** at 40° in0. 017 *M* $CHCl_3$ solution.

Reaction of 2-Phenyl-1-pyrroline and Phenyl Isocyanate at 110°.—A solution of 5.02 g (0.035 mol) of freshly distilled 2-phenylpyrroline and 4.13 g (0.035 mol) of phenyl isocyanate in 75 ml of toluene was refluxed for 21 hr. An orange color developed but faded on cooling. Distillation of the toluene gave a semisolid residue which was dissolved in warm CCl_4. Addition of hexane gave a pale brown gum (A).

Evaporation of the hexane solution gave an oil which contained phenyl isocyanate (odor) and a basic substance. A methylene chloride solution of the oil was extracted with 5 *N* HCl; basification of the aqueous phase gave a yellow oil which was treated with picric acid to give 4.0 g (0.011 mol, 31%) of 2-phenylpyrroline picrate, mp 200° dec (lit.[16] 198° dec).

The residue from the methylene chloride phase was partially crystalline; after trituration with warm ethyl acetate, the solid was collected to give 0.3 g, mp 138–140°. Recrystallization from isopropyl alcohol–hexane gave colorless crystals of **1-phenyl-3-[1-(3-benzoyl)propyl]urea** (**3**): mp 141–142°; ν_{Nujol} 3380, 1690, 1650 cm^{-1}; δ (pyr-d_5) 1.35 (q, 2, J = 6 Hz), 2.33 (t, 2, J = 6 Hz), 2.83 ppm (q, 2, J = 6 Hz).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; 0, 11.33. Found: C, 72.71; H, 6.50; O, 11.31.

The gum (A) precipitated with hexane was crystallized by digesting with ether; a total of 3.6 g of crystalline solid was obtained. The melting point was very broad and thin layer chromatography showed a mixture of two compounds, with the less polar (faster moving) one in larger amount. The ratio of the two products was about 3:1 based on thin layer chromatography and the amounts finally isolated. The actual yields cannot be stated because of large losses on recrystallization.

Crystallization from methanol–water and then 2-propanol–water gave the major component, mp 168–170°. Further recrystallization from benzene–hexane furnished a pure sample of **2-phenyl-1-phenylcarbamoyl-2-pyrroline-3-carboxanilide** (**4**): mp 170–171°; $\lambda_{max}^{CH_2Cl_2}$ 316 mμ (ε 18,000); ν_{Nujol} 3400, 1680, 1650 cm^{-1}; δ^{CDCl_3} 3.00 (t, 2, J = 9 Hz; H_4), 4.11 (t, 2, J = 9 Hz; H_5), 6.19 (s, NH), 6.72 (s, NH), 7.1–7.6 ppm (m, aryl).

Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.17; H, 5.52; O, 8.35. Found: C, 74.89; H, 5.74; O, 8.32.

The aqueous methanol mother liquors from the initial crystallization of **4** were concentrated to give crystals, mp 180–183°, corresponding to the slower moving component on thin layer chromatography. Further crystallization from aqueous ethanol gave 2-phenyl-1-pyrroline-3-carboxanilide (**5**): mp 183–184°;

(14) R. Nehring and W. Seeliger, *Ann. Chim.*, **698**, 167 (1966).

(15) Melting points were determined with a Fisher-Johns block. Infrared spectra were obtained, except where otherwise stated, with a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were obtained with a Varian A-60A instrument.

(16) D. F. Starr, H. Bulbrook, and R. M. Hixon, *J. Amer. Chem. Soc.*, **54**, 3971 (1932).

(17) In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet; the numeral following the multiplicity is the whole number of protons by integration.

λ_{max}^{MeOH} 243 mμ (ε 28,000); ν_{Nujol} 3300, 1655; pK_a' (50% MeOH) 4.1[18] [pK_a' (50% MeOH) of 2-phenyl-1-pyrroline was 5.9].

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.82; H, 5.82; N, 10.49.

2-Benzoyl-4(N'-phenylureido)butananilide (7).—A suspension of 200 mg of **4** in 6 ml of 6 *N* HCl was warmed on the steam bath. After a few minutes the solid **4** became gummy and, on further heating and stirring, the gum crystallized. The solid was collected, washed with water, and air-dried to give 187 mg, mp 195–198°. Recrystallization from pyridine–water gave colorless crystals of **7**: mp 201–202°; ν_{Nujol} 3400, 1695, 1680, 1650 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.78; N, 10.47. Found: C, 72.37; H, 5.97; N, 10.68.

4-(N'-Phenylureido)butananilide (8).—A mixture of 181 mg of the 2-benzoylanilide **7**, 5 ml of 15% NaOH, and 4 ml of ethanol was stirred at 80° for 6 hr. The solid changed in appearance during this treatment from a fine powder to larger crystals. After addition of water the solid was collected, washed with water, and air-dried to give 85 mg (63%), mp 238°. Recrystallization from pyridine–water gave colorless crystals of **8**: mp 240–241°; ν_{Nujol} 3400, 1650 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.77; H, 6.74; N, 14.10.

The alkaline filtrate from above was partially neutralized (pH 10) and evaporated to dryness. The solid residue of sodium benzoate and inorganic salt was treated with thionyl chloride, evaporated, and treated with excess aniline. After acidification the solid product was collected; the melting point was 150–160°. Recrystallization from ethanol gave a sample of benzanilide whose ir spectrum corresponded to that of an authentic sample.

Synthesis of 8 from 4-Aminobutanoic Acid.—4-(N'-Phenylureido)butanoic acid was prepared by dropwise addition of 4.7 ml (0.043 mol) of phenyl isocyanate, with vigorous stirring over a 30-min period, to a solution of 4.10 g (0.04 mol) of 4-aminobutanoic acid in 20 ml of 2 *N* NaOH. After stirring for an additional 12 hr, a small amount of insoluble solid was removed and the solution was acidified; the ureido acid was collected, washed with water, and dried to give 8.0 g of colorless crystals, mp 127–128° (lit.[19] mp 126°).

To a solution of 2.2 g of this acid in 20 ml of 1,2-dimethoxyethane (glyme) was added 0.95 ml of oxalyl chloride. After a transient yellow color had faded and a small amount of solid separated, the mixture was stirred for 1 hr and evaporated *in vacuo* to a white solid residue (minimal conditions were used to suppress cyclization of the acid chloride). A solution of 0.9 ml of aniline in 15 ml of glyme was then added, and after stirring for 30 min, the mixture was diluted with water. The resulting voluminous solid precipitate was collected. Much of this solid was soluble in aqueous alkali and was presumably unreacted ureido acid. The alkali-insoluble material was collected, washed, and air-dried to give 250 mg of solid of indefinite melting point. This solid was warmed in pyridine, some insoluble material was removed, and the pyridine was evaporated to give colorless crystals of **8**, mp 238°; the infrared spectrum corresponded, in position and relative intensities of 17 peaks, with that of a sample obtained by hydrolysis of **7**.

(18) We thank Dr. J. M. Vandenbelt and Mrs. C. Spurlock, Parke, Davis and Co., for the pK_a' measurements.

(19) German Patent 929,191 (June 20, 1955); *Chem. Abstr.*, **52**, 5457*f* (1958).

2-Benzoyl-4-benzamidobutananilide (6).—A mixture of 150 mg of the 1-pyrroline-3-carboxanlide (**5**), 0.24 g of benzoyl chloride, and 1 ml of 10% aqueous NaOH was shaken vigorously in a stoppered tube until the solid had become gummy and then resolidified. The aqueous solution was decanted, and the residue dissolved in ethanol. The solution was treated with charcoal, filtered, and diluted with water, and the resulting poorly formed crystals were collected to give 73 mg of off-white solid, mp 187–193°; thin layer chromatography showed the presence of a small amount of unreacted **5**. Recrystallization from ethanol and then chloroform–hexane gave colorless prisms of **6**: mp 198–199°; ν_{Nujol} 3300, 1690, 1660, 1645 cm^{-1}; δ (pyr) 2.73 (m, 2), 3.90 (m, 2), 5.00 ppm (t, 1, J = 7 Hz; H_2).

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.78; H, 5.96; N, 6.97.

Reaction of 2-Phenyl-1-pyrroline and Phenyl Isocyanate at 170°.—A solution of 3.68 g (25 mmol) of pyrroline and 2.74 ml (25 mmol) of isocyanate in 25 ml of decane was refluxed with stirring for 2 hr. A dark oil which separated during the heating period solidified on cooling. Tlc showed four components, with **5** as the major spot. The solid was slowly crystallized from methanol at 0°, giving 1.9 g of pale yellow crystals which was largely **5** (thin layer chromatography). Recrystallization from tetrahydrofuran gave 1.3 g of **5**, mp 184–185°.

2-Phenyl-1-pyrroline-3-carboxanilide (5) from 4.—A solution of 765 mg of **4** in 7 ml of xylene containing 180 mg of aniline was refluxed for several hours, during which time a white precipitate of diphenylurea separated. The hot mixture was filtered, and 340 mg (80%) of urea was collected; on cooling, the filtrate deposited 436 mg (83%) of crystals of **5**, mp 173–175°; the infrared spectrum was identical with that of the sample of **5** described above.

2-Phenyl-1-*p*-toluenesulfonyl-2-imidazoline.—To a solution of 5.0 g of 2-phenylimidazoline[20] in 20 ml of pyridine containing 3.46 g of triethylamine was added during 30 min a solution of 6.5 g of *p*-toluenesulfonyl chloride in 30 ml of methylene chloride. After several hours, ether was added and the precipitated triethylamine hydrochloride was collected. The filtrate was washed thoroughly with water, dried, and evaporated to an oil which crystallized at 0°. Recrystallization of the crude solid (9.9 g, mp 74–78°) from methanol–water and then carbon tetrachloride–hexane gave white needles, mp 86–87°.

Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.80; H, 5.19; N, 9.04.

A solution of 1.5 g (5 mmol) of the tosylimidazoline and 0.6 g (5 mmol) of phenyl isocyanate in 5 ml of benzene was stored at 25° overnight. Thin layer chromatography showed no indication of reaction. After 12-hr reflux there was still no evidence of reaction; after adding aniline at this point, diphenylurea and unchanged imidazoline were recovered in 90% yields.

Registry No.—**1**, 700-91-4; **2**, 16054-51-6; **3**, 16054-56-1; **4**, 16054-52-7; **5**, 16109-69-6; **6**, 16054-57-2; **7**, 16054-53-8; **8**, 16054-54-9; 2-phenyl-1-*p*-toluenesulfonyl-2-imidazoline, 16054-55-0; phenyl isocyanate, 103-71-9.

(20) R. Forsyth, V. K. Nimkar, and F. L. Pyman, *J. Chem. Soc.*, 800 (1926).

Sodium Borohydride Reduction of Cross-Conjugated 1-Pyrrolines. The Reinvestigation of the Formation of a 1-Azabicyclo[3.2.0]heptane[1]

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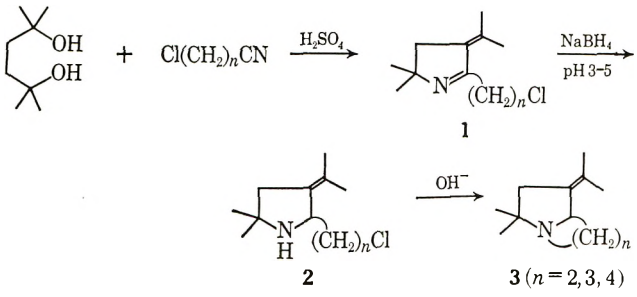
The cyclization of 2-(2-chloroethyl)-3-isopropylidene-5,5-dimethyl-1-pyrroline (**1**) has been reexamined and found to give, in addition to the previously reported 1-azabicyclo[3.2.0]heptane system (**3**, $n = 2$), two other products, 3-isopropylidene-5,5-dimethyl-2-vinylpyrrolidine (**5**) and 2-ethyl-3-isopropylidene-5,5-dimethylpyrrolidine (**4**). The latter two products were formed from the intermediate 2-vinyl-1-pyrroline derivative (**7**) by 1,2 and 1,4 addition of sodium borohydride. A study to determine the effect of varying conditions on the reduction of **7** was made and in all cases the 3-isopropylidene group was unaffected whereas 1,4 addition was the predominant path taken. Spin-decoupling experiments were performed on the 1-pyrrolines and long-range coupling between the isopropylidene methyl protons and the ring protons was observed.

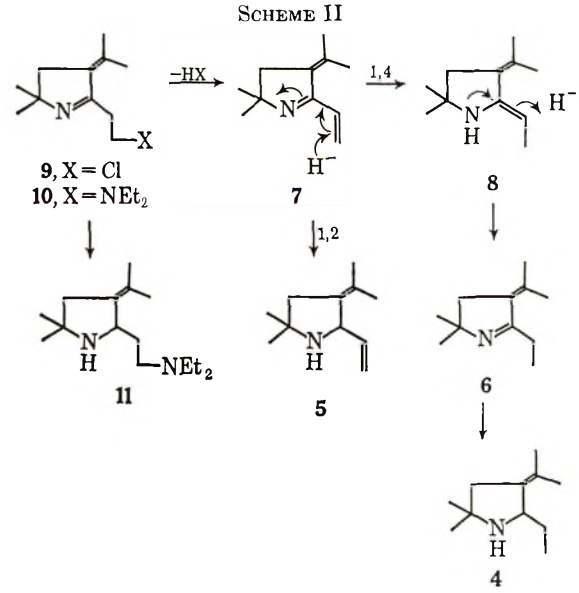
In 1961, the formation of 1-azabicycloalkanes (**3**) was reported[2] to occur *via* the sequential process shown in Scheme I. The bicyclic bases were obtained in good

SCHEME I



yields without isolation of any of the intermediates, **1** and **2**. In connection with another study, the 1-azabicyclo[3.2.0]heptane, **3** ($n = 2$), was required and upon examination of an 8-year-old sample by gas chromatography it was found to consist of a three-component mixture. In order to determine whether the bicyclic base had deteriorated in storage or whether the previously reported compound was indeed a mixture, the synthesis was repeated in exactly the same manner. Although the infrared spectrum and elemental analysis of "pure" **3** ($n = 2$) were in accord with the previously reported results, the gas chromatogram revealed three distinct peaks in the ratio 2.5:1:2.4. The nmr spectrum of the mixture confirmed the complexity of "pure" **3** ($n = 2$) and exhibited signals in the vinyl region (4.6–6.1 ppm) as well as signals which disappeared upon the addition of heavy water. The mixture was separated by collection from the gas chromatograph effluent and each fraction examined by nmr. The first fraction, which represented 42.4% of the mixture, possessed a well-defined triplet at 0.89 ppm (3 H, $J = 7$ Hz), a quartet partially hidden at 1.2–1.6 ppm (2 H, $J = 7$ Hz), a broad signal centered at 3.78 ppm (1 H), two sharp singlets at 1.03 (3 H) and 1.35 ppm (3 H), a broad intense peak at 1.67 ppm (6 H), an AB quartet centered at 1.95 and 2.27 ppm (2 H, $J = 14$ Hz), and a broadened peak at 1.75 ppm (1 H) which was exchangeable with deuterium oxide. The infrared spectrum possessed a broad band at 2.95 μ as the only distinctive feature. These data suggested that the initial component of the mixture was the 2-ethylpyrrolidine derivative, **4**. The second fraction collected, representing 16.9% of the mixture, possessed an exchangeable proton signal (~1.3 ppm), the characteristic terminal vinyl signals at 4.6–6.1 ppm (3 H), a doublet at 4.25 ppm (1 H, $J = 8$ Hz), a broad singlet at 1.65 ppm (6 H), two sharp singlets at 1.08 (3 H) and 1.26 ppm (3 H), and a diffuse AB quartet centered at 2.27 ppm. The infrared spectrum exhibited absorption at 2.95 and 6.08 μ. These data were consistent with the 2-vinylpyrrolidine, **5**. The third and final component representing 40.7% of the mixture did not exhibit any change in its nmr spectrum upon the addition of heavy water. The spectrum contained two sharp singlets at 0.92 (3 H) and 1.12 ppm (3 H), a broad triplet and a diffuse triplet (indicating long-range coupling) at 1.56 (3 H) and 1.69 ppm (3 H), respectively, an AB quartet at 2.30 and 2.65 (2 H, $J = 10$ Hz), a multiplet centered at 3.30 ppm (2 H), and a diffuse doublet at 4.35 (1 H). The infrared spectrum possessed no absorption in the 3-μ region. This component was considered to be the 1-azabicyclo[3.2.0]heptane, **3** ($n = 2$), originally reported.[2] To confirm the structures assigned to **4** and **5**, their synthesis was accomplished using 2,5-dimethyl-2,5-hexanediol and propionitrile and acrylonitrile, respectively,[3] to obtain the 1-pyrrolines, **6** and **7** (Scheme II). The former was reduced in 94%

SCHEME II

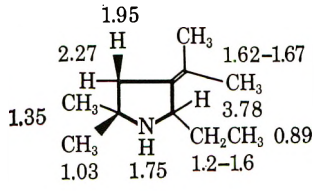


(1) This study was supported by the National Institutes of Health (NIGMS-06248-08) and the U. S. Army Research and Development Command (DA-49-193-MD-2991). This is Contribution No. 328 to the Army Research Program on Malaria.

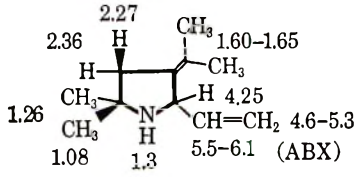
(2) A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 4399 (1961).

(3) A. I. Meyers and J. J. Ritter, *ibid.*, **23**, 1918 (1958).

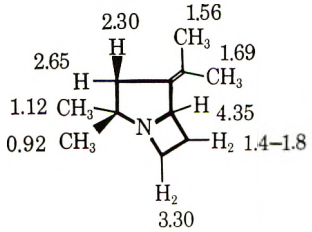
yield to the pyrrolidine derivative, **4**, utilizing aqueous sodium borohydride at pH 3–5. Comparison of this product with that isolated from the aforementioned mixture showed that they were identical in every respect. On the other hand, reduction of the 2-vinylpyrroline, **7**, under these conditions gave a 97% yield of a mixture which contained two components identical, with respect to their retention times, with **4** and **5** isolated earlier. Furthermore, both products were collected from the effluent of a gas chromatograph and exhibited nmr spectra identical with **4** and **5**. The origin of **4** (and **5**) is undoubtedly due to 1,2- and 1,4-hydride addition upon **7** resulting in **8** and **5**. The former, which is an enamine, is protonated to **6** in the acidic medium and is subsequently reduced to **4**. The successive reduction of conjugated double bonds by metal hydrides has been amply discussed in a recent review.[4] Since **7** represented an unusual cross-conjugated system, addition information regarding the factors affecting the mode of reduction were considered to be of interest. Varying conditions (time, temperature, and quantity of borohydride) were studied and the results are summarized (Table I). It can be seen that support for the above mechanism (**7** → **8** → **6** → **4**) is adequately obtained by the isolation of **6** when less than 1.0 molar equiv of sodium borohydride is employed (entry 2). The slight variation in the ratio of **4** to **5** (2–3:1) under all conditions when sufficient borohydride was used (entries 1, 4, 5, 6) is a good indication that the vinyl derivative **7** is the intermediate during the concurrent formation of the 1-azabicyclo[3.2.0]-heptane, since **4** and **5** accompanied the latter within these limits (2.5:1).



4



5



3 ($n=2$)

The appearance of **7** as a by-product in the formation of **9** by the previously described route[2] is to be expected since β-substituted 1-pyrrolines readily eliminate hydrogen halides or amines (**10**) to form the vinyl conjugated systems. This elimination takes place merely on standing or with slight warming. It was observed that the aminoethylpyrroline, **10**, could not be distilled even under the mildest conditions and when attempts were made to determine its purity by gas chromatography only the peak characteristic of **7** was visible. However, if crude and freshly prepared **10** was reduced with sodium borohydride, it was smoothly converted into the pyrroline **11** which was completely stable during distillation. This fact is not surprising since the driving force (conjugation) for elimination has been removed. Of further interest is the fact, that in every case studied, the exocyclic double bond on the ring was completely unaffected by the borohydride reduction. It is quite probable that, even though the isopropylidene group is conjugated to the C=N link, the bulk of the methyl groups inhibit hydride attack. Steric effects upon borohydride reductions have been noted previously.[4]

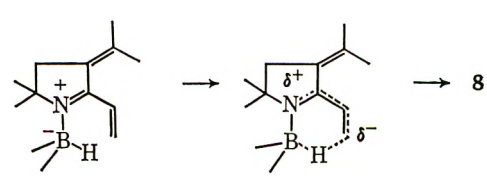
TABLE I

SODIUM BOROHYDRIDE REDUCTION OF 3-ISOPROPYLIDINE-5,5-DIMETHYL-2-VINYL-1-PYRROLINE (**7**)[a]

Entry	Moles of $NaBH_4$/mole of **7**	T, °C	Time, hr	Total recovery, %	Compound, % **4**	**5**	**6**	**7**
1	1.0	0–5	1	97	66	34	..	..
2	0.5	0–5	1	95	11	29	31	29
3	1.0	(−15)–(−20)	1	85	49	33	11	6
4	2.0	0–5	1	95	67	33	..	..
5	1.0	0–5	3	98	65	35	..	..
6	2.0	0–5	3	97	70	30	..	..

[a] Product composition was determined using a gas chromatograph containing a 12-ft column packed with 5% KOH–Chromosorb P coated with 20% Dow Corning DC-710 at 130°. All reactions were carried out in aqueous solutions at pH 3–5 except entry 3, which was performed in the presence of added ethanol (1:1).

The predominance of 1,4 addition of borohydride in every case can be attributed to a chelation effect of the 2-vinylpyrroline with the hydride reagent giving rise to a complexed intermediate and a subsequent transition state of similar geometry. 1,2 addition would be somewhat inhibited by the presence of the 2-vinyl substituent. The nmr spectra of the 1-pyrrolines, **6** and **7**,

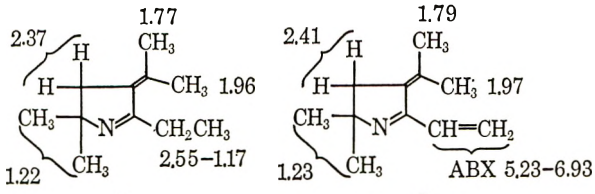


and their reduced derivatives, **4** and **5**, deserve some comment. Examination of the 60-MHz spectrum of **7** reveals that the methyl protons of the isopropylidene group appear as diffuse triplets at δ 1.79 ($J \simeq 1$ Hz) and 1.97 ppm ($J = 2$ Hz). The C-4 protons, normally expected to appear as a singlet (the *gem*-dimethyls at C-5 form a sharp six-proton singlet) resonate at δ 2.4 ppm as a broad singlet. When the latter signal is irradiated, both methyl signals are clearly decoupled to the expected singlets indicating homoallylic coupling between the protons at C-4 and the isopropylidene group.[5] Since homoallylic coupling is known to be greater in transoid than in cisoid systems, the methyl

(4) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).

(5) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 110.

group at 1.79 ppm is assigned *cis* to the C-4 protons and the methyl group at 1.97 ppm assigned *trans*. Similar spectral properties were observed for the 2-ethyl pyrroline, **6**, on the basis of decoupling experiments. The spectrum of **5**, on the other hand, showed no long-range coupling between the isopropylidine group and the C-4 protons. Irradiation of the AB quartet at 2.22 and 1.36 ppm failed to alter the two overlapping singlets at 1.60–1.65 ppm. Similar lack of long-range coupling was also observed in **4**. It is, therefore, concluded that the long-range coupling observed in **6** and **7** is due to the rigidity of the ring which contains four sp^2 centers (not including the 2-substituents) and is absent in **4** and **5** owing to the increased flexibility of the five-membered ring. Since coupling depends upon $[\cos^2\theta\ (CH_2C{=}C)][\cos^2\theta\ (CH_3C{=}C)]$ relationship of the dihedral angles of the homoallylic protons involved,[6] the rigidity of **6** and **7** allows the C-4 protons and the methyl protons to assume a 90° orientation with respect to the C=C. When the C=N is reduced, the ring, with its added flexibility, may assume several successive conformations resulting in the destruction of the dihedral angles necessary to produce long-range coupling.



6 **7**

Experimental Section[7]

The nmr spectra were taken on a Varian A-60 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Spin decoupling was performed on a Varian V-6058 instrument. Infrared spectra were taken on a Perkin-Elmer 257 grating spectrophotometer. The gas chromatography experiments were performed on a F & M 500 gas chromatograph equipped with a disk integrator. The accuracy of the determinations were ±2%.

3-Isopropylidene-5,5-dimethyl-1-azabicyclo[3.2.0]heptane (3, n = 2).—The previously reported[2] synthesis was repeated and the pure azabicycloheptane derivative obtained by gas chromatographic separation as described earlier: bp 110° (40 mm); $n^{25}D$ 1.4785.

Anal. Calcd for $C_{11}H_{19}N$: C, 80.00; H, 11.51; N, 8.48. Found: C, 79.98; H, 11.21; N, 8.49.

2-Ethyl-3-isopropylidene-5,5-dimethyl-1-pyrroline (6) and 3-isopropylidene-5,5-dimethyl-2-vinyl-1-pyrroline (7) were prepared as described in a previous report.

2-Ethyl-3-isopropylidene-5,5-dimethylpyrrolidine (4).—A solution of **6** (16.5 g, 0.1 mol) in 1.2 *M* sulfuric acid (15 ml) was cooled to 0° with stirring and the pH adjusted to 3–4 by the addition of 6 *M* sodium hydroxide. The reduction and isolation was carried out in exactly the same manner as the typical procedure for the reduction of **7** (below). There was obtained 15.8 g (94.5%) of the reduced product, **4**, bp 39–40° (1 mm). The spectral properties have been discussed in the text.

Anal. Calcd for $C_{11}H_{21}N$: C, 79.15; H, 12.57; N, 8.38. Found: C, 79.09; H, 12.36; N, 8.29.

Reduction of 3-Isopropylidene-5,5-dimethyl-2-vinyl-1-pyrroline (7). Typical Procedure (Entry 1, Table I).—A solution of **7** (8.15 g, 0.05 mol) in 20 ml of 1.5 *M* sulfuric acid was cooled to 0° in an open beaker. The electrodes of a pH meter (Beckman Zeromatic) were inserted and 6 *M* sodium hydroxide added to render the solution pH 3–4. A solution of sodium borohydride (1.9 g, 0.05 mol) in 10 ml of water containing 1 drop of 35% sodium hydroxide was added dropwise with magnetic stirring to the above maintaining the temperature between 0 and 5° and the pH 3–5 by the periodic addition of 4 *M* sulfuric acid. The addition of the reducing solution required 15 min (as in all cases in Table I) and then the mixture was stirred for 1 hr at 0° and pH 3–5. The mixture was then made strongly alkaline with 35% sodium hydroxide maintaining the temperature of the beaker contents below 15° during the neutralization. The alkaline solution was extracted with ether; the latter solution was dried (Na_2SO_4), concentrated, and distilled giving 8.0 g (97%) of a mixture of **4** and **5**, bp 110–117° (40 mm). A sample was removed and introduced into the gas chromatograph giving the data tabulated.

2-(2-Diethylaminoethyl)-3-isopropylidene-5,5-dimethyl-1-pyrroline (10).—To a cold (0°), stirred solution of 3-diethylaminopropionitrile (25.3 g) in 200 g of concentrated sulfuric acid was added, in portions through a powder funnel, 2,5-dimethyl-2,5-hexanediol (29.2 g) over a 30-min period. The mixture was stirred at 0–5° for 2 hr and poured onto 400 g of chipped ice. The aqueous mixture was extracted with chloroform until the latter extracts were colorless and then made alkaline with 35% sodium hydroxide. Care was taken to maintain the temperature of the solution below 25° during the neutralization. The oil which had separated was extracted with ether, dried (K_2CO_3), and concentrated to give 25.7 g of crude **10**. Thin layer chromatography (dioxane) indicated that the product was only slightly contaminated with a minor component. Attempted distillation at 70° (0.1 mm) resulted in considerable elimination of the amine moiety giving a mixture of **10** and the vinyl pyrroline **7**.

The crude product (**10**) had ir bands (neat) at 6.09 (C=C), 6.28 μ (C=N); nmr ($CDCl_3$), δ 2.75 (s, 4, $>NCH_2CH_2N<$), 2.62 (q, 4, $-CH_2CH_3$), 2.40 (m, 2, C,4), 2.00 (t, 3, J = 2 Hz, $=CCH_3$), 2.81 (t, 3, J = 0.5 Hz, $=CCH_3$), 0.9–1.4 [s, t, 12, $(CH_3)_2$, $-CH_2CH_3)_2$].

The product was used without further attempts at purification for the subsequent experiment.

2-(2-Diethylaminoethyl)-3-isopropylidene-5,5-dimethylpyrrolidine (11).—A solution of **10** (11.8 g, 0.05 mol) in 50 ml of 4 *M* sulfuric acid was cooled to 0–5° in a beaker and fitted with electrodes from a pH meter. The pH was adjusted to 3-5 by the dropwise addition of 6 *M* sodium hydroxide. Sodium borohydride (1.9 g, 0.05 mol) dissolved in 15 ml of water containing 1 drop of the aforementioned pH and temperature. After stirring for 1.5 hr, the solution was rendered alkaline (pH 9–10) and extracted repeatedly with ether. The extracts were dried (K_2CO_3), concentrated, and distilled to give 5.8 g (50%) of **11**: bp 66–70° (0.1 mm); ir (neat), 2.96 (NH); nmr (neat), δ 3.86 (m, 1, H-2).

Anal. Calcd for $C_{15}H_{30}N_2$: C, 75.67; H, 12.60; N, 11.76. Found: C, 75.30; H, 12.88; N, 11.44.

Registry No.—Sodium borohydride, 1303-74-8; **3** (n = 2), 16336-07-5; **4**, 16336-08-6; **7**, 16336-09-7; **10**, 16336-10-0; **11**, 16336-11-1.

(6) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).

(7) Analyses performed by Galbraith Laboratories, Knoxville, Tenn.

7-Substituted 2,3-Diazabicyclo[2.2.1]heptane Derivatives. Synthesis of a Stable Ketone Hydrate

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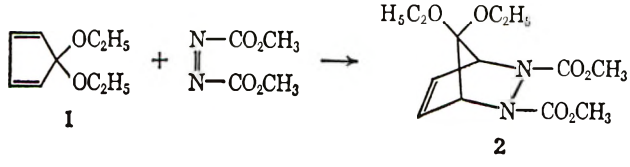
The synthesis of 2,3-phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (**4**) and its saturated analog (**5**) is described. These ketals are inert toward hydrolysis. Ozonolysis of 2,3-dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]heptane (**10**), prepared by hydrogenation of the Diels–Alder product of dimethylfulvene and diethyl azodicarboxylate, results in formation of the stable ketone hydrate 2,3-dicarbethoxy-7,7-dihydroxy-2,3-diazabicyclo[2.2.1]heptane (**13**).

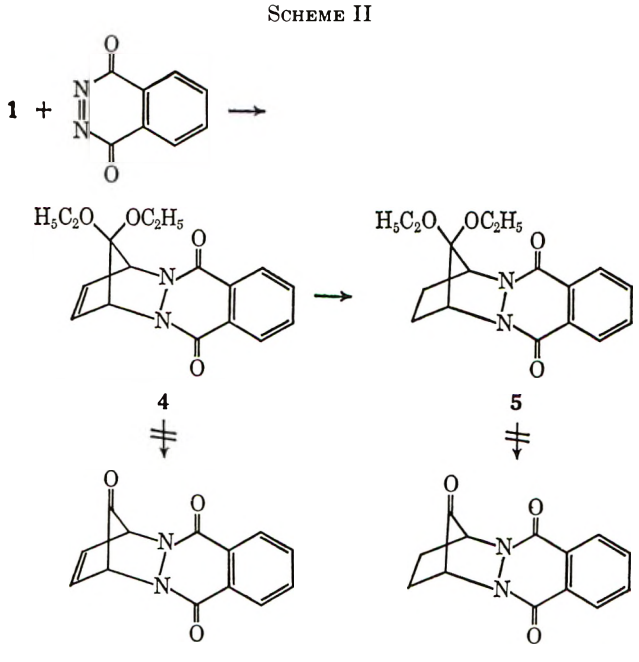
The work reported here is concerned with attempts to provide synthetic routes to 7-substituted 2,3-diazabicyclo[2.2.1]heptanes. After completion of this work, Allred and Anderson[2] reported the first successful preparation of this type of compound by the Diels–Alder reaction of the diethyl ketal of cyclopentadienone (**1**) and dimethyl azodicarboxylate (Scheme I). We

SCHEME I



had unsuccessfully attempted the same route. In the presence of a 1 *M* excess of diethyl azodicarboxylate (**3**) we were unable to trap **1**. However, the more reactive dienophile, 1,4-phthalazinedione, readily intercepted **1** to give a good yield of the expected adduct **4** which gave the corresponding dihydro compound **5** upon hydrogenation (Scheme II). Although a variety of condi-

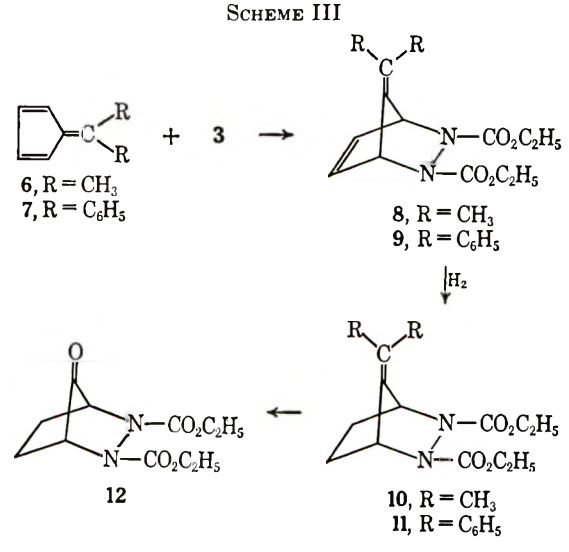
SCHEME II



tions were employed (see Experimental Section) ketals **4** and **5** were inert toward hydrolysis and formation of the corresponding 7-keto derivatives. This was an unexpected result since 7,7-dimethoxybicyclo[2.2.1]hept-2-ene, its saturated analog, and the dimer of the diethyl ketal of cyclopentadienone are readily hydrolyzed at room temperature by dilute mineral acids.[3,4] The unreactivity of **4** and **5** toward hydrolysis, however, is in agreement with the results of Allred and Anderson.[2] They found that the ketal **2**, its saturated analog, and the corresponding 2,3-dimethyl compound are also inert toward hydrolysis.

In view of the inability to generate a keto function at the 7 position by the above synthetic route an alternate procedure was examined. This procedure has as its starting point a Diels–Alder reaction of a fulvene with **3** and is outlined in Scheme III. Both **6** and **7** reacted

SCHEME III



with **3** exothermally and quantitatively, as evidenced by dissipation of the orange color of the reactants. The infrared and nmr spectra of the reaction mixture showed only trace amounts of residual starting materials.

The Diels–Alder adduct **8** was isolated as a pale yellow oil which had an infrared and nmr spectrum consistent with the assigned structure. Efforts to purify this oil by column chromatography, gas chromatography, molecular distillation, and crystallization were unsuccessful and instead resulted in its decomposition or conversion to other materials. This was evidenced by the increasing orange color of the oil, the appearance of N–H stretching in the infrared spectrum, and changes in the nmr spectrum to one of greater complexity. It appears that **8** undergoes slow Diels–

(1) Abstracted from the thesis of J. A. Alford, submitted in partial fulfillment of the M.S. degree requirements at Clemson University, May 1966.

(2) E. L. Allred and C. Anderson, *J. Org. Chem.*, **32**, 1874 (1967).

(3) P. G. Gassman and P. G. Pope, *ibid.*, **29**, 160 (1964).

(4) P. E. Eaton and R. A. H. Hudson, *J. Amer. Chem. Soc.*, **87**, 2769 (1965).

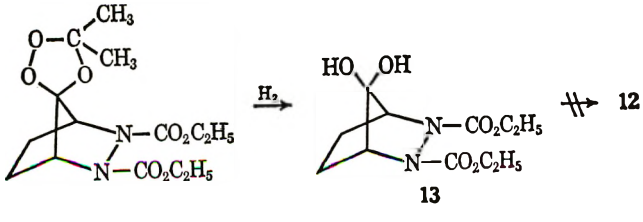
Alder reversal at room temperature followed by an abstraction–addition reaction to give a substituted hydrazide. Similar behavior has been previously reported for the Diels–Alder adduct of 3,6-pyridazinedione and 6.[5]

Freshly prepared **8** rapidly absorbed 1 molar equiv of hydrogen, in which the endocyclic double bond was preferentially reduced to give **10**. Compound **10** was ozonized in a methanolic solution and the intermediate ozonide was catalytically hydrogenated[6] with palladium. Subsequent nonaqueous work-up gave an oil which upon prolonged standing deposited a white crystalline solid. This solid was found to be very water soluble, a property unexpected for the presumed product **12**. The water-soluble ozonolysis product is not the 7-keto compound **12** but is instead the corresponding *gem*-diol **13**. The infrared, nmr, and elemental analysis data are all consistent with structure **13**. The infrared spectrum showed strong O–H stretching and lacked carbonyl absorption at 5.6 which is characteristic of 7-ketobicycloheptanes.[7] The nmr spectrum ($CDCl_3$) consisted of a six-proton triplet (CH_3) at 1.3 ppm, a four-proton quartet (CH_2) centered at 4.3 ppm, a four-proton broadened quartet (ring CH_2) centered at 1.95 ppm, a two-proton singlet (bridgehead C–H) at 4.12 ppm, and a two-proton broad singlet at 5.1 ppm (OH). Positive assignment of the O–H and its distinction from that of the bridgehead protons was accomplished by deuterium exchange with D_2O containing a small amount of HCl. The nmr spectrum of deuterium exchanged **13** was exactly the same as that of unexchanged **13** except that the signal at 5.1 ppm was considerably diminished.

Subsequent preparations of **13** took advantage of its water solubility by extracting the ether solution of the reduced ozonide with water. The water extracts were then evaporated to give crude **13**.

This same reaction sequence was tried using diphenylfulvene as the diene. The adduct **9** crystallized out of the reaction mixture as a stable white solid. Ozonolysis of **11** and work-up in a manner identical with that described for **10** did not give any detectable quantity of **13**.

Formation of diol **13** by catalytic reduction of the ozonide is explained by the reaction



13

However, it is surprising that **13** does not undergo spontaneous dehydration to give the 7-keto compound **12** or exchange with solvent methanol to give what is usually the more thermodynamically favored dimethyl ketal. The extraordinary and unexpected stability of the hydrate **13** is further evidenced by the fact that it is unchanged when heated at 100° at 0.005 mm as determined by elemental analysis.

(5) T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).
(6) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(7) F. H. Allen, *ibid.*, **62**, 653 (1962).

As previously mentioned, a variety of dimethyl and diethyl ketals of 7-keto-2,3-diaza[2.2.1]bicycloheptanes are inert toward hydrolysis. Allred and Anderson[2] have suggested that the reason for the stability of these ketals toward hydrolysis is due to ineffective acid catalysis as a result of preferential protonation of nitrogen. It is difficult to invoke this argument to explain the remarkable stability of **13**. Unlike ketals, ketone hydrates, in the absence of special stabilizing effects, suffer spontaneous dehydration without the necessity of acid catalysis. Furthermore, **13** undergoes rapid exchange with D_2O containing a small amount of HCl. This result suggests that **13** does indeed undergo rapid protonation at the hydroxyl group. It therefore appears that the stability of **13** and corresponding ketals must be attributed to some other effect.

Experimental Section

Melting points were taken by the capillary tube method and are corrected. Nmr spectra were obtained with a Varian Model A-60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories.

2,3-Phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (4).—To a solution of 1,4-phthalazinedione[5] (prepared from 29.04 g (0.16 mol) of the sodium salt of phthalhydrazide and 0.16 mol of *t*-butyl hypochlorite) at −77° was added a solution of 5,5-diethoxycyclopentadiene (prepared from 50.56 g (0.16 mol) of the dibromo ketal and 50.0 g (0.446 mol) of potassium *t*-butoxide, which had been precooled to −77°). The two phase system was stirred rapidly at −70°. After 30 min a white precipitate began to form and the green color had completely disappeared. The reaction mixture was filtered at −70° to give 31.3 g (61.7%) of **4**, mp 185–188°. Recrystallization from benzene afforded an analytical sample, mp 188–189°.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.02; H, 5.78; N, 9.02.

The infrared spectrum (KBr) contained absorption maxima at 6.05 and 6.17 μ (C=O). The nmr spectrum (CCl_3D) contained a multiplet centered at 1.12 ppm composed of two triplets (CH_3), an octet centered at 3.58 ppm composed of two quartets (CH_2), a triplet at 5.70 ppm (C–H bridgehead), a triplet at 6.71 ppm (vinyl=CH), and two multiplets at 7.80 and 8.30 ppm (aromatic).

2,3-Phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]heptane (5).—A solution of 4.0 g (0.0127 mol) of **4** in 200 ml of ethyl acetate was hydrogenated over 100 mg of Adams catalyst. After the uptake of hydrogen ceased, the solution was filtered and the solvent removed under vacuum. The remaining white solid, 3.95 g (99%), was recrystallized from benzene, mp 183–184.5°. The nmr spectrum was essentially the same as that for **4** with the exception that it now contained a multiplet centered at 2.2 ppm (ring CH_2) and the vinyl CH at 6.71 ppm was no longer present.

Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.68; H, 6.51; N, 9.10.

Attempted Hydrolysis of Ketal 5.—Hydrolysis of 1.0-g samples of **5** under a variety of conditions shown in Table I was unsuccessful. In all cases the reaction mixture was poured into ice water after the specified reaction time. The acid was neutralized with sodium bicarbonate and the mixture was extracted several times with methylene chloride or chloroform and dried over magnesium sulfate. The solution was filtered and solvent removed under vacuum. In all cases except the last, a yield of greater than 90% of starting material was recovered. Melting points, mixture melting points, and infrared spectra were all identical with that of starting material. In concentrated sulfuric acid at 70° complete decomposition occurred and no starting material or product was isolated.

2,3-Dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]hept-5-ene (8).—To a solution of 2.12 g (0.02 mol) of **6**[8] in 20 ml of tetrahydrofuran was added 2.92 g (0.02 mol) of ethyl azodicarboxylate. The reaction was exothermic and after 2 hr the orange color was completely dissipated. The infrared and inte-

(8) J. Thiele, *Ber.*, **33**, 666 (1900).

TABLE I
EXPERIMENTAL CONDITIONS USED IN ATTEMPTED HYDROLYSIS OF 5

Expt	Reaction medium	Temp, °C	Time, hr
1	25 ml of 5% H_2SO_4–25 ml of dioxane	Room temperature	24
2	66 ml of 10% H_2SO_4–33 ml of dioxane	Reflux	24
3	20 ml of 47% HI–10 ml of acetic acid	Room temperature	24
4	25 ml of 90% acetic acid	Reflux	24
5	25 ml of 70% perchloric acid	0	0.25
6	25 ml of concentrated sulfuric acid	Room temperature	1
7	30 ml of 70% sulfuric acid	Room temperature	1.5
8	25 ml of methylene chloride and 1.0 g of $AlCl_3$	Room temperature	0.5
9	25 ml of concentrated sulfuric acid	70	24

grated nmr spectra taken at this time were consistent with structure **8**. The nmr spectrum showed a triplet at 1.18 ppm (CH_3), a singlet at 1.68 ppm (CH_3), a quartet at 4.1 ppm (CH_2), a broad singlet at 5.22 ppm (bridgehead), and a triplet at 6.6 ppm (vinyl). Attempts to crystallize the yellow oil from a variety of solvents were unsuccessful. Distillation resulted in decomposition and polymerization, whereas column chromatography on Bio-Rad activity one neutral alumina resulted in reverse Diels–Alder reaction and some apparent decomposition of the azo compound as evidenced by the evolution of a gas. Elution with a benzene–ether mixture and evaporation of solvent gave an orange oil which appeared to be identical with that obtained by "aging" the original mixture for several days.

2,3-Dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]heptane (10).—A solution containing 0.4 mol of freshly prepared **8** dissolved in 350 ml of tetrahydrofuran was catalytically reduced with 1 g of 10% palladium on charcoal. Absorption of about 1.1 molar equiv of hydrogen proceeded very rapidly. The reaction mixture was filtered and the solvent was removed *in vacuo*. Distillation of the residual oil gave an 80% yield of product, bp 113–115° (0.04 mm).

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.45; H, 7.89; N, 10.12.

The nmr spectrum ($CDCl_3$) consisted of a triplet at 1.28 ppm (CH_2), a singlet at 1.75 ppm (CH_3), a broad singlet at 1.82 ppm (ring CH_2), a quartet at 4.25 ppm (CH_2), and a broad singlet at 4.85 ppm (bridgehead).

2,3-Dicarbethoxy-7,7-dihydroxy-2,3-diazabicyclo[2.2.1]heptane (13).—A solution of 28.2 g (0.1 mol) of **10** in 500 ml of absolute methanol was ozonized at −30° in the usual way. After reaction was complete the reaction mixture was catalytically reduced with 1 g of 10% palladium on charcoal. Approximately 70% of theoretical hydrogen was consumed very rapidly. The catalyst was filtered and solvent removed *in vacuo* to give a light yellow residual oil. The product, **13**, can be crystallized from this residual oil by trituration with ether; however, a much more convenient isolation procedure was to dissolve the oil in ether and extract with water. Removal of water *in vacuo* gave 14 g of a residual white solid, mp 129–133°. Recrystallization from acetone–cyclohexane gave 12 g (44%) of **13**, mp 131–133°. See discussion for spectral data.

Anal. Calcd for $C_{11}H_{18}N_2O_6$: C, 48.17; H, 6.62; N, 10.21. Found: C, 48.39; H, 6.80; N, 10.18.

6,6-Diphenylfulvene (7) was prepared by a modification of the method of Thiele.[8] To 1 l. of tetrahydrofuran, which had been distilled over lithium aluminum hydride, was added 24 g (1 mol) of sodium hydride, followed by the slow addition of 66.1 g (1 mol) of freshly distilled cyclopentadiene. After the evolution of hydrogen had ceased, a solution of 182.2 g (1 mol) of benzophenone in 800 ml of tetrahydrofuran was added over a period of 1 hr. The solution was stirred for 1 additional hr and poured into 2 l. of ice water and extracted with four 500-ml portions of 30–60° petroleum ether. The combined extracts were washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent was removed by evaporation. The remaining red solid was recrystallized from 30–60° petroleum ether to give 199 g (86%) of red solid, mp 81–82° (lit.[8] mp 82°).

2,3-Dicarbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]hept-5-ene (9).—To a solution of 3.31 g (0.0144 mol) of **7** in 40 ml of cyclohexane was added 2.50 g (0.0144 mol) of ethyl azodicarboxylate and the deep red solution was stirred for 24 hr at room temperature. The resulting white precipitate was filtered and washed with cold cyclohexane to give 4.74–5.51 g (81–95%) of product. Recrystallization from hexane afforded an analytical sample, mp 76–78°.

Anal. Calcd for $C_{24}H_{24}O_4N_2$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.18; H, 6.04; N, 6.75.

The infrared spectrum (liquid film) showed absorption maxima at 5.74 and 5.90 μ (C=O). The nmr spectrum (CCl_4) showed a triplet at 1.1 ppm (CH_3), a quartet at 4.1 ppm (CH_2), a triplet at 5.34 ppm (bridgehead), a triplet at 6.75 ppm (vinyl), and a singlet at 7.2 ppm (aromatic).

2,3-Dicarbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]heptane (11).—A 4.04-g (0.01 mol) sample of **9** was reduced over 100 mg of Adams catalyst in 100 ml of ethyl acetate at atmospheric pressure. The uptake of hydrogen was extremely slow after 1 equiv had been consumed (1.4 hr). The reaction mixture was filtered and concentrated under vacuum, and the remaining oil was crystallized from pentane. Recrystallization from pentane gave 3.3 g (81.5%) of product, mp 89–90.5°.

Anal. Calcd for $C_{24}H_{26}O_4N_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.71; H, 6.48; N, 6.88.

The infrared spectrum (liquid film) showed absorption maxima at 5.74 and 5.90 μ (C=O). The nmr spectrum (CCl_4) showed a triplet at 1.12 ppm (methyl), a singlet at 1.95 ppm (ring methylene), a quartet at 4.10 ppm (methylene), a triplet at 4.77 ppm (bridgehead), and a singlet at 7.2 ppm (aromatic).

Ozonolysis of 11.—Ozonolysis of **11** and work-up of the reduced ozonide in a manner identical with that described for **10** gave no water soluble material.

Registry No.—**4**, 16425-73-3; **5**, 16462-52-5; **7**, 2175-90-8; **8**, 16425-69-7; **9**, 16425-70-0; **10**, 16425-71-1; **11**, 16425-67-5; **13**, 16425-72-2.

Stereochemistry of Pyrrolidine Addition to Bicyclo[2.2.2]oct-2-ene-2-carbonitrile[1]

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In the reaction of pyrrolidine with bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1) the product is shown to be exclusively *trans*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2). The configuration is established by hydrolyzing 1 to the acid hydrochloride under epimerizing conditions which afford exclusively *trans*-3-pyrrolidinobicyclo-[2.2.2]octane-2-carboxylic acid hydrochloride (11) and reconverting this substance exclusively to 2 via the amide. The configuration of 11 is established with the aid of nmr spectra of model compounds: *trans*-3-aminobicyclo-[2.2.2]octane-2-carboxylic acid hydrochloride (15) and *cis*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (17). The apparent coupling constants ($J_{2,3}$) for 11 and 15 are identical and the corresponding constant for 2 is close to the same value, while $J_{2,3}$ for 17 is almost exactly the value expected for the *cis* configuration in which the dihedral angle is 0°.

In continuing studies directed toward synthesis of bicyclic acid derivatives of potential interest as anticancer agents,[4] it became desirable to study possible routes to a bicyclo[2.2.2]octane-2-carbonitrile containing a tertiary amino group as a model for a nitrogen mustard derivative. An obvious means of achieving this end appeared to be addition of pyrrolidine to bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1). Such a reaction is clearly analogous to cyanoethylation,[5] which appears in general to be reversible.[6,7] Kinetic data obtained by Ogata and Okano[8] agree with addition of the amine *via* rate-determining nucleophilic attack on the β carbon of an acrylonitrile, followed by a rapid intramolecular proton shift. Furthermore, Michael-type additions afford products varying from pure *trans* isomer through mistures to pure *cis* isomer, with the former being the one generally isolated.[9]

These considerations suggest the possible production of two epimeric adducts when pyrrolidine is added to 1: *trans*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2), and *cis*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (3). The mechanism study cited above implies that 2 should be more readily produced than 3; and the reversible character of the addition reaction, coupled with implied greater thermodynamic stability of 2 (Fisher–Hirschfelder models), likewise favors predominance of 2 over 3 in the product (Chart I).

Two successful syntheses were developed for preparation of 1 (Chart I). The over-all yields were comparable, but the first sequence was both more economical and more readily adaptable to large-scale synthesis. Method A begins with addition of chloromaleic anhydride to 1,3-cyclohexadiene to give *cis*-2-chlorobicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (4),[10] hydrogenation of which afforded *cis*-2-chlorobicyclo[2.2.2]-octane-2,3-dicarboxylic anhydride (5). This was then converted into bicyclo[2.2.2]oct-2-ene-2-carboxylic acid (6) by a typical dehalogenative decarboxylation (fragmentation).[4,11,12] Conversion of 6 into an acid chloride, which was at once treated with ammonium hydroxide solution, afforded bicyclo[2.2.2]oct-2-ene-2-carboxamide (7), which was dehydrated to 1 by refluxing with thionyl chloride.

Method B involves initial addition of propiolaldehyde to 1,3-cyclohexadiene to give bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (8), selective hydrogenation of which gave bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (9). Oximation[13] of 9 afforded bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (10), dehydration[14] of which produced 1.

The reaction of 1 with pyrrolidine was followed by glpc (at several temperatures), and only a single sharp peak was observed under all conditions, indicating the production of but one of the two possible isomers (2 and 3). Proof of configuration of this adduct as 2 was obtained in part by hydrolysis to a carboxylic acid hydrochloride (11) (under conditions conducive to epimerization,[15] which was then converted into its amide (12); and finally 12 was dehydrated to the nitrile, which proved to be identical with the original 2 (nmr and infrared spectra, glpc). At no stage in these operations was it possible to detect other than one isomer, even in the crude reaction products. Thus either no epimerization has taken place in the sequence, 2 → 11 → 12 → 2 (Chart II), or an even number of epimerizations, which are necessarily total, has occurred. The probability of the latter happening is vanishingly small, and hence it may be inferred that the configuration of the nitrile (2) and that of the acid hydrochloride (11) are the same.

The remainder of the configuration proof for 2 comes from preparation of model compounds for comparative nmr study and is supported by the nmr spectrum of 2 itself. By using milder conditions than given by Petrov[16] for the addition of dimethyl fumarate to 1,3-cyclohexadiene more than twice the yield of *trans*-2,3-dicarbomethoxybicyclo[2.2.2]octane (13) was obtained. Half saponification gave *trans*-3-carbometh-

(1) Abstracted in part from the Ph.D. dissertation of C. M. Wynn, The University of Michigan, 1965, and supported in part by a grant (CA05406) from the National Cancer Institute to The University of Michigan.

(2) U. S. Public Health Service Predoctoral Fellow (1-Fl-GN-20, 168-01 National Institute of General Medical Sciences), 1963–1965, Koppers Foundation Summer Research Fellow, 1963, E. I. du Pont de Nemours and Co. Teaching Fellow, 1962–1963, Union Carbide Corp. Summer Research Fellow, 1962.

(3) To whom inquiries should be addressed at the Department of Chemistry, The University of Connecticut, Storrs, Conn. 06268.

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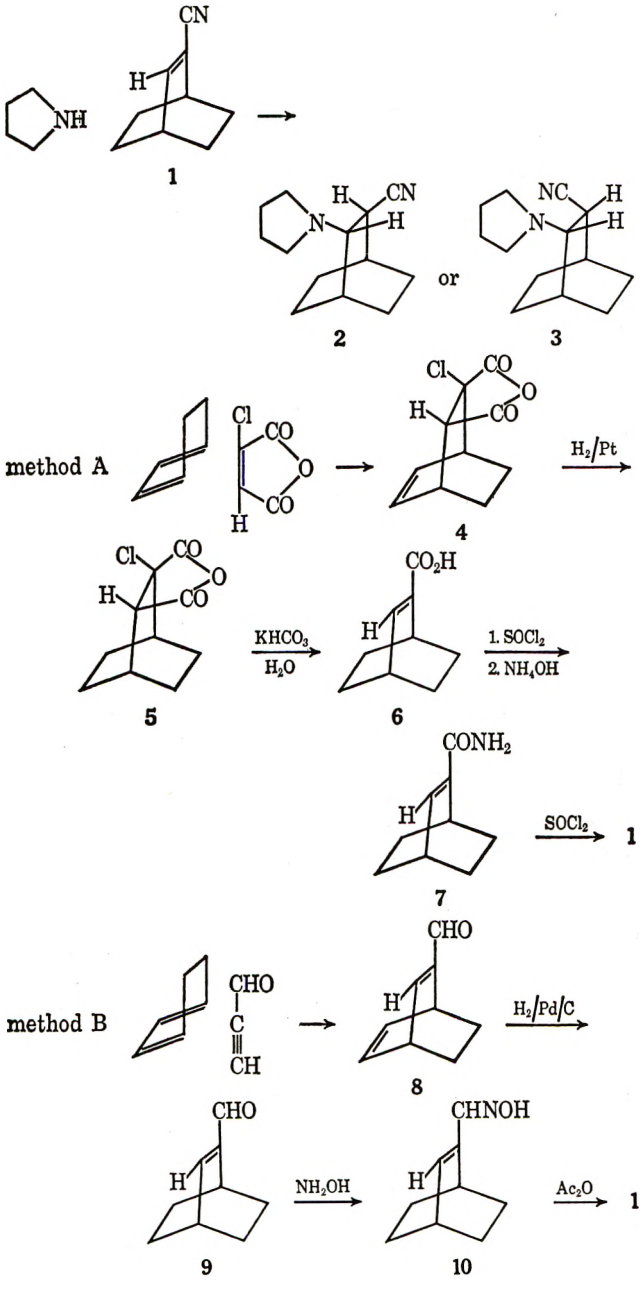
(16) A. A. Petrov and N. P. Sopov, *Sb. Statei Obshch. Khim.*, **2**, 853 (1953); *Chem. Abstr.*, **49**, 5830*b* (1955).

CHART I
SYNTHESES OF 2 AND 1

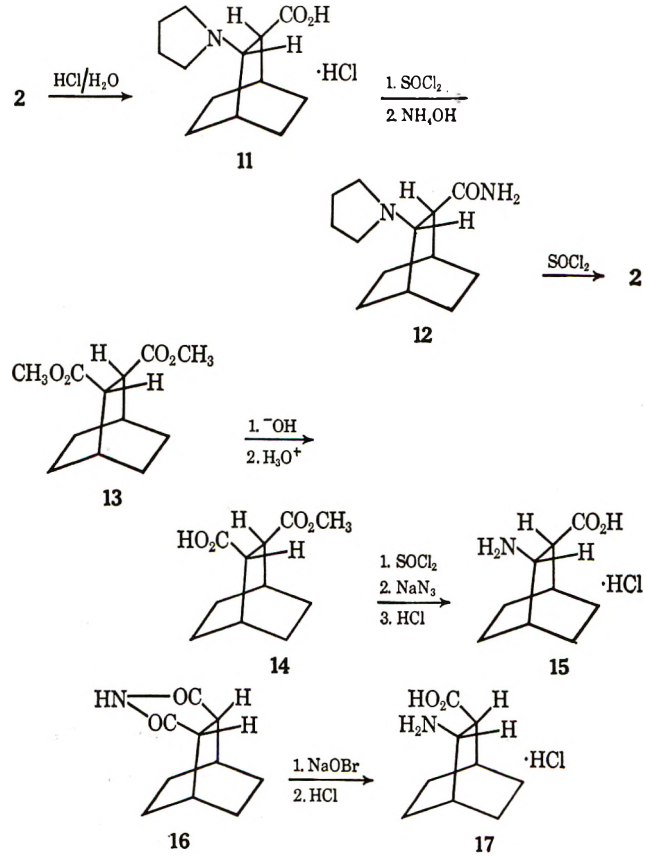


oxybicyclo[2.2.2]octane-2-carboxylic acid (**14**), which was converted *via* the Curtius reaction ("wet" method)[17] to *trans*-3-aminobicyclo[2.2.2]octanecarboxylic acid hydrochloride (**15**) (Chart II).

The second model compound was prepared from *cis*-bicyclo[2.2.2]octane-2,3-dicarboximide[18-21] (**16**) *via* the Hofmann rearrangement[22] which affords *cis*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (**17**). That **15** and **17** are indeed *cis–trans* isomers is clear from the fact that they afford different *p*-toluenesulfonamides (Experimental Section) and display different coupling constants ($J_{2,3}$). The configurations must be as assigned, and involve no epimerization (or an even number of epimerizations in the preparation of **15**), or they are reversed (and involve an odd number of epimerizations in the preparations of both **15** and **17**) (Chart II).

The conversion of **16** to **17** can admit of but one epimerization (*cis* to *trans*, *via* enolization). If this occurs, any common enolizations in the sequence **13** → **15** should favor *trans* products, leaving only the reaction of **14** with thionyl chloride as a potential reverse (*trans* to *cis*) epimerization. Although epimerization of this general type has been reported,[23] the nmr spectra of **15** and **17** suggest over-all retention of configurations in both reaction sequences. Thus, while the (apparent) coupling constants for the *trans* 2,3 protons in **15** and the *cis* 2,3 protons in **17** are somewhat larger than those predicted by the Karplus equation,[24] they agree with the values given by Williamson and Johnson's revised expression[25] in which $J = 10$ cps when the dihedral angle is 0° (*cis* in the present system) and $J = 4$ cps when the angle is 120° (*trans* in the present system). Thus for **17**, $J_{2,3} = 10.3 \pm 0.2$ cps, and for **15**, $J_{2,3} = 6.3 \pm 0.2$ cps. The latter value is identical with the value for $J_{2,3}$ for **11**, which strongly supports a *trans* configuration for **11**. Since it has already been inferred that the configuration for **2** is the same as that for **11**, the value $J_{2,3} = 5.1 \pm 0.2$ for **2** confirms the *trans* configuration for the adduct of pyrrolidine and **1**. Thus, the only isomer observed in the conjugate addition of pyrrolidine to bicyclo[2.2.2]oct-2-ene-2-carbonitrile has the *trans*

CHART II
AMINO ACID SYNTHESES



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configuration, in keeping with inferences drawn from kinetics of the cyanoethylation reaction[8] and the examination of Fisher–Hirschfelder models, the only unusual observation being the failure to detect by any method a measurable amount of the epimeric *cis* isomer.

Experimental Section[26-29]

cis-2-Chlorobicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (4).[10]—A solution of 58.0 g (0.73 mol) of 1,3-cyclohexadiene and 96.0 g (0.73 mol) of chloromaleic anhydride in 100 ml of ethyl acetate was refluxed overnight. The solvent and unreacted starting material were removed by water pump distillation and the product was sublimed at 100° (1 mm) to give 114.0 g (73.9%), mp 176–178°, of a colorless waxy solid, mp 187–189° (after five sublimations at 100° and 1 mm).

Anal. Calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27; Cl, 16.66. Found: C, 56.82; H, 4.47; Cl, 16.53.

cis-2-Chlorobicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (5).—A solution of 59.8 g (0.28 mol) of *cis*-2-chlorobicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (4) in 100 ml of ethyl acetate was hydrogenated at 3 atm with 0.5 g of Adams platinum dioxide catalyst. After filtration and removal of ethyl acetate, sublimation at 100° (1 mm) gave 58.0 g (96.2%) of a colorless waxy solid, mp 201–203°.

Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; Cl, 16.52. Found: C, 56.04; H, 5.23; Cl, 16.35.

Bicyclo[2.2.2]oct-2-ene-2-carboxylic Acid (6).—A solution of 10.4 g (0.104 mol) of potassium bicarbonate in 40 ml of water was added to 11.0 g (0.052 mol) of *cis*-2-chlorobicyclo[2.2.2]octane-2,3-dicarboxylic anhydride (5). The resulting solution was heated at 100° for 1 hr, cooled, and acidified with concentrated hydrochloric acid, and then cooled in a refrigerator for 1 hr. The white solid was filtered, washed with water, and dried *in vacuo*. A white crystalline solid (14.80 g, 61.7%), mp 90–91°, was obtained. Recrystallization from water–ethanol raised the melting point to 93–94°.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.88; H, 7.94.

Bicyclo[2.2.2]oct-2-ene-2-carboxamide (7).—A 4.6-g (0.03 mol) sample of bicyclo[2.2.2]oct-2-ene-carboxylic acid (6) was refluxed for 1 hr with 46 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was cooled in ice and treated dropwise with 50 ml of ice-cooled 28% ammonium hydroxide solution. After cooling and filtration, the white solid was washed with water and dried *in vacuo*, giving 1.4 g (31%), mp 128–132°, of a white crystalline solid, mp 140–141° (after three recrystallizations from water–ethanol).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.50; H, 8.61; N, 9.12.

Bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1).—A 4.6-g (0.03 mol) sample of bicyclo[2.2.2]oct-2-ene-2-carboxamide (7) was refluxed for 24 hr with 46 ml of thionyl chloride, the excess of which was removed using a water pump; distillation gave 3.4 g (84%) of a colorless oil, bp 40–46° (0.3 mm). The oil darkens on standing and should be stored under refrigeration in a dark bottle.

Anal. Calcd for $C_9H_{11}N$: C, 81.15; H, 8.33; N, 10.52. Found: C, 80.51; H, 8.24; N, 10.28.

Bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (8).—A solution of 39.0 g (0.490 mol) of 1,3-cyclohexadiene and 23.5 g (0.435 mol) of propiolaldehyde was stirred at room temperature for 1 week. Reaction progress was followed by observation of the decrease in triple bond absorption (2140 cm^{-1}) in the infrared spectrum. Distillation of the reaction mixture gave 38.6 g (66.0%) of a colorless liquid, bp 84–85° (20 mm). Nmr analysis showed the aldehyde proton at τ 0.52, the vinyl proton at 2.76 (quartet), two unconjugated vinyl protons at 3.68 (triplet), bridgehead protons at 5.76 and 6.25, and the remaining protons in an envelope centered about 8.80 (deuteriochloroform solvent).

Anal. Calcd for $C_9H_{10}O$: C, 80.54; H, 7.51. Found: C, 80.40; H, 7.32.

Bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (9).—Hydrogen (0.10 mol) was added to 13.4 g (0.1 mol) of bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (8) in 100 ml of ethyl acetate with 0.3 g of 5% palladium-on-carbon catalyst. After filtration and removal of ethyl acetate, distillation gave 10.1 g (74.1%) of a colorless liquid, bp 86–89° (20 mm). Nmr analysis showed the aldehyde proton at τ 0.52, the conjugated vinyl proton at 2.76 (quartet), bridgehead protons at 6.80 and 7.20, and the remaining protons in an envelope centered about 8.73 (deuteriochloroform solvent).

Bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (10).—A solution of 1.0 g (0.0074 mol) of bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (9), 1.0 g (0.014 mol) of hydroxylamine hydrochloride, 6 ml of pyridine, and 6 ml of absolute alcohol was refluxed for 24 hr, then poured into an evaporating dish and the was solvent removed in a current of air. The residue was taken up in ether and washed with 5% hydrochloric acid solution. The ether solution was dried over magnesium sulfate; after filtration and removal of ether, 0.59 g (53%), mp 88.5–90.0°, of a white solid, mp 89–90° (after three recrystallizations from ethanol), was obtained.

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.51; H, 8.54; N, 9.34.

Bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1).—A solution of 0.64 g (0.0042 mol) of bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (10) and 4 ml of acetic anhydride was refluxed for 24 hr, then carefully poured into 15 ml of cold water. The aqueous solution was extracted with ether; the ether solution was then washed with 10% sodium carbonate solution and dried over magnesium sulfate. After filtration and removal of ether, the remaining liquid was purified by evaporative distillation at 100° (1 mm) to give 0.30 g (53%) of a colorless liquid whose infrared spectrum was superimposable on that of 1 obtained by dehydration of bicyclo[2.2.2]-oct-2-ene-2-carboxamide (7).

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2) and/or *cis*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (3).**—A 7.98-g (0.06 mol) sample of bicylo[2.2.2]oct-2-ene-2-carbonitrile (1) was refluxed for 24 hr with 8.52 g (0.12 mol) of pyrrolidine, the excess of which was removed by distillation, and the residual dark brown liquid was dissolved in 5% hydrochloric acid solution and then extracted with ether. After basification with 28% ammonium hydroxide solution, the aqueous phase was extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, distillation gave 7.00 g (57.2%) of a colorless liquid at 90–94° (0.1 mm). Glpc analyses using a silicone oil 200 on Haloport-F column at 130 and 150° and a silicone gum rubber on Chromosorb P column at 140 and 160° each showed a single sharp peak. Glpc analysis (silicone gum rubber column at 140°) of the reaction mixture at room temperature showed peaks corresponding to starting materials and the isomer isolated from the refluxing reaction mixture (see above). There was no indication of a second isomer.

Nmr analysis showed the proton α to the nitrile group at τ 7.72 (a pair of quartets with unresolved fine structure, splitting by the proton α to the pyrrolidino group is 5.1 ± 0.2 cps.). The five protons α to the pyrrolidino nitrogen appeared in a poorly resolved group centered about τ 7.48 (deuteriochloroform solvent); picrate, mp 234–235° dec.

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87. Found: C, 76.32; H, 9.90.

Anal. Calcd for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.60; H, 5.25; N, 16.30.

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carboxylic acid Hydrochloride (11).**—A solution of 4.90 g (0.024 mol) of *trans*-2-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2) and/or *cis*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (3) and 8 ml of concentrated hydrochloric acid was refluxed for 24 hr. The solution was evaporated to dryness and triturated with 100 ml of hot *n*-butyl alcohol. Evaporation of the butanol gave 5.95 g (95.4%), mp 232–236°, of a white crystalline solid, mp 240–241° dec (after recrystallization from absolute alcohol). Nmr analysis showed the proton α to the carboxyl group at τ 7.21 (quartet, splitting by the proton α to the pyrrolidino group is 6.3 ± 0.2 cps, which is the same as that for *trans*-3-amino-bicyclo[2.2.2]-octane-2-carboxylic acid (15) and splitting by the bridgehead

(26) Boiling and melting points are uncorrected.

(27) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra obtained from Nujol mulls (solids) or liquid films, Perkin-Elmer Model 21 infrared spectrometer. Nmr spectra (Varian A-60) were obtained by Mr. F. Parker and Mr. G. Schütze of this department (internal tetramethylsilane, 60 Mc).

(28) Mr. R. Pietcher of Varian Associates, Pittsburgh, Pa., kindly ran a spectrum of II using an HA-100 Varian spectrophotometer system.

(29) The following materials were obtained from Hi-Laboratory, Whitmore Lake, Mich.: 1,3-cyclohexadiene, propiolaldehyde, α-chloroacrylonitrile, and *cis*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride.

proton is 2.4 ± 0.2 cps). The five protons α to the pyrrolidino nitrogen appeared downfield in a wide poorly resolved group centered about τ 6.60 (deuterium oxide solvent).

Anal. Calcd for $C_{13}H_{22}ClNO_2$: C, 60.10; H, 8.54; Cl, 13.65; N, 5.39. Found: C, 60.07; H, 8.49; Cl, 13.66; N, 5.40.

trans-**3-Pyrrolidinobicyclo[2.2.2]octane-2-carboxamide (12).**—A 4.60-g (0.018 mol) sample of *trans*-3-pyrrolidinobicyclo[2.2.2]-octane-2-carboxylic acid hydrochloride (**11**) was stirred at room temperature for 24 hr with 46 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was cooled in ice and treated dropwise with 50 ml of ice-cooled 28% ammonium hydroxide solution. After dilution with water, the solution was extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and, after removal of the ether, gave 1.93 g (49.1%) of a white solid, mp 155–159°. Two recrystallizations from absolute alcohol raised the melting point to 165.0–165.5°.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.01; H, 9.92; N, 12.58.

trans-**3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2).**—A 1.93-g (0.0087 mol) sample of *trans*-3-pyrrolidinobicyclo-[2.2.2]octane-2-carboxamide (**12**) was heated at 45° for 38 hr with 20 ml of thionyl chloride, the excess of which was distilled, and the residual light brown liquid was added to 5% sodium hydroxide solution, and then this solution was extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, distillation gave 3.81 g (80.1%) of a colorless liquid, bp 91–95° (0.1 mm). The infrared and nmr spectrum of this liquid are superimposable on those of the adduct of bicyclo[2.2.2]oct-2-ene-2-carbonitrile (**1**) and pyrrolidine. Their glpc retention times were identical using a silicone oil 200 on Haloport-F column at 130 and 150° and a silicone gum rubber on Chromosorb P column at 140 and 160°.

trans-**3-Carbomethoxybicyclo[2.2.2]octane-2-carboxylic Acid (14).**—A solution of 41.0 g of potassium hydroxide pellets in 350 ml of absolute methanol was slowly added to a well-stirred solution of 125.0 g (0.553 mol) of *trans*-2,3-dicarbomethoxybicyclo-[2.2.2]octane (**13**)[30] in 350 ml of absolute methanol. The stirring was continued at room temperature for 24 hr, and then 1.2 l. of water was added and the resulting solution extracted twice with 600-ml portions of ether. The ether extracts were dried over magnesium sulfate, filtered, and, after removal of the ether, gave 3.7 g of recovered **13**. The aqueous phase was acidified with concentrated hydrochloric acid, then extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and, after removal of the ether, gave 110.5 g (94.2%), mp 97–100°, of a white crystalline solid, mp 102.0–103.5° (after two recrystallizations from water–ethanol).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.12; H, 7.72.

trans-**3-Aminobicyclo[2.2.2]octane-2-carboxylic acid Hydrochloride (15).**—A 5.1-g (0.024 mol) sample of *trans*-2-carbomethoxybicyclo[2.2.2]octane-3-carboxylic acid (**14**) was refluxed for 1 hr with 25 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was dissolved in 60 ml of acetone, then cooled in ice. A solution of 1.7 g of sodium azide in 4.5 ml of water was added dropwise to the ice-cooled solution and, after stirring for 1 hr, 120 ml of water was added and the resulting solution extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, the remaining azide was refluxed overnight in 12 ml of dry xylene. This solution was cooled in an ice bath and 25 ml of concentrated hydrochloric acid was added. After refluxing overnight, the solution was evaporated in an air stream, water was added, and the solution extracted with ether. The aqueous phase was evaporated in an air stream and dried *in vacuo* giving 3.0 g (61%), mp 213–225°, of a creamy white solid, mp 225–230° dec (after recrystallization from water–ethanol). Nmr analysis showed the proton α to the carboxyl group at τ 7.34 (quartet; splitting by the proton α to the amino group is 6.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps). The proton α to the amino group appeared at τ 6.12 (quartet, splitting by the proton α to the carboxyl group is 6.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps) (deuterium oxide solvent); *p*-toluenesulfonamide, mp 176–177°.

Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.55; H, 7.84; Cl, 17.24; N, 6.81. Found: C, 52.51; H, 7.86; Cl, 17.29; N, 6.72.

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.43; N, 6.55; N, 4.33; S, 9.90. Found: C, 59.35; H, 6.58; N, 4.40; S, 9.88.

cis-**3-Aminobicyclo[2.2.2]octane-2-carboxylic Acid Hydrochloride (17).**—A sample of 1.62 g (0.01 mol) of bromine was slowly added to an ice-cooled solution of 5.03 g of potassium hydroxide pellets in 45 ml of water; 1.79 g (0.01 mol) of *cis*-bicyclo[2.2.2]octane-2-dicarboximide (**16**)[21] was slowly added and the resulting solution heated at 60° for 2 hr. After cooling, the solution was acidified with concentrated hydrochloric acid and evaporated to dryness. The crude solid was triturated with cold water (leaving unreacted **16**), evaporated to dryness, triturated with hot *n*-butyl alcohol (leaving inorganic salts), and then the butanol was evaporated to dryness. The residual solid was recrystallized from absolute alcohol to give 0.51 g (24.8%) of a white crystalline solid, mp 227–230°. Nmr analysis showed the proton α to the carboxyl group at τ 6.82 (quartet, splitting by the proton α to the amino group is 10.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps). The proton α to the amino group appeared at τ 6.22 (quartet, splitting by the proton α to the carboxyl group is 10.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps) (deuterium oxide solvent); *p*-toluenesulfonamide, mp 159°.

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.43; H, 6.55; N, 4.33; S, 9.90. Found: C, 59.27; H, 6.59; N, 4.40; S, 9.94.

Registry No.—**1**, 14948-74-4; **2**, 16317-18-3; picrate of **2**, 16317-19-4; **4**, 16317-20-7; **5**, 16317-21-8; **6**, 16317-22-9; **7**, 16317-23-0; **8**, 16317-24-1; **9**, 16317-25-2; **10**, 16317-26-3; **11**, 16317-27-4; **12**, 16317-28-5; **14**, 16317-29-6; **15**, 16317-30-9; *p*-toluenesulfonamide of **15**, 16394-36-8; **17**, 16317-32-1; *p*-toluenesulfonamide of **17**, 16317-31-0; pyrrolidine, 123-75-1.

Acknowledgment.—The authors wish to acknowledge the very effective assistance of Mr. Gunther Schütze in the synthesis of certain of the compounds reported herein.

(30) H. Koch, *Monatsh.*, **93**, 1343 (1962).

Base-Promoted Reactions of Epoxides. V. 1-Alkylcycloalkene Oxides[1]

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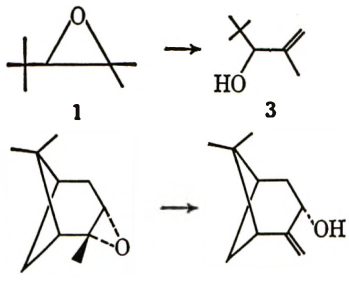
The lithium diethylamide isomerizations of the C_6–C_8 1-methylcycloalkene oxides result initially in formation of the corresponding 2-methylenecycloalkanols. Under the appropriate conditions this reaction provides a convenient preparative source of these alcohols. However, these materials are subject to an interesting further isomerization which leads to 2-methylcycloalkanones and 2-methyl-2-cycloalkenols under more severe reaction conditions. 1-*t*-Butylcyclooctene oxide gives the two possible allylic alcohols derived from β elimination (1- and 2-*t*-butyl-2-cyclooctenol) upon similar base isomerization. None of the products encountered in this study requires an α-elimination mechanism to account for its formation.

In earlier papers of this series,[1-3] the reactions of a variety of cyclic and acyclic epoxides caused by strongly basic, nonnucleophilic reagents were examined. Two major competing reaction pathways were suggested, the relative efficiencies of which depend on the specific molecule in question. In systems where a favorable *trans*, coplanar, transition-state geometry can be readily attained, β elimination to give allylic alcohols is preferred. When such is not the case, the products are thought to evolve from α elimination at an epoxide ring carbon and carbenoid insertion into a neighboring carbon–hydrogen bond.

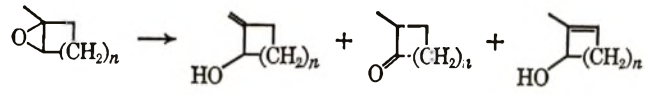
The lithium diethylamide treatment of β-diisobutylene oxide (**1**) and α-pinene oxide (**2**) resulted in a remarkably clean conversion to the respective allyl alcohols **3** and **4**.[2] Exclusive β elimination into the substituent methyl groups was rationalized as a consequence of the unique ability of the methyl group to provide a relatively unhindered version of the necessary β-elimination geometry. In the present work the 1-methylcycloalkene oxides of ring-size five through eight have been examined in order to ascertain the suitability of base rearrangement as a synthetic route to the corresponding exocyclic methylene alcohols.



1 **3**

2 **4**

After considerable exploratory work, experimental conditions were devised which effected the predominant conversion of the six-, seven-, and eight-ring epoxides to the desired isomeric methylene alcohols in good yields. Thus, treatment of 1-methylcyclohexene oxide (**5**) with lithium diethylamide in refluxing ether for 1 day gave 2-methylenecyclohexanol (**6**) as 79% of the distilled product along with a minor amount (11%) of 2-methylcyclohexanone (**7**). Similar conditions transformed 1-methylcycloheptene oxide (**8**) to 1-methylenecycloheptanol (**9**). However, reaction in refluxing benzene generated a more complex mixture which contained 2-methylcycloheptanone (**10**) and 2-methyl-2-cycloheptenol (**11**) in addition to **9**. 1-Methylcyclooctene oxide (**12**) was isomerized to 2-methylenecyclooctanol (**13**) containing 6% of 2-methylcyclooctanone (**14**) when reacted with diethylamide in ether at room temperature for 5 hr. Again, more severe reaction conditions resulted in a mixture of **13**, **14**, and 2-methyl-2-cyclooctenol (**15**). Finally, it should be mentioned that 1-methylcyclopentene oxide (**16**) gave no 2-methylenecyclopentenol (**17**) under even the mildest conditions examined; 2-methylcyclopentanone (**18**) and 2-methyl-2-cyclopentenol (**19**) were the important products. Therefore, insofar as preparative utility is concerned, it appears that the diethylamide rearrangement of 1-methylcycloalkene oxides provides a viable and general synthetic route to the corresponding 2-methylenecycloalkanols, so long as careful attention is devoted to experimental detail.[4]



3[a]	5	6	7	...
4[a]	8	9	10	11
5[a]	12	13	14	15
2[a]	16	17	18	19

[a] *n*

The obvious conclusion derived from the reactions run under more severe conditions is that the initially formed 2-methylenecycloalkanols are subject to further reaction in strongly basic media which leads to the 2-methylcycloalkanones and 2-methyl-2-cycloalkenols. Experimental confirmation of this deduction was secured by showing that the methylene alcohols **9** and **13** did, in fact, undergo the proposed conversions. Similar processes appear likely for the five- and six-ring analogs. The absence of 2-methylenecyclopentanol (**17**) in the product from **16** is notable, but the formation of 2-methyl-2-cyclopentenol as the sole allylic alcohol rather convincingly implicates the methylene compound as the precursor of the endocyclic allylic alcohol, since simple β elimination internal to the carbocycle would be expected to yield the 5-methyl derivative in addition to **19**.

The secondary isomerizations of the methylene alcohols appear to be best rationalized in terms of reversible allylic metallation of the corresponding lithium alkoxide and attendant double bond migration during the lifetime of the resulting allyllithium species or in the

(1) Part IV: J. K. Crandall and L. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4527 (1967).

(2) J. K. Crandall and L. Chang, *J. Org. Chem.*, **32**, 435, 532 (1967).

(3) J. K. Crandall and L. C. Lin *J. Amer. Chem. Soc.*, **89**, 4526 (1967).

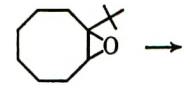
(4) Professor E. Warnhoff has kindly informed us that *trans*-caryophyllene oxide is converted into the corresponding exocyclic methylene compound in good yield.

process of its protonation.[5] Bond migration into the ring away from the alkoxide function leads to the lithium alkoxide of the endocyclic allylic alcohols (or related organolithium intermediates), while isomerization toward the alkoxide group eventually generates the lithium enolates of the methylcycloalkanones. The first transformation is a relatively routine one, but the isomerization leading to ketones is not, to our knowledge, a recognized mode of allylic alcohol rearrangement under strongly basic conditions. Support for the proposed mechanism for interconversion of the two allylic alcohols is found in the demonstration that partial isomerization of **11** and **15** to the exocyclic isomers **9** and **13** does occur. It is probably significant that ketones **10** and **14** were not found in these experiments since this surprising result was checked several times. The last observation is consistent with the results of our earlier work.[2,6] For example, 2-cycloheptenol has been rigorously shown not to yield cycloheptanone under isomerization conditions.[2] 2-Cycloheptenol is, however, converted into 1,3-cycloheptadiene upon such treatment, and a similar process probably accounts for the small amount of olefinic materials found in several of the above isomerizations (see Experimental Section). Thus, it would appear that there is a special feature of the exocyclic methylene alcohols, probably geometric in origin, which renders their behavior exceptional with respect to more usual allylic alcohols. Rational proposals accounting for the unusual features of ketone formation can be contrived, but detailed discussion seems best delayed until additional experimental information is available.

In an attempt to promote transannular reactions of the type observed with the unsubstituted seven- and eight-membered cycloalkene oxides (for example, **20** → **21**),[2,7] 1-methylcycloheptene oxide was treated with *t*-butyllithium, a reagent which has been found to enhance metallation at the epoxide ring. However, the major products were again ketone **10** and alcohol **9**, along with a new material identified as 1-*t*-butyl-2-methylcycloheptanol.

20 **21**

The last part of this study involved the preparation of 1-*t*-butylcyclooctene oxide (**22**), a molecule which is not capable of elimination into the substituent group. For this reason, we expected that this material might parallel the parent cyclooctene oxide in its reactions.[7] However, the only isomeric compounds formed upon lithium diethylamide treatment were the two possible allylic alcohols, 1-*t*-butyl-2-cyclooctenol (**23**) and 2-*t*-butyl-2-cyclooctenol (**24**). In addition, 2-*t*-butyl-1,3-cyclooctadiene (**25**) and a second unidentified olefin (probably the 1-*t*-butyl isomer) were found. The



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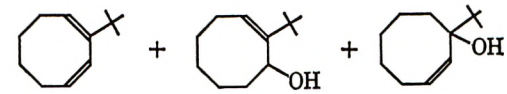
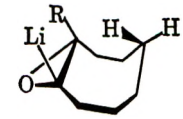


25 **24** **23**

same two allylic alcohols were secured as the major products with *t*-butyllithium as the basic reagent.

These results can be explained, after the fact, on the basis of the steric influence of the bulky *t*-butyl substituent. We have suggested earlier[2] that a transition-state conformation similar to **26** is necessary to rationalize the stereochemistry of alcohol **21** formed from the parent cyclooctene oxide. In the same transition-state geometry for the *t*-butyl compound (**27**), there may be enough destabilization owing to nonbonded interactions of the substituent that decomposition occurs by more favorable pathways, namely β elimination.[8] Similar effects can be anticipated for other substituents. An alternate possibility for the suppression of α elimination is simply that the *t*-butyl group inhibits metallation at the epoxide ring, a process which must precede the



26, R = H
27, R = *t*-Bu

transannular insertion reaction. In any event, it is clear that substituted medium-ring epoxides will not necessarily parallel the parent compounds in their base rearrangements.

Experimental Section

General.—All nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Data are given in ppm relative to tetramethylsilane as internal standard in carbon tetrachloride solution. Infrared spectra were recorded on Perkin-Elmer 137 and 137G spectrometers and were taken on neat samples unless indicated otherwise. Gas chromatography (glpc) was performed on a 5 ft × 0.125 in. 15% Carbowax 20M column on an Aerograph A-600 (analytical) instrument and on a 10 ft × 0.375 in. 15% Carbowax 20M column or a 20 ft × 0.375 in. 20% Carbowax 20M column on an Aerograph A-700 (preparative) instrument. Percentage composition data were estimated by peak areas and are uncorrected. All melting points were determined in capillary tubes. Microanalyses were performed by Midwestern Microlab, Inc., and Huffman Laboratories, Inc. Anhydrous magnesium sulfate was used throughout as a drying agent.

Preparation of Epoxides.—Epoxides were prepared by a modification of the procedure of Korach, *et al.*[9] To an ice-cold, mechanically stirred mixture of 1 equiv of olefin and 3 equiv of powdered, anhydrous sodium carbonate in methylene chloride was added dropwise 1.1 equiv of 40% peracetic acid which had been treated with a small amount of sodium acetate. The mixture was stirred at room temperature until the methylene chloride solution gave a negative test with moist starch–iodide paper. The solid salts were removed by suction filtration and washed well with additional methylene chloride. The solvent was re-

(5) A general discussion of allylic carbanions is found in D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 176–210.

(6) Unpublished results of L. C. Lin and A. C. Clark. Interestingly, cycloheptene and cyclooctene oxides are converted by lithium diethylamide *in tetrahydrofuran* into mixtures of the allylic alcohols *and their double bond isomers* to the exclusion of bicyclic products.[2]

(7) A. C. Cope, H. H. Lee, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2849 (1958).

(8) The β elimination may proceed with a *cis*, coplanar geometry: M. Svoboda, J. Zavada, and J. Sicher, *Collect. Czech. Chem. Commun.*, **32**, 2104 (1967); J. Sicher and J. Zavada, *ibid.*, **32**, 2122 (1967).

(9) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

moved from the filtrate by distillation through a Vigreux column, and the residue was purified by distillation through a spinning band column. The following epoxides were prepared by this method: 1-methylcyclopentene oxide (16),[10] yield 61%, bp 108–110°, infrared bands at 10.8, 12.0 μ, epoxide ring proton in the nmr spectrum at δ 3.07, methyl at 1.39; 1-methylcycloheptene oxide (8), yield 65%, bp 70–75° (50 mm), ir 11.0, 12.2 μ, nmr, a one-proton triplet at δ 2.68 (epoxide ring proton, J = 9 cps), methyl singlet at 1.22 and the other ten protons at 2.0–1.2 (*Anal.* Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.26; H, 11.22); 1-methylcyclooctene oxide (12),[11] yield 63%; bp 97–100° (33 mm), ir 10.9, 12.0 μ; and 1-*t*-butylcyclooctene oxide (22), yield 45%, bp 72–76° (6 mm), ir 10.7, 11.9 μ, nmr, a one-proton multiplet at δ 2.75 (epoxide ring-proton), *t*-butyl singlet at 0.96 and the other twelve protons between 2.5 and 1.3 (*Anal.* Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.06; H, 12.06).

1-Methylcyclohexene Oxide (5).—Epoxidation of 1-methylcyclohexene with peracetic acid led to 2-methylcyclohexanone; however, epoxidation with *m*-chloroperbenzoic acid gave the desired epoxide. To an ice-cold, mechanically stirred solution of 20 g of 1-methylcyclohexene in 200 ml of methylene chloride was added 44 g of 85% *m*-chloroperbenzoic acid in portions. The mixture was stirred at room temperature until the methylene chloride solution gave a negative test with starch–iodide paper (3 days). The solid salts were removed by suction filtration and washed well with additional methylene chloride. The methylene chloride solution was washed with saturated sodium carbonate solution and water and dried. The solvent was removed by distillation through a Vigreux column, and the residue was distilled through a spinning band column to give 17.9 g (80%) of pure 1-methylcyclohexene oxide, bp 85–88° (30 mm).[12] This material shows bands at 7.28, 11.0, and 11.9 μ, and its nmr spectrum displays a one-proton triplet at δ 2.78 (epoxide ring proton, J = 2 cps), and the other 11 protons are at 2.0–0.9 with a methyl singlet at 1.23.

Typical Procedure for Rearrangement of Epoxides by Lithium Diethylamide.—To an ice-cold solution of 2.5 equiv of diethylamine in anhydrous ether was added 2.5 equiv of commercial 15% butyllithium in hexane under a nitrogen atmosphere. After 10 min a solution of 1 equiv of the appropriate epoxide in anhydrous ether was added; the mixture was heated to reflux for the specified period. The reaction mixture was cooled and poured into water; the organic layer separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water. After drying, the solvent was removed by distillation through a column, and the residue was purified by distillation. If the product was a mixture, further purification was effected by preparative glpc. Product identification was by comparison of spectral data with those of authentic samples obtained from commercial sources or by literature methods unless indicated otherwise.

Rearrangement of 1-Methylcyclopentene Oxide (16).—The reaction was carried out with 4.9 g of **16** in 300 ml of ether in the usual fashion for 5 hr. Distillation of the product gave 3.62 g (74%) of a pale liquid of wide boiling range. In addition to several trace products it contained 10% of 2-methylcyclopentanone and 82% of 2-methyl-2-cyclopentenol[13] which were identified by spectral data. 2-Methylcyclopentanone shows infrared absorption at 5.75 and 7.3 μ. Its nmr spectrum shows a methyl doublet (J = 6 cps) at δ 1.03 and a broad band at 2.03 for the other seven protons. 2-Methyl-2-cyclopentenol has infrared bands at 3.0, 3.3, and 7.3 μ. Its nmr spectrum displays a one-proton multiplet at δ 5.48 (C=C*H*), a two-proton multiplet at 4.3 (C*H*O*H*), a methyl singlet at 1.7, and the other four protons at 2.4–1.8.

The aqueous portion of work-up was made basic and extracted with ether to give additional 2-methyl-2-cyclopentenol. The total yield of this alcohol was 65%.

Rearrangement of 1-Methylcyclohexene Oxide (5).—Rearrangement of 5.6 g of **5** in refluxing ether for 1 day gave 3.25 g of distilled product. Analysis by glpc indicated the presence of three components in an 11:79:10 ratio. The first component was identified as 2-methylcyclohexanone.[14] The second component was identified as 2-methylenecyclohexanol[15] on the basis of its spectra: ir, 2.98, 6.08, and 11.1 μ; nmr absorption as one-proton broad singlets at δ 4.85 and 4.74 (C=CH_2), a two-proton multiplet at 3.97 (C*H*O*H*), and the other protons at 2.4–1.2. The third component is a higher molecular weight compound believed to be 2-methylenecyclohexyl 2-methyl-2-cyclohexenyl ether on the basis of its spectral properties: ir 3.28, 6.06, and 11.2 μ; nmr, a one-proton multiplet at δ 5.40 (C=C*H*), two-proton multiplets at 4.74 (C=CH_2) and 3.77 (C*H*OC*H*) and 17 additional protons at 1.9–1.4.[16]

Rearrangement of 1-Methylcycloheptene Oxide (8).—When the reaction was carried out with 1.26 g of **8** in 100 ml of ether at reflux for 1 day, there was obtained 1.30 g (102%) of a colorless oil, bp 88–90° (25 mm). Examination by glpc indicated the presence of a single compound which was identified as 2-methylenecycloheptanol on the basis of its spectral properties: ir 2.9, 3.24, 6.12, and 11.1 μ; nmr, one-proton singlets at δ 4.97 and 4.78 (C=CH_2), a one-proton multiplet at 4.16 (C*H*OH), a one-proton singlet at 3.9 (O*H*), a two-proton multiplet at 2.17 (C=CCH_2), and the remaining eight methylene protons as a broad band at 1.5.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.81; H, 11.15.

A second run on 3.8 g of **8** in 250 ml of ether gave about 9% each of two additional compounds. The first new compound was identified as 2-methylcycloheptanone[17] by its spectral data: ir, 5.88 and 7.28 μ; nmr, a broad three-proton multiplet at δ 2.4 for the protons adjacent to the carbonyl group, eight methylene protons as a broad band at 1.7, and a methyl doublet centered at 0.98 (J = 7 cps). The second new compound was assigned as 2-methyl-2-cycloheptenol again on spectral grounds: ir 3.0, 3.28, and 7.26 μ; nmr, a one-proton multiplet at δ 5.50 (C=C*H*), a two-proton multiplet at 4.10 (C*H*O*H*), and the other 11 protons as a broad band at 1.72.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.48; H, 11.19.

A run on 4.5 g of **8** in refluxing benzene for 2 days gave 3.07 g (68%) of a colorless oil which contained 2-methylcycloheptanone, 2-methylenecycloheptanol, and 2-methyl-2-cycloheptenol in a 50:35:15 ratio. There was also obtained 0.35 g (8%) of a lower boiling fraction which consisted of two isomeric olefins. The infrared spectra of both compounds have bands at 3.30 and 7.30 μ. Their nmr spectra are very similar and both show three protons at δ 5.4–5.8 and nine protons at 2.5–1.6. These compounds are believed to be 1- and 2-methyl-1,3-cycloheptadiene.

Rearrangement of 2-Methylenecycloheptanol (9).—2-Methylenecycloheptanol (1.01 g) was treated with lithium diethylamide in the usual fashion using benzene as the solvent. Distillation of the product gave 0.57 g (57%) of a colorless oil, bp 88–97° (16 mm). Examination of this material by glpc showed the presence of 2-methylcycloheptanone, 2-methylenecycloheptanol, and 2-methyl-2-cycloheptenol in a 45:36:14 ratio.

Reaction of 2-Methyl-2-cycloheptenol (11) with Lithium Diethylamide.—The reaction was carried out with 137 mg of **11** in refluxing benzene for 53 hr. Removal of the solvent gave 114 mg of a crude product. Analysis by glpc showed the presence of 2-methylenecycloheptanol and 2-methyl-2-cycloheptenol in a 14:86 ratio in addition to a small amount of solvent.

Rearrangement of 1-Methylcyclooctene Oxide (12).—Rearrangement of 1.40 g of **12** in ether at room temperature for 1 day gave 1.32 g (94%) of distilled product which contained two compounds in a 94:6 ratio. The major product was assigned the structure 2-methylenecyclooctanol[12] (**13**) on the basis of spectral data and preparation of its phenylurethane: mp 98–99° (lit.[11] mp 98–100°); ir, 3.0, 3.28, 6.10, and 11.1 μ; nmr, one-proton multiplets at δ 5.06 and 4.87 (C=CH_2), a one-proton triplet (J = 6 cps) at 4.07 (C*H*OH), a one-proton singlet at 3.14 (O*H*), a two-proton multiplet at 2.17 (C=CCH_2), and ten additional protons at 1–2. The minor product was assigned as 2-methyl-2-cyclooctenol (**15**) on spectral grounds: ir, 3.0, 3.27, 6.0, and 7.26 μ; nmr, a one-proton triplet (J = 8 cps) at 5.38 (C=C*H*), a one-proton multiplet at 4.22 (C*H*OH), a one-proton broad band at 3.4 (O*H*), and the other 13 protons at 2.2–1.2 with a methyl singlet at 1.63.

(10) T. Wagner-Jauregg and M. Roth, *Chem. Ber.*, **93**, 3036 (1960).
(11) A. C. Cope and P. E. Burton, *J. Amer. Chem. Soc.*, **82**, 5439 (1960).
(12) R. Filler, B. R. Camara and S. M. Naqvi, *ibid.*, **81**, 658 (1959).
(13) M. C. Mitter and P. C. Dutta, *J. Indian Chem. Soc.*, **25**, 306 (1948).
(14) Sadtler Index Infrared Spectra, No. 8401.
(15) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 939 (1953).
(16) 2-Cyclopentenol undergoes a similar facile ether formation upon standing in the liquid phase or in the course of preparative glpc purification.
(17) R. Jacquier and H. Christol, *Bull. Soc. Chim. Fr.*, 600 (1957).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.91; H, 11.21.

An identical 1-day run at reflux temperature gave 1.22 g (87%) of a colorless oil, bp 108–112° (15 mm). It contained 2-methylcyclooctanone,[18] 2-methylenecyclooctanol, and 2-methyl-2-cyclooctenol in a 10:43:47 ratio. 2-Methylcyclooctanone was identified by spectral data: ir, 5.90 and 7.31 μ; nmr, a three-proton multiplet at δ 2.2–2.8 for protons adjacent to the carbonyl group, ten methylene protons at 1.3–2.2, and a methyl doublet centered at 0.97 (J = 7 cps).

A 2-day run on 3.9 g of **12** in 300 ml of refluxing benzene gave 4.0 g (101%) of a pale liquid, bp 103–112° (aspirator vacuum), which contained the above three products in a 22:5:68 ratio in addition to two other trace products.

Reaction of 2-Methyl-2-cyclooctenol (15) with Lithium Diethylamide.—The reaction was carried out with 241 mg of **15** in refluxing benzene for 2 days. Removal of the solvent gave 214 mg of a crude product. Analysis by glpc indicated the presence of 89% of 2-methyl-2-cyclooctenol and 10% of 2-methylenecyclooctanol.

Reaction of 2-Methylenecyclooctanol (13) with Lithium Diethylamide.—The reaction on 126 mg of **13** in 20 ml of refluxing benzene for 1 day gave 115 mg of a crude product after removal of the solvent which contained 16% of 2-methylcyclooctanone, 18% of 2-methylenecyclooctanol, and 66% of 2-methyl-2-cyclooctenol.

Rearrangement of 1-*t*-Butylcyclooctene Oxide (22).—The rearrangement was carried out with 1.82 g of **22** in 100 ml of refluxing benzene for 3 days. Distillation of the product gave 1.63 g of a pale oil, bp 89–95° (7 mm). Examination of this material by glpc indicated the presence of four compounds in a 15:4:34:47 ratio. The first compound was assigned as 2-*t*-butyl-1,3-cyclooctadiene by spectral data: ir, 3.3, 7.2 and 7.4 μ; nmr, a two-proton multiplet at δ 5.87 (C*H*=C*H*), a one-proton triplet (J = 8 cps) at 5.48 (CH_2CH=C), four-proton multiplets at 2.02 (C=CCH_2) and 1.37 (CH_2), and a nine-proton singlet at 1.04 for the *t*-butyl group; uv (cyclohexane), λ_{max} 218 mμ (ϵ 5300).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.64; H, 12.27.

The second compound was also an olefin as indicated by its infrared spectrum and is probably 1-*t*-butyl-1,3-cyclooctadiene.

The third compound was assigned the structure 1-*t*-butyl-2-cyclooctenol on the basis of its spectral data: ir, 2.8, 7.2, and 7.38 μ; nmr, a two-proton multiplet at δ 5.57 (C*H*=C*H*), a nine-proton singlet at 0.94 [C(CH_3)$_3$], and an additional 11 protons at 1.2–2.4.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.21; H, 12.09.

The last compound was identified as 2-*t*-butyl-2-cyclooctenol again on the basis of spectral data: ir, 3.0, 3.3, 7.2, and 7.35 μ; nmr, a one-proton triplet (J = 9 cps) at δ 5.46 (C=C*H*), a nine-proton singlet at 1.1 [C(CH_3)$_3$], and 11 additional protons at 1.2–2.8.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.12; H, 12.08.

General Procedure for the Reaction of Alkyllithium Reagents with Epoxides.—To a solution of 3 equiv of commercial alkyllithium in hydrocarbon solvent was added 1 equiv of an epoxide in solvent under a nitrogen atmosphere. The mixture was heated to reflux temperature for 1 day. After cooling the reaction mixture was poured into water, and the layers were separated. The aqueous layer was extracted twice with ether, and the organic layers were washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, water, and dried. The solvent was removed by distillation through a Vigreux column and the residue was distilled. Separation of components was effected by preparative glpc. Product identification was by comparison of spectral data with authentic samples obtained from commercial sources or by literature methods, unless otherwise stated.

Reaction of 1-Methylcycloheptene Oxide (8) with *t*-Butyllithium.—The reaction was carried out with 1.26 g of **8** in pentane for 2 days. Distillation gave 0.92 g (84%) of a colorless liquid, bp 82–90° (20 mm). Three major products were present in a 9:62:11 ratio in addition to several trace products. The first two compounds were identified as 2-methylcycloheptanone and 2-methylenecycloheptanol. The third compound was assigned the structure 1-*t*-butyl-2-methylcycloheptanol by comparison of retention times and infrared spectra with an authentic sample obtained by treating 2-methylcycloheptanone with *t*-butyllithium. It has infrared bands at 2.8, 7.24, and 7.31 μ, and the nmr spectrum shows a one-proton multiplet at δ 2.2 (C*H*), an 11-proton multiplet between 1.9 and 1 (CH_2, O*H*), and a methyl doublet centered at 1.0 with one peak buried under the *t*-butyl singlet at 0.91.

Reaction of 1-*t*-Butylcyclooctene Oxide (22) with *t*-Butyllithium.—The reaction of 1.82 g of **22** in 100 ml of pentane at reflux for 3 days gave 1.62 g (89%) of a colorless oil, bp 90–96° (2 mm). Examination of this material by glpc indicated the presence of three compounds in a 9:46:44 ratio. The first compound decomposed upon preparative glpc and was not identified. It is probably a ketone as indicated by a carbonyl absorption in the infrared spectrum of the glpc isolated material. The last two compounds were identified as 1-*t*-butyl-2-cyclooctenol and 2-*t*-butyl-2-cyclooctenol, respectively.

Reaction of 2-Methylenecycloheptanol (9) with *t*-Butyllithium.—The alcohol (134 mg) was treated with *t*-butyllithium in the usual fashion to give 187 mg of crude product. Analysis by glpc indicated the presence of five components in addition to solvent and some low-boiling material. The first component (4%) was 2-methylcycloheptanone, and the second compound (14%) was unidentified; the next three compounds were 2-methylenecycloheptanol (62%), 2-methyl-2-cycloheptenol (9%), and 1-*t*-butyl-2-methylcycloheptanol (9%).

Registry No.—**5**, 1713-33-3; **8**, 16240-37-2; **9**, 16240-38-3; **11**, 16240-39-4; **12**, 16240-40-7; **15**, 16240-41-8; **16**, 16240-42-9; **18**, 1120-72-5; **19**, 3718-58-9; **22**, 16240-43-0; **23**, 16240-47-4; **24**, 16240-46-3; **25**, 16240-44-1; 1-*t*-butyl-2-methylcycloheptanol, 16240-45-2.

Acknowledgment.—Support of this work by the National Science Foundation (GP-6610) in the form of a research grant is greatly appreciated. The spirited technical assistance of R. A. Colyer and K. Frost with certain preparative aspects of this work is also acknowledged with pleasure.

(18) E. Muller and M. Bauer, *Ann. Chim.*, **554**, 92 (1962).

Unsaturated Heterocyclic Systems. XXXIX. Transannular Cyclizations in Medium-Sized Unsaturated Azalactams[1]

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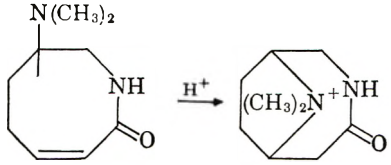
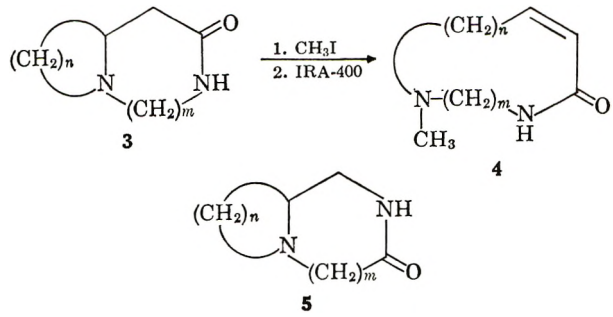
Two medium-sized α,β-unsaturated azalactams in which the tertiary nitrogen center forms a segment of the ring system have been prepared and their transannular cyclization in the presence of hydriodic acid was investigated. The synthetic route to these heteroatomic mesocycles consisted at its early stages in the Schmidt ring expansion of appropriate azabicyclic ketones in which the basic nitrogen atom occupies a bridgehead position. The consistent reactivity pattern manifested by these amino ketones toward hydrazoic acid is discussed.

In a recent paper, Paquette and Wise described a unique type of transannular reaction which involved the cyclization of an α,β-unsaturated lactam such as **1** in the presence of acid.[2] The transannular bonding process was found to be strongly dependent upon the preferred conformational orientations of the medium-sized heterocyclic rings. For example, the N-methyl lactam derived from **1** merely underwent protonation at the basic nitrogen center when exposed to acid, presumably because introduction of the methyl substituent effectively prevented the dimethylamino group from attaining a favorable bonding position with respect to the β-olefinic carbon atom.



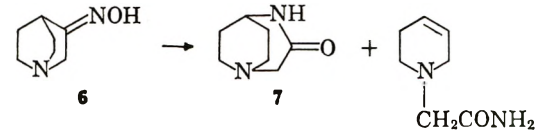
1 **2**

To examine the generality of such cyclizations, we were led to investigate possible transannular interactions in unsaturated lactams such as **4**. Since it had been established earlier that unsaturated lactam **1** and its congeners could be readily obtained by Hofmann degradation of the related quaternary ammonium salts, *e.g.*, **2**,[2,3] it followed that **3** should likewise be convertible into **4**. From the synthetic viewpoint, therefore, it was desirable that a method be found which would lead to an amide such as **3** in preference to the isomeric amide **5**.



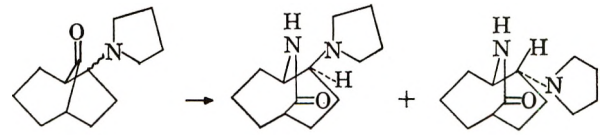
3 **4** **5**

To this end, the possibility was considered that the requisite amides might be available by Schmidt ring expansion of the corresponding amino ketones or by Beckmann rearrangement of their ketoximes. A Russian group had reported that Beckmann rearrangement of 3-quinuclidone oxime (**6**) yielded 1,4-diazabicyclo[3.2.2]nonan-3-one (**7**, 28.3%) and Δ^3-dehydropiperidyl-1-acetamide (**8**, 56.6%).[4] These same workers also



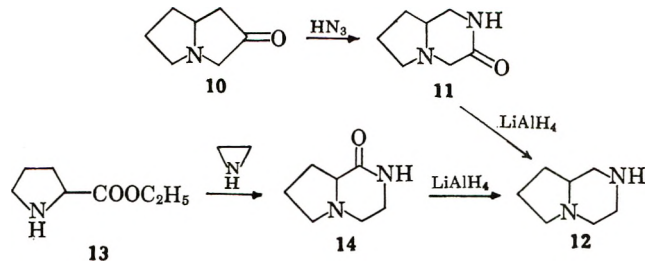
6 **7** **8**

found that Schmidt ring expansion of 3-quinuclidone afforded a 50:50 mixture of **7** and **8** in a total yield of 54%.[4] Plostniecks observed that exposure of amino ketone **9** to hydrazoic acid produced two isomeric amides, both resulting from migration of the bond closer to the nitrogen substituent.[5] On the basis of Plostnieck's report and because conditions for Schmidt reactions on symmetrical amino ketones have been thoroughly investigated by earlier workers,[2,3,6] this procedure was selected for further study.



9

When 1-azabicyclo[3.3.0]octan-3-one (**10**) was treated with hydrazoic acid, a single azalactam was obtained in good yield. This product was shown to be **11** on the basis of its lithium aluminum hydride reduction to diamine **12**, an authentic sample of which was synthesized in an unequivocal manner from 1,4-diazabicyclo[4.3.0]nonan-5-one (**14**) prepared in turn by the condensation of ethyl prolinate (**13**) and ethylenemine.[7]



10 **11** **12** **13** **14**

1-Azabicyclo[4.3.0]nonan-4-one (**15**) was similarly found to afford a single lactam (**16**) which again resulted

(1) For paper XXXVIII of this series, see L. A. Paquette and M. Rosen, *J. Org. Chem.*, **33**, 2130 (1968).

(2) L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965).

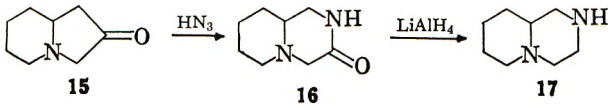
(3) L. A. Paquette and L. D. Wise, *J. Org. Chem.*, **30**, 228 (1965).

(4) E. E. Mikhlina and M. V. Rubtsov, *Zh. Obshch. Khim.*, **33**, 2167 (1963); M. V. Rubtsov, E. E. Mikhlina, V. Ya. Vorob'eva, and A. D. Yanina, *ibid.*, **34**, 2222 (1964); E. E. Mikhlina, V. Ya. Vorob'eva, V. I. Shedchenko, and M. V. Rubtsov, *Zh. Org. Khim.*, **1**, 1336 (1965).

(5) J. Plostniecks, *J. Org. Chem.*, **31**, 634 (1966).

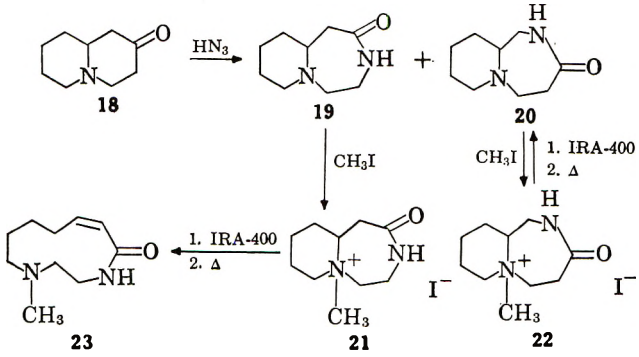
(6) R. J. Michaels and H. E. Zaugg, *ibid.*, **25**, 637 (1960).

(7) M. E. Freed and A. R. Day, *ibid.*, **25**, 2108 (1960).



exclusively from migration of the carbon–carbon bond most distant from the nitrogen atom. The structural assignment was confirmed by reduction to **17** which proved to be identical with an authentic sample prepared in a predescribed manner.[7]

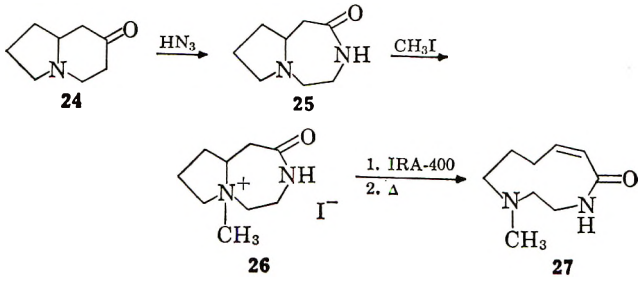
By contrast, in the Schmidt reaction of 1-azabicyclo-[4.4.0]decan-4-one (**18**), **19** was found to predominate



over **20**. Assignment of structure was achieved indirectly by conversion of each azalactam (**19** and **20**) into its methiodide (**21** and **22**, respectively) and subjection of the individual quaternary ammonium salts to Hofmann elimination. Whereas **21** (as its methohydroxide) gave evidence of smooth loss of water to provide α,β-unsaturated lactam **23**, the methohydroxide of **22** proved to be quite resistant to degradation; instead, reconversion of **20** *via* demethylation was observed. This behavior was anticipated from our earlier observation that pyrolysis of the methohydroxide of **16** yielded the original lactam (**16**) as the only identifiable product.

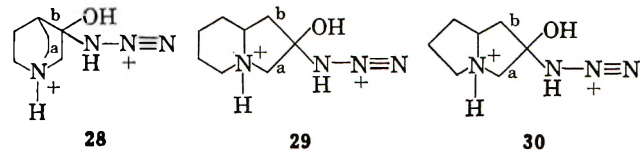
α,β-Unsaturated amide **23** exhibited principal infrared peaks in carbon tetrachloride solution at 3300 (N–H) and 1665 cm^{-1} (amide carbonyl group). The ultraviolet spectrum displayed only end absorption. In its nmr spectrum ($CDCl_3$), the chemical shifts of the two vinyl protons are close and the over-all pattern looks like a broad doublet centered at approximately δ 5.90 with two main peaks separated by 7 Hz; the N-methyl group is seen as a singlet at δ 2.30.

In the case of the last amino ketone to be examined, exposure of **24** to hydrazoic acid led to the formation of **25**. Although **25** was the only amide isolated (22% yield), the highly hygroscopic nature of the crude reaction mixture served to preclude isolation of the expected minor isomer. The structure of **25** follows from its facile conversion *via* methiodide **26** into the medium-sized unsaturated azalactam **27**. Although **27** could not be obtained as crystals, its spectra were totally consistent with the structural formulation. In this instance, the vinyl proton α to the carbonyl group was



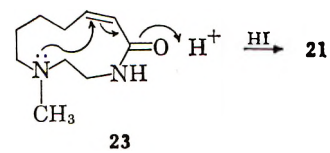
clearly seen as a doublet at δ 6.21 (J = 7 Hz). The small vinyl coupling constant would seem to indicate the presence of a *cis* olefinic bond in **27**,[8] and its geometry has been assigned accordingly.

At this point, it was evident that a consistent reactivity pattern was being manifested by the amino ketones under Schmidt conditions. Thus, in intermediates such as **28**–**30** the strong electron-attracting characteristics of the protonated ring-nitrogen atom are seen to reduce the migratory aptitude of the neighboring carbon–carbon σ bond (labeled a) to electron-deficient azide nitrogen. The operation of this inductive effect permits the



alternative carbon–carbon σ bond (labeled b) to rearrange preferentially. The exclusive formation of **7**, **11**, and **16** gives evidence of this fact. Introduction of an additional methylene group between the ring nitrogen and the carbonyl group can be expected to diminish substantially this inductive effect and in such examples the migratory aptitudes of the two bonds would be expected to be comparable and to exhibit less directional specificity. This conclusion is supported by the behavior of **9**, **18**, and **24**.

In view of these developments, therefore, our study was restricted to a consideration of the behavior of α,β-unsaturated azalactams **23** and **27** in acid. Addition of ethanolic hydriodic acid to an ethereal solution of **23** afforded initially a gummy material which, after heating for a few minutes in methanol to complete the reaction, gave rise to a crystalline methiodide. Evidence that the reaction product was indeed the bicyclic methiodide **21** resulting from transannular ring closure was found in the superimposability of its infrared and nmr spectra upon those of **21**. A similar reaction readily transformed **27** into **26**. Therefore, we conclude that the introduction of a tertiary nitrogen atom into the



ring of a medium-sized α,β-unsaturated lactam does not adversely effect the propensity of such systems (*e.g.*, **1**) for protium-induced transannular cyclization. Also, the results described herein suggest that such transannular interactions may be of a general nature.

Experimental Section[9]

General Procedure for the Schmidt Reaction. 1,4-Diazabicyclo[4.3.0]nonan-3-one (11).—To a solution of 2.0 g (0.014

(8) O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2014 (1963); G. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963).

(9) Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined with a Cary 14 recording spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer purchased with funds made available through the National Science Foundation. The mass spectrum was measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

mol) of **10**[10] in 40 ml of chloroform was added dropwise 9 ml of sulfuric acid while maintaining the temperature at 0°. Sodium azide (2.2 g, 0.033 mol) was added portionwise with vigorous stirring during 1 hr, the temperature being kept below 30°. The mixture was subsequently heated to 50° for 0.5 hr, cooled, and poured onto 20 g of crushed ice. Solid potassium carbonate was added until the evolution of gas had ceased. Aqueous 50% potassium hydroxide solution (20 ml) was added and the mixture was filtered to remove the inorganic salts. The chloroform layer in the filtrate was separated and the aqueous layer was extracted twice with 10-ml portions of chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give 1.0 g (44%) of **11**: mp 120–121.5°, after recrystallization from ethyl acetate and sublimation; $\nu_{max}^{CCl_4}$ 3300, 3100 (N–H), and 1670 cm^{-1} (amide carbonyl).

For the purpose of characterization, **11** was converted into its methiodide by refluxing in ethanol with excess methyl iodide, mp 280–281.5° dec (methanol).

Anal. Calcd for $C_8H_{15}IN_2O$: C, 34.04; H, 5.36; N, 9.93. Found: C, 34.25; H, 5.42; N, 9.95.

1,4-Diazabicyclo[4.3.0]nonan-5-one (14).—A solution of 5.0 g (0.035 mol) of ethyl prolinate (**13**) and 1.0 g of ethyl prolinate hydrochloride in 45 ml of ethanol was heated to reflux and 1.55 g (0.036 mol) of ethylenimine in 15 ml of ethanol was added during 0.5 hr. The solution was refluxed for 24 hr, cooled, and evaporated, whereupon a crude liquid was obtained. Distillation of this material gave 1.2 g (25%) of **14**: bp 110–120° (0.4 mm); ν_{max}^{neat} 3250 cm^{-1} (NH) and 1670 cm^{-1} (amide carbonyl).

The methiodide of **14** melted at 250–252° dec (ethanol–methanol).

Anal. Calcd for $C_8H_{15}IN_2O$: C, 34.04; H, 5.36; N, 9.93. Found: C, 34.09; H, 5.37; N, 9.85.

1,4-Diazabicyclo[4.3.0]nonane (12). A. Reduction of 12.—A solution of 1.0 g (7.1 mmol) of **11** in 20 ml of dry tetrahydrofuran was added with stirring to a slurry of 600 mg of lithium aluminum hydride in 20 ml of the same solvent. The mixture was heatd at reflux for 10 hr, cooled, and decomposed by the addition of water. The residue was filtered and extracted with dichloromethane. The combined filtrates were dried, filtered, and evaporated to give upon distillation 0.4 g (45%) of **12**: bp 69–70° (10 mm); ν_{max}^{neat} 3350 cm^{-1} (N–H).

The phenylthiourea of **12** melted at 122.5–124° (cyclohexane) (lit.[7] mp 122–123°).

Anal. Calcd for $C_{14}H_{19}N_3S$: C, 64.33; H, 7.33; N, 16.08. Found: C, 64.33; H, 7.27; N, 16.08.

B. Reduction of 14.—From 1.0 g (0.007 mol) of **14** and 1.0 g of lithium aluminum hydride, there was obtained in like fashion 0.4 g (45%) of **12** which was converted directly into its crystalline phenylthiourea derivative, mp 123–125° (cyclohexane).

The infrared and nmr spectra of the phenylthioureas were superimposable and a mixture melting point of the two compounds was undepressed.

1,4-Diazabicyclo[4.4.0]decan-3-one (16).—Following the procedure outlined for the preparation of **11**, 4.7 g (0.054 mol) of **15**[11] and 4.1 g (0.055 mol) of sodium azide yielded 3.4 g (65%) of **16**: mp 111–113°, after recrystallization from ethyl acetate and sublimation; ν_{max}^{Nujol} 3360 (N–H) and 1670 cm^{-1} (amide carbonyl).

A sample of **16** was converted into its methiodide in the aforementioned manner, mp 273–275° (aqueous ethanol).

Anal. Calcd for $C_9H_{17}IN_2O$: C, 36.24; H, 5.73; N, 9.27. Found: C, 36.50; H, 5.78; N, 9.46.

Attempted Hofmann Elimination of 16.—An aqueous solution of 2.0 g of the above methiodide was passed through a column of Amberlite IRA-400 resin (hydroxide form) and the resulting aqueous solution of the methohydroxide was evaporated to a syrupy residue. Pyrolysis of this residue gave a solid brown mass which was taken up in ethyl acetate. Addition of ether to this solution caused brown crystals to deposit; these were collected and recrystallized from benzene (charcoal decolorization) to give a white solid which was identified as **16** by infrared comparison and by mass spectral analysis (parent peak, m/e 154).

1,4-Diazabicyclo[4.4.0]decane (17).—A 500-mg (0.003 mol) sample of **16** was treated with 300 mg (0.005 mol) of lithium aluminum hydride in the manner described above. The resulting light yellow liquid (300 mg) was converted directly into its phenylthiourea derivative, mp 115–115.5° (cyclohexane) [lit.[7] mp 118–119° (ethanol)]. An authentic sample of this derivative was prepared;[7] the infrared and nmr spectra of the two samples were superimposable and a mixture melting point showed no depression.[12]

1,4-Diazabicyclo[5.4.0]undecan-5-one (19) and 1,5-Diazabicyclo[5.4.0]undecan-4-one (20).—Following the procedure outlined for the preparation of **11**, 10.5 g (0.067 mol) of **18**[13] and 9.0 g (0.16 mol) of sodium azide yielded 10.5 g of a brown semisolid which was recrystallized twice from ethyl acetate to give 1.9 g (20%) of pure **19** as white needles: mp 135–136°; $\nu_{max}^{CCl_4}$ 3200, 3050 (N–H) and 1690 cm^{-1} (amide carbonyl).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.23; H, 9.67; N, 16.48.

The combined mother liquors were cooled and white rhomboid crystals, mp 95–105°, were deposited. Repeated fractional recrystallization of this solid from hexane–ethyl acetate failed to sharpen or alter its melting point. This purified material (0.8 g) was, therefore, treated directly with ethanolic methyl iodide. From this reaction, there could be isolated 0.2 g of a highly crystalline white solid, mp 234–236° dec (methanol), which proved to be the methiodide of **20**: ν_{max}^{KBr} 3500, 3300 (N–H), and 1650 cm^{-1} (amide carbonyl).

Anal. Calcd for $C_{10}H_{19}IN_2O$: C, 38.70; H, 6.17; N, 9.03. Found: C, 38.73; H, 6.31; N, 9.07.

Attempted Hofmann degradation of this last methiodide by the procedure outlined above was found to produce **20**. The quantity isolated was too small for elemental analysis; however, the material displayed a mass spectral parent peak at m/e 168.

Preparation and Hofmann Elimination of Methiodide 21.—A solution of 2.3 g (0.0137 mol) of **19**, 3.5 g of methyl iodide, and 40 ml of ethanol was refluxed for 1.5 hr and cooled. The resulting crystalline solid was separated by filtration and recrystallized from methanol to give 3.1 g (73%) of **21**, mp 263–264°.

Anal. Calcd for $C_{10}H_{19}IN_2O$: C, 38.70; H, 6.17; N, 9.03. Found: C, 38.73; H, 6.31; N, 9.07.

An aqueous solution of 3.8 g (0.012 mol) of **21** was passed through a column of 70 g of Amberlite IRA-400 ion exchange resin (hydroxide form) and the solution of the methohydroxide that was collected was evaporated to a syrupy residue which slowly solidified. Pyrolysis of this solid at 107–111° (0.22 mm) gave a white crystalline distillate, recrystallization of which from hexane afforded 0.7 g (30%) of **23**: mp 67–69°; $\nu_{max}^{CCl_4}$ 3300 (NH) and 1670 cm^{-1} (amide carbonyl).

The methiodide of **23**, prepared in the customary manner, was found to melt at 229–231° (ethanol).

Anal. Calcd for $C_{11}H_{21}IN_2O$: C, 40.75; H, 6.53; N, 8.64. Found: C, 40.54; H, 6.60; N, 8.86.

1,4-Diazabicyclo[5.3.0]decan-5-one (25).—When a 4.0-g (0.029 mol) sample of **24**[14] and 3.4 g (0.052 mol) of sodium azide were allowed to react in the manner described above a highly hygroscopic white solid was obtained. This material was recrystallized from hexane to give 1.0 g (22%) of **25**, mp 65–70°. Due to the hygroscopic nature of this solid, its methiodide (**26**) was formed directly, mp 234.5–236° (ethanol–methanol).

Anal. Calcd for $C_9H_{17}IN_2O$: C, 36.50; H, 5.79; N, 9.46. Found: C, 36.57; H, 5.67; N, 9.31.

Hofmann Elimination of 26.—An aqueous solution of 1.5 g (0.5 mmol) of **26** was passed through a column of Amberlite IRA-400 ion exchange resin (hydroxide form) and the aqueous eluate of the methohydroxide was evaporated to leave a syrupy residue. Pyrolysis of the residue at a pot temperature of 100–150° (0.1 mm) gave 0.4 g (20%) of **27** as a liquid: ν_{max}^{neat} 3350, 3100 (NH) and 1640 (amide carbonyl) and 1620 cm^{-1} (C=C); λ_{max}^{EtOH} end absorption; $\delta_{TMS}^{CDCl_3}$ 6.21 (doublet, J = 7 Hz, 1 H, vinyl proton adjacent to carbonyl), 5.54 (overlapping doublets, J = 7 and 7 Hz, 1 H, vinyl proton β to carbonyl), 2.33 (singlet, 3 H, N-methyl group).

Because of the limited quantity, this material was not purified further.

Transannular Cyclization of 23.—A solution of 0.10 g (0.6 mmol) of **23** in 5 ml of ether was treated with a 1:1 solution of 50% hydriodic acid in ethanol until no cloudiness persisted. The ether was decanted and the residue was taken up in several millimeters of boiling methanol. After the solution was allowed

(10) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942).

(11) M. J. Martell, Jr., and T. O. Soine, *J. Pharm. Sci.*, **52**, 331 (1963).

(12) Subsequent to the completion of this work, we became aware of yet another synthesis of **17**: T. Yamazaki, M. Nagata, K. Ogawa, and F. Nohara, *Yakugaku Zasshi*, **87**, 668 (1967); *Chem. Abstr.*, **67**, 90770 (1967).

(13) G. R. Clemo, T. P. Metcalfe, and R. Raper, *J. Chem. Soc.*, 1429 (1936).

(14) R. T. Holden and R. Raper, *ibid.*, 2545 (1963).

to cool, the crystalline solid which formed was collected by filtration to give 0.049 g (29%) of **21**, mp 264.5–265.5°. The infrared and nmr spectra of this material were identical with those of authentic **21**.

Transannular Cyclization of 27.—A solution of 0.4 g of **27** and 5 ml of ether was treated with 0.2 ml of a 1:1 solution of 50% hydriodic acid in ethanol. The ether was decanted and the residue was taken up in methanol. Because a crystalline solid was not deposited from the methanolic solution, the solvent was evaporated to leave a thick residue which was dried at 50° (1.0 mm) over phosphorous pentoxide for 2 days. The infrared and nmr spectra of the dried residue (0.45 g) proved to be superimposable on those of **26**.

Registry No.—**11**, 16620-83-0; methiodide of **11**, 16620-59-0; **12**, 5654-83-1; **14**, 16620-61-4; methiodide of **14**, 16620-62-5; **16**, 15932-74-8; methiodide of **16**, 16620-64-7; **19**, 16620-84-1; methiodide of **20**, 16620-85-2; **21**, 16620-86-3; **23**, 16620-88-5; methiodide of **23**, 16620-87-4; **25**, 16620-89-6; **26**, 16620-90-9; **27**, 16620-91-0.

Acknowledgment.—The authors are grateful to Dr. Rodger Foltz for the mass spectral determinations.

The Preparation of 2-Hydroxyamino-α,α,α-trifluoro-*p*-toluenesulfonamide by Catalytic Hydrogenation and Its Use in the Synthesis of 2,3-Dihydro-4H-1,2,4-benzothiadiazin-4-ol 1,1-Dioxides. Studies in Infrared and Proton Magnetic Resonance Spectra

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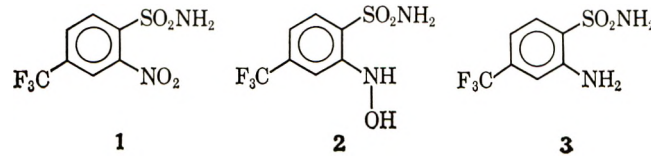
Received December 5, 1967

The hydrogenation of 2-nitro-α,α,α-trifluoro-*p*-toluenesulfonamide (**1**) over a palladium catalyst in ethanol proceeded rapidly (0.5 hr) at room temperature; hydrogen uptake ceased with the absorption of 2 molar equiv to give a 90% yield of pure 2-hydroxyamino-α,α,α-trifluoro-*p*-toluenesulfonamide (**2**). Reduction of **2** to the amine (**3**) required a temperature of 50–60° and about 3 hr. The acid-catalyzed cyclization of **2** with formaldehyde and acetaldehyde led to the novel 2,3-dihydro-4H-1,2,4-benzothiadiazin-4-ol 1,1-dioxides (**4a, b**). The ir and pmr spectra of these and related reference compounds have made possible precise spectral assignments to the several different types of NH protons in these compounds.

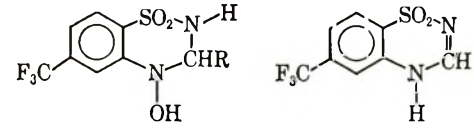
A recent paper[1] has described the intramolecular trapping of the intermediate hydroxyamino derivatives formed during the platinum-catalyzed reductions in ethanol of 2-nitro-2′-carboxy-, 2-nitro-2′-carbalkoxy-, and 2-nitro-2′-cyanobiphenyl; in addition, these hydrogenations formed appreciable amounts of the cyclization products arising *via* the intramolecular cyclization of the corresponding amine derivatives. The one exception was found in the reduction of 2,2′-dinitro-6,6′-dicyanobiphenyl; here, the 2,2′-dihydroxyamino-6,6′-dicyanobiphenyl which formed neither underwent intramolecular cyclization nor conversion to the diamino derivative during hydrogenation, but did cyclize during subsequent recrystallization. This report was noteworthy, since the literature contains but one earlier reference[2] to the isolation of any product other than amines (or their derivatives) from the catalytic hydrogenation of nitro compounds and that reference also involved the intramolecular trapping of the hydroxyamino and amino derivatives formed during the reduction of ethyl 2-nitrophenylacetate.

We have studied the palladium-catalyzed hydrogenation of a suspension of 2-nitro-α,α,α-trifluoro-*p*-toluenesulfonamide (**1**) in ethanol. At *ca.* 20–25°, hydrogen uptake is rapid (~0.5 hr) and ceases after the absorption of 2 molar equiv of hydrogen. Filtration of the suspended catalyst, concentration of the filtrate, and recrystallization of the residual solid gave a 90% yield of pure hydroxyamino derivative (**2**). If, however, following the absorption of the 2 molar equiv of hydrogen, the temperature was raised to 50–60° a slow uptake of hydrogen was initiated and *ca.* 3.5 hr were required to complete the reduction to the amine (**3**) even though **2** was completely in solution. Finally, when the isolated **2** was subjected to hydrogenation with fresh solvent and catalyst at 50–60° a similar slow reduction to **3** was observed.



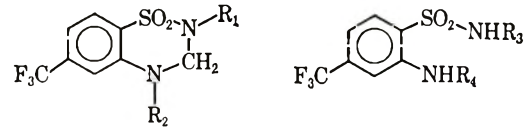
1 **2** **3**

The acid-catalyzed cyclization reactions[3] of **2** with formaldehyde and acetaldehyde gave the novel 2,3-dihydro-4H-1,2,4-benzothiadiazin-4-ol 1,1-dioxides (**4a** and **b**). The reaction of **4a** with formic acid for 1 hr at 90° gave two compounds, **5**, the expected dehydration product, and **6a**, the 4-formyl ester.



4a, R = H
b, R = CH_3

5



6a, R_1 = H; R_2 = O_2CH
b, R_1 = R_2 = H
c, R_1 = H; R_2 = CHO
d, R_1 = CHO; R_2 = H
e, R_1 = C_2H_5; R_2 = H
f, R_1 = H; R_2 = C_2H_5

7a, R_3 = C_2H_5; R_4 = H
b, R_3 = H; R_4 = C_2H_5

(1) C. W. Muth, J. R. Elkins, M. L. DeMatte, and S. T. Chiang, *J. Org. Chem.*, **32**, 1106 (1967).

(2) F. J. DiCarlo, *J. Amer. Chem. Soc.*, **68**, 1420 (1944).

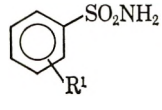
(3) H. L. Yale and J. T. Sheehan, *J. Org. Chem.*, **26**, 4315 (1961).

The acid-catalyzed cyclization of **3** with formaldehyde gave **6b**; the same procedure with **7a** gave the 2-ethyl- (**6e**), and with **7b** the 4-ethyl- (**6f**) derivatives of **6b**. The reaction of **6b** with formic acid for 1 hr at 90° gave the 4-formyl derivative (**6c**) as the major product; a careful search did not reveal the presence of any 2-formyl derivative (**6d**). When the same reactants were heated under reflux, a complex mixture of products resulted, and of these, only **6c** in small yield, was identified.

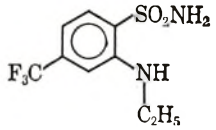
The ir and pmr spectra of the above compounds were studied in detail, and certain spectral assignments for the several different types of protons are discussed in the two sections below; the uv spectra were determined on only a few compounds when these uv data proved to be indiscriminate as to the structural details of interest in this study.

Infrared Spectra.—For the earlier work[3,4] in the elucidation of the structures of 1,2,4-benzothiadiazine 1,1-dioxides, low resolution spectra of the crystalline solids were adequate. In the present work, high-resolution spectra in deuteriochloroform (1 mg/ml) were necessary to minimize intermolecular hydrogen bonding.[5]

In **6b**, the 4- and 2-NH stretch absorptions were observed at 3440 and 3330 cm^{-1}, respectively; confirmatory evidence for these assignments was found in the model spectra of **6e** and **f**, where the corresponding maxima were seen at 3440 and 3330 cm^{-1}. In **6c**, the 2-NH absorption was found at 3340 cm^{-1}. In **4a** and **b**, two maxima were seen at 3540 and 3330 cm^{-1}; the former was attributable to the unbonded 4-OH[6] and the latter to the 2-NH stretch vibrations. The spectrum of **1** showed two maxima at 3455 and 3350 cm^{-1}; the spectrum of **2** showed four maxima at 3560,[6] 3440, 3340, and 3300 cm^{-1} while **3** gave four maxima at 3470, 3440, 3370, and 3340 cm^{-1}. The several NH stretch assignments in **2** and **3** cannot be made unambiguously; however, it would appear that the asymmetrical and symmetrical stretch of the NH_2 of $R-SO_2NH_2$ groups are usually found at *ca.* 3450 and 3350 cm^{-1}, as seen in the spectra of **1**, **8a–f**, **9**, and **10**; it follows, then, that the 3440- and 3340-cm^{-1} maxima in **2** and **3** are probably associated with that group in each compound; and, finally, that the band at 3300 cm^{-1} in **2** is attributable to the N–H vibrational mode of the hydroxyamino group.



8a, R^1 = H, 3450, 3350 cm^{-1}
b, R^1 = *p*-CH_3, 3445, 3345 cm^{-1}
c, R^1 = *o*-CH_3, 3445, 3345 cm^{-1}
d, R^1 = *o*-CF_3, 3470, 3360 cm^{-1}
e, R^1 = *m*-CF_3, 3450, 3350 cm^{-1}
f, R^1 = *p*-CF_3, 3450, 3350 cm^{-1}



9, 3445, 3350, 3280 cm^{-1}

$CH_3SO_2NH_2$

10, 3450, 3350 cm^{-1}

Proton Magnetic Resonance Spectra.—The proton magnetic resonance spectra were determined in deuteriodimethyl sulfoxide.[7] In **6b**, the 2 proton was seen as a doublet at τ 2.10 (J = 8 cps) while the 4 proton was a broad peak centered at τ 2.47. Both the 2 and 4 protons were coupled with the 3 protons, since the latter appeared as a quartet at τ 5.28 ($J_\alpha = J_\beta = 2.5$; $J_{\alpha\beta} = 8.3$)[8] which collapsed to a singlet at τ 5.28 after equilibration with deuterium oxide. In **6c**, the 2 proton was not coupled with the 3 protons and was seen together with the 5 proton as a broad, two-proton singlet centered at τ 1.33; the deshielding by the 4-formyl group of the pair of 3 protons resulted in the latter being shifted downfield 60 cps and appearing as a singlet at τ 4.68; after equilibration with deuterium oxide, the spectrum showed the broad one-proton peak of the 5 proton at τ 1.33. In **6e**, the 4 and 3 protons were seen as a broad peak at τ 2.38 and as a doublet at τ 5.03 (J = 3), respectively, and in **6f**, the 2 and 3 protons were signals forming a broad peak at τ 2.12 and a doublet at τ 5.20 (J = 8), respectively; deuteration of **6e** and **6f** resulted in the appearance of two singlets at τ 5.03 and 5.20, respectively. In **4a**, the 2 proton was coupled with the 3 protons and appeared as a triplet at τ 1.07 (J = 8); the proton of the 4-hydroxyl group, not coupled with the 3 protons, appeared as a singlet at τ −0.33; the 3 protons formed a doublet at τ 5.25 (J = 8) which collapsed to a singlet at τ 5.23 after equilibration with deuterium oxide. In **4b**, the protons at 2 and 4 were seen as broad peaks at τ 2.34 and −2.28, respectively, while the single 3 proton appeared as a multiplet at τ 5.08 (J = 20); treatment with deuterium oxide gave a multiplet at τ 5.07 (J = 20).

In **3**, the two pairs of equivalent protons of the sulfonamido and the amino groups were seen as singlets at τ 2.52 and 3.75, respectively; both pairs were exchangable.

Experimental Section[9]

2-Nitro-α,α,α-trifluoro-*p*-toluenesulfonamide (**1**).—A suspension of 367 g (0.82 mol) of bis(2-nitro-α,α,α-trifluoro-*p*-tolyl) disulfide in 1800 ml of 90% acetic acid was diffused with gaseous chlorine at 35–40° for 6 hr. The clear solution which formed was concentrated *in vacuo* from a hot water bath, the residue was treated with 500 ml of toluene, and the toluene solution, containing the sulfonyl chloride, was added dropwise at room temperature to 500 ml of aqueous ammonia (*d* 0.9). The solution was heated on the steam bath for 1 hr to give crude **1**; this was extracted with 400 ml of 20% aqueous sodium hydroxide and filtered, and the filtrate treated with excess 20% aqueous hydrochloric acid. The solid was filtered, washed with cold water, and recrystallized from water to give 362 g (84% yield) of **1**: mp 169–170°; λ_{max}^{EtOH} mμ (ε) 276 (sh) (16,000), 266 (16,500).

(4) H. L. Yale, K. Losee, and J. Bernstein, *J. Amer. Chem. Soc.*, **82**, 2042 (1960).

(5) The author is indebted to Miss Barbara Keeler of this institute for these spectra. The effects of concentration on hydrogen bonding could not be carried out owing to the low solubility of these compounds in deuteriochloroform.

(6) Unbonded hydroxyl groups are not very sensitive to changes in molecular structure, so that this group in **2**, **4a**, and **4** would be expected to have similar absorption maxima. *Cf.* R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1966, p 61.

(7) The author is indebted to Dr. A. I. Cohen of this institute for these spectra.

(8) This notation is that of ref 6, p 81.

(9) All melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected. Elemental analyses were carried out by Mr. J. F. Alicino and his associates of this institute.

Anal. Calcd for $C_7H_5F_3N_2O_4S$: C, 31.11; H, 1.86; N, 10.37. Found: C, 31.14; H, 1.93; N, 10.33.

2-(Hydroxyamino)-α,α,α-trifluoro-*p*-toluenesulfonamide (2).—Two identical experiments, each involving 30.0 g (0.11 mol) of **1**, 5.0 g of 5% Pd–C, and 300 ml of absolute ethanol were shaken at 20–25° under 50 psi of hydrogen; approximately 0.5 hr was required for the uptake of 0.22 mol. Work-up of the combined runs gave 51.0 g (90% yield) of colorless **2**: mp 184–185° dec after recrystallization from water; λ_{max}^{EtOH} mμ (ε) 313 (3100), 247 (8200), 213 (23,300).

Anal. Calcd for $C_7H_7F_3N_2O_3S$: C, 32.83; H, 2.76; N, 10.93. Found: C, 32.74; H, 2.73; N, 10.93.

The compound was soluble in dilute aqueous sodium hydroxide forming an orange-yellow solution; acidification gave a colorless solution from which unchanged **2** precipitated; a test of **2** with aqueous ferric chloride was negative.

2-Amino-α,α,α-trifluoro-*p*-toluenesulfonamide (3). A. By Hydrogenation of 1.—Two identical reaction mixtures as in the above experiment were hydrogenated at 50–60° under 50 psi of hydrogen; approximately 3.5 hr were required for the absorption of 0.33 mol. The two runs were combined and worked up to give 54.0 g (96% yield) of colorless **3**: mp 148–149° after recrystallization from water; λ_{max}^{EtOH} mμ (ε) 320 (4200), 247 (10,100), 213 (24,100).

Anal. Calcd for $C_7H_7F_3N_2O_2S$: N, 11.66; S, 13.35. Found: N, 11.80; S, 13.35.

The compound was soluble in dilute aqueous sodium hydroxide forming a colorless solution; acidification precipitated unchanged **3**.

B. By Hydrogenation of 2.—A solution of 25.6 g (0.1 mol) of **2**, 5.0 g of 5% Pd–C, and 300 ml of absolute ethanol was heated to 50–60° and shaken under 50 psi of hydrogen. Again, *ca.* 3 hr were required for the theoretical uptake of hydrogen to occur. Work-up as above gave 21.3 g (88% yield) of **3**, mp 148–149° after recrystallization from water.

2,3-Dihyro-2-ethyl-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine 1,1-Dioxide (6e).—A solution of 2.51 g (0.0094 mol) of 2-amino-N-ethyl-α,α,α-trifluoro-*p*-toluenesulfonamide,[3] 0.82 g (0.01 mol) of 37% aqueous formaldehyde, 1.0 ml of 10% aqueous hydrochloric acid, and 50 ml of 95% ethanol was heated under reflux for 24 hr and concentrated to dryness *in vacuo*. The residue was recrystallized from hexane to give 2.20 g (84% yield) of **6e**, mp 72–74°.

Anal. Calcd for $C_{10}H_{11}F_3N_2O_2S$: C, 42.84; H, 3.96; N, 10.00. Found: C, 42.85; H, 3.85; N, 10.27.

2,3-Dihydro-4-ethyl-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine 1,1-Dioxide (6f).—A solution of 2.68 g (0.01 mol) of 2-(ethylamino)-α,α,α-trifluoro-*p*-toluenesulfonamide,[3] 0.82 g (0.01 mol) of 37% aqueous formaldehyde, 1.0 ml of 10% aqueous hydrochloric acid, and 50 ml of 95% ethanol was heated under reflux for 3 hr and concentrated to dryness *in vacuo*. The residue was recrystallized from Skellysolve E to give 2.42 g (85% yield) of **6f**, mp 99–101°.

Anal. Calcd for $C_{10}H_{11}F_3N_2O_2S$: C, 42.84; H, 3.96; N, 10.00. Found: C, 42.72; H, 3.83; N, 10.14.

2,3-Dihydro-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazin-4-ol 1,1-Dioxide (4a).—Employing the procedure used to prepare **6f** but with **2** gave a 95% yield of **4a**: mp 164–166° after recrystallization from 10% 2-propanol–90% water; λ_{max}^{EtOH} mμ (ε) 320 (2600), 255 (9200), 213 (18,200).

Anal. Calcd for $C_8H_7F_3N_2O_3S$: C, 35.82; H, 2.63; N, 10.44; S, 11.95. Found: C, 36.05; H, 2.66; N, 10.41; S, 12.17.

2,3-Dihydro-3-methyl-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine-4-ol 1,1-Dioxide (4b).—A solution of 2.54 g (0.01 mol) of **2**, 0.44 g (0.01 mol) of acetaldehyde, 1.0 ml of 10% aqueous hydrochloric acid, and 50 ml of 95% ethanol was heated under reflux for 24 hr and concentrated to dryness *in vacuo*. The brown syrupy residue was covered with 10% aqueous hydrochloric acid and kept at room temperature until it solidified. The brown solid was recrystallized once from benzene and once from toluene to give 0.60 g (21% yield) of **4b**, mp 160–162 dec.

Anal. Calcd for $C_9H_9F_3N_2O_3S$: N, 9.91; S, 11.36. Found: N, 9.84; S, 11.47.

2,3-Dihydro-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine 1,1-Dioxide (6b).—The procedure employed with **6f** but starting with **3** gave a 95% yield of **6b**: mp 163–165° after recrystallization from water; λ_{max}^{EtOH} mμ (ε) 327 (35,000), 253 (12,500), 213 (22,300).

Anal. Calcd for $C_8H_7F_3N_2O_2S$: C, 38.10; H, 2.80; N, 11.11. Found: C, 38.30; H, 2.89; N, 11.34.

The compound was soluble in dilute aqueous sodium hydroxide forming a colorless solution; acidification precipitated unchanged **6b**.

2,3-Dihydro-3-methyl-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine 1,1-Dioxide.—This compound was synthesized in view of the low yield obtained with **4b** above. A 0.01 *M* run, employing the same conditions but substituting **3** for **2** gave a 74% yield of product, mp 195–197°.

Anal. Calcd for $C_9H_9F_3N_2O_2S$: C, 40.60; H, 3.41; N, 10.50. Found: C, 40.40; H, 3.40; N, 10.23.

Dehydration of 4a to 5.—A suspension of 0.5 g (0.0019 mol) of **4a** and 5 ml of 98–100% formic acid was heated under anhydrous conditions on the steam bath for 1 hr and concentrated to dryness *in vacuo*. The residue was desiccated for 24 hr over potassium hydroxide pellets to give a sticky solid; this was extracted with 10 ml of anhydrous ether to give 0.20 g of a colorless solid, mp 175–187°. The latter was extracted with 5 ml of boiling anhydrous toluene and the hot suspension filtered. The colorless crystals which separated from the cooled filtrate were filtered to give 0.070 g of **6a**, mp 169–171°.

Anal. Calcd for $C_9H_7F_3N_2O_4S$: C, 36.48; H, 2.38; N, 9.43; CHO, 10.83. Found: C, 36.43; H, 2.23; N, 9.37; CHO, 10.91.

The toluene-insoluble material was recrystallized from water to give 0.050 g of **5**, mp 263–265°; a mixture melting point with authentic **5**[3] was 263–265°, and the ir spectra of the two samples were identical.

Anal. Calcd for $C_8H_5F_3N_2O_2S$: C, 38.40; H, 2.02; N, 11.20. Found: C, 38.45; H, 2.27; N, 11.05.

The 10-ml anhydrous ether extract (see above) was evaporated to dryness to give a yellow oil. The oil could be induced to solidify partially following extraction with hexane; this semisolid material was only partially soluble in boiling benzene. The hot benzene solution was decanted from an oil and allowed to cool; an oil separated but scratching converted this to a solid, mp 90–170°; its ir spectrum showed both NH and CO absorption. It was apparent that the formic acid reaction had led to a complex mixture of products.

In $CDCl_3$, the ir spectrum of **6a** showed the anticipated maxima at 3330 cm^{-1} for the 2-NH proton. In d_6-DMSO, the pmr spectrum of **6a** gave the expected broad two-proton peak of the 2 and 5 hydrogens at τ 1.33; the three protons were again deshielded by the carbonyl oxygen and appeared as a broad singlet at τ 4.67. The formyl proton was a singlet at τ 0.87. Following equilibration with deuterium oxide, the signal at τ 1.33 was seen as a broad one-proton peak; the remainder of the spectrum was unchanged.

Reaction of 6b with Formic Acid. A. 2,3-Dihydro-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine-4-carboxaldehyde 1,1-Dioxide (6c).—A mixture of 2.0 g (0.0079 mol) of **6b** and 20 ml of 98–100% formic acid was heated for 1 hr on the steam bath under anhydrous conditions and then concentrated to dryness *in vacuo*. The crystalline residue, mp 173–177°, weighed 2.05 g. Recrystallization from 20 ml of 2-propanol gave 1.57 g (71% yield) of colorless **6c**, mp 184.5–186.0°.

Anal. Calcd for $C_9H_7F_3N_2O_3S$: C, 38.56; H, 2.52; N, 10.00. Found: C, 38.67; H, 2.37; N, 10.28.

The 2-propanol mother liquors from the recrystallization of **6c** were evaporated to dryness. The residual oil was induced to crystallize by the addition of 5 ml of bezene. Filtration gave 0.48 g of solid, mp 120–130°. The ir spectrum showed a single CO and two NH bands. Recrystallization from 10 ml of benzene–hexane (1:1) gave 0.20 g of solid, mp 126–132°, with unchanged ir spectrum. Elemental analyses (Found: C, 38.64; H, 2.86; N, 11.06) were indicative of a mixture of products.

B.—When the reactants of procedure A were heated under reflux for 18 hr and concentrated to dryness *in vacuo*, the residual oil showed two strong NH and one carbonyl band in the ir. The oil was induced to crystallize by the addition of 50 ml of anhydrous ether to give 0.96 g of solid, mp 194–196°; this solid had the same ir spectrum as the oil. Attempts to obtain a single homogenous product from this solid were unsuccessful.

The 50 ml of anhydrous ether (see above) was evaporated to dryness. The residue, 1.4 g of oil, was dissolved in 15 ml of boiling benzene, the solution filtered, and the filtrate cooled to give 0.15 g of crude **6c**; recrystallization from 2-propanol gave 0.13 g of pure **6c**, mp 184.5–186.0°; the ir spectrum of this material and the **6c** described above were identical.

Registry No.—**1**, 577-61-7; **2**, 16156-17-5; **3**, 657-70-5; **4a**, 16156-19-7; **4b**, 16156-20-0; **5**, 655-67-4; **6a**, 16156-22-2; **6b**, 720-49-0; **6c**, 16156-24-4; **6e**, 16156-25-5; **6f**, 16156-26-6; **8a**, 98-10-2; **8b**, 70-55-3; **8c**, 88-19-7; **8d**, 1869-24-5; **8e**, 672-58-2; **8f**, 830-43-3; **9**, 724-94-7; **10**, 3144-09-0; 2,3-dihydro-3-methyl-6-(trifluoromethyl)-4H-1,2,4-benzothiadiazine 1,1 dioxide, 16156-28-8.

Alkylation of Alkylidenebisdimethylamines

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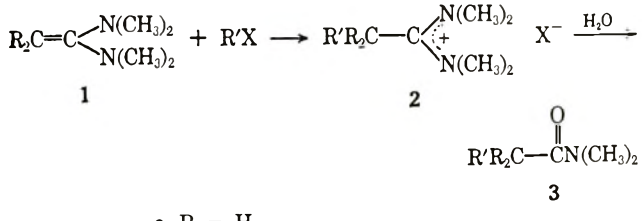
Alkylation of alkylidenebisdialkylamines (enediamines) with alkyl halides gave both C and N alkylation. Carbon alkylation afforded the amidinium salts, **2**, which were readily hydrolyzed to the amides, **3**. This carbon–carbon bond-forming reaction thus provides a convenient new route to substituted amides. The initial products of N alkylation are unstable and react with the starting enediamine, in the case of 2-methylpropenylidenebisdimethylamine, to yield condensation product, **6**, and an N,N-dimethylalkylamine. Elimination of hydrogen halide from butyl halides by the strongly basic enediamines also was observed.

Alkylation of enamines has become an important synthetic tool for the preparation of substituted ketones and aldehydes.[1,2] Analogously, the alkylation of alkylidenebisdialkylamines (enediamines), which have recently become conveniently accessible,[3] offers a new route to carboxylic acids and amides. Although the alkylation of enediamines with methyl and ethyl iodides has been observed previously,[4] the scope of this reaction and its utility for organic synthesis have not been elaborated.

Results

Alkylation of vinylidenebisdimethylamine (**1a**) and 2-methylpropenylidenebisdimethylamine (**1b**) with methyl iodide, benzyl bromide or chloride, and allyl bromide in acetonitrile solution gave the amidinium salts **2c–h** in good yield. The salts were characterized by elemental analysis and nmr spectroscopy and in the case of **2c** and **2e** by comparison with authentic samples prepared by independent syntheses. The reaction of vinylidenebisdimethylamine with butyl bromide and of 2-methylpropenylidenebisdimethylamine with butyl bromide and iodide, as well as benzyl chloride, afforded mixtures of salts from which the amidinium salts could not be isolated.



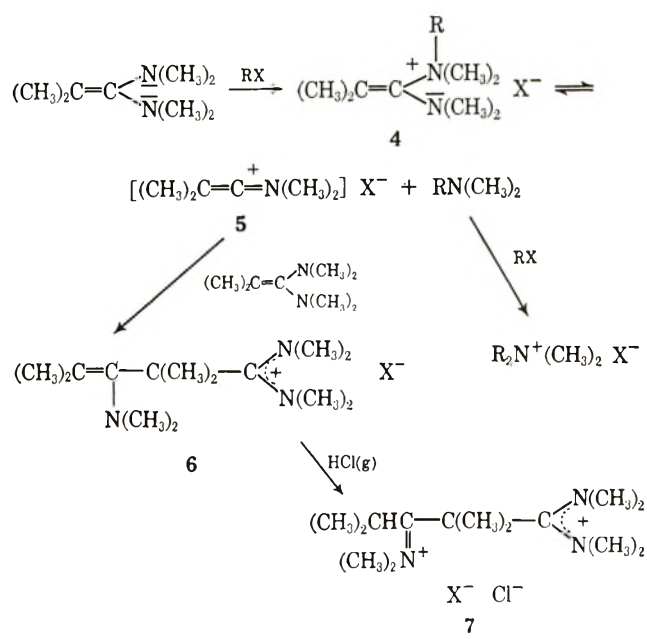
1 **2** **3**

a, R = H
b, R = CH_3
c, R = H; R′ = CH_3
d, R = R′ = CH_3
e, R = H; R′ = $C_6H_5CH_2$
f, R = CH_3; R′ = $C_6H_5CH_2$
g, R = H; R′ = CH_2=$CHCH_2$
h, R = CH_3; R′ = CH_2=$CHCH_2$
i, R = H; R′ = *n*-C_4H_9
j, R = CH_3; R′ = *n*-C_4H_9

The amidinium salts, or the crude salt mixtures in those cases where no amidinium salt could be isolated, were hydrolyzed with dilute sodium hydroxide to afford moderate to good yields of the N,N-dimethylamides, **3e–j**. The yields of amides, shown in Table I, were calculated on the basis of the starting alkylidenebisdimethylamine and therefore represent over-all yields.

The reaction of benzyl chloride with 2-methylpropenylidenebisdimethylamine also afforded 6% of N,N-dimethylbenzylamine in addition to the expected amide (**3f**). Examination by nmr spectroscopy of the aqueous solution remaining after extraction of the amide indicated considerable quantities of ammonium or amidinium salts. These were precipitated as the fluorophosphates and fractionally crystallized to obtain 18% of dibenzyldimethylammonium fluorophosphate and 13% of the condensation product **6**, X = PF_6 (Scheme I). Compound **6** was characterized by

SCHEME I



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

elemental analysis and nmr spectroscopy and by conversion with dry hydrogen chloride to a second salt whose nmr spectrum was consistent with structure **7**. Compound **6** in the form of its iodide also was isolated

(1) J. Szmuszkovicz, *Advan. Org. Chem.*, 25, 58, **4** (1963).
(2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(3) H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966); *J. Amer. Chem. Soc.*, **88**, 850 (1966).
(4) D. H. Clemens, A. J. Bell, and J. L. O'Brien, *J. Org. Chem.*, **29**, 2932 (1964).

TABLE I

SUBSTITUTED AMIDES FROM ALKYLATION OF ALKYLIDENEBISDIMETHYLAMINES

Reactants	Products	Yield,[a] %
Vinylidenebisdimethylamine		
Benzyl chloride	N,N-Dimethylhydrocinnamamide	48
Allyl bromide	N,N-Dimethyl-4-pentenamide	43
Butyl bromide	N,N-Dimethylhexanamide	33
2-Methylpropenylidenebisdimethylamine		
Benzyl bromide	N,N,2,2-Tetramethylhydrocinnamamide	42
Benzyl chloride	N,N,2,2-Tetramethylhydrocinnamamide	34
Allyl bromide	N,N,2,2-Tetramethyl-4-pentenamide	51
Butyl iodide	N,N,2,2-Tetramethylhexanamide	18
Butyl bromide	N,N,2,2-Tetramethylhexanamide	>1

[a] Over-all yield based on starting reactants.

in 5.4% yield from the reaction of butyl iodide with 2-methylpropenylidenebisdimethylamine.

The reaction of butyl bromide with 2-methylpropenylidenebisdimethylamine gave 69% of the amidinium salt (**2**, R = CH_3; R′ = H; X = Br) corresponding to abstraction of hydrogen bromide by the enediamine. This salt, as the iodide, also was detected by nmr spectroscopy in the product mixture from the reaction of butyl iodide with **1b**, and the analogous salt (**2**, R = R′ = H; X = Br) was detected in the reaction of butyl bromide with **1a**.

Discussion

The results of this study show that the alkylation of enediamines is a convenient new route to substituted amides. Of the amides prepared, those containing a quaternary carbon atom, **3f**, **h**, **i**, are new compounds. The yields obtained here (Table I) for the alkylation of enediamines are comparable with those reported for the alkylation of enamines of aldehydes[5,6] and cyclic ketones.[2] The data in Table I show that higher yields of alkylation product are obtained with the less-hindered enediamines and the more reactive alkyl halides. The effect of halide reactivity parallels that observed for enamine alkylations.[5-7]

Elimination of hydrogen halide was a major side-reaction in the case of the butyl halides and was the only reaction observed with 2-bromopropane. This was not entirely unexpected, since the enediamines are powerful bases, comparable to the amidines,[8] protonation giving an amidinium salt in which the positive charge can be delocalized over both nitrogen atoms and the central carbon.

A second side reaction observed was alkylation on nitrogen. This was demonstrated in the reaction of benzyl chloride and 2-methylpropenylidenebisdimethylamine by the isolation of N,N-dimethylbenzylamine, the dibenzyldimethylammonium salt, and condensation product **6**. Minor amounts of these products also were detected by nmr spectroscopy in the product mixture from the reaction of benzyl bromide with this enediamine. Isolation of compound **6** from the reaction of butyl iodide with **1b** indicated that N-alkylation had taken place in this case as well. No direct evidence was found for N-alkylation in the vinylidenebisdimethylamine alkylations. However, nmr spectroscopy revealed residual ammonium or amidinium species in the hydrolysate from the crude butyl bromide adduct, indicating that N-alkylation probably had occurred. Certainly some N-alkylation is to be expected with the unsubstituted enediamine since self-condensation is the major reaction observed in the alkylation of enamines from unhindered aldehydes.[5,9]

The formation of the condensation product **6** and the other products of N-alkylation can be rationalized in terms of the processes outlined in Scheme I. Nucleophilic attack by nitrogen affords the initial ammonium salt **4**, which can eliminate 1 mol of trialkylamine to give the ketenimmonium salt **5**. Attack by a second mole of enediamine on **5** affords **6**. The trialkylamine can attack a second mole of alkyl halide to afford the dialkyldimethylammonium salt. An alternate view is that enediamine attacks **4** displacing trialkylamine and giving **6** directly. In view of the steric requirements which would be involved in such a displacement, however, the alternative process appears more attractive.

The failure of compound **6** to undergo hydrolysis under the same conditions as the amidinium salts, **2**, can be explained on the basis of steric hindrance[10] to hydrolysis. Hydrolysis can be effected under forcing conditions, *i.e.*, 30 hr in refluxing 2 *N* sodium hydroxide, but a complex mixture of products was obtained from which no single product could be isolated.

Experimental Section

Melting points are corrected; boiling points are uncorrected. Nmr data are reported in τ units using tetramethylsilane as internal standard. Molecular weights were determined by mass spectroscopy. All manipulations, reactions, and distillations, except those dealing with the amides, were carried out in a dry nitrogen atmosphere.

Materials.—Vinylidenebisdimethylamine, propenylidenebisdimethylamine, and 2-methylpropenylidenebisdimethylamine were prepared as described previously.[3] Allyl bromide, benzyl chloride and bromide, butyl bromide and iodide, and acetone were dried over magnesium sulfate and distilled before use. Acetonitrile (Matheson Coleman and Bell Spectroquality) was used as received.

N,N,N′,N′-Tetramethyl-3-phenylpropionamidinium hexafluorophosphate.—A solution of 5.28 g (0.30 mol) of N,N-dimethylhydrocinnamamide[11] (bp 111–112° (0.6 mm), $n^{25}D$ 1.5300), 3.06 g (0.15 mol) of tetrakis(dimethylamino)titanium,[12] and 10 ml of dry ether was heated to reflux for 2 hr. The reaction mixture was filtered and the filtrate distilled to obtain 2.0 g (33%)

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of 3-phenylpropenylidenebisdimethylamine: bp 83–87° (0.55 mm); nmr spectrum (in CCl_4), (s) 2.83, (m) ~8.50, (s) 7.32, (s) 7.57 (5:3:6:6).

A benzene solution of 3-phenylpropenylidenebisdimethylamine was treated with dry hydrogen chloride and the resulting N,N,-N′,N′-tetramethyl-3-phenylpropionamidinium chloride was collected by filtration. Addition of sodium hexafluorophosphate solution to an aqueous solution of the amidinium chloride afforded the corresponding hexafluorophosphate, mp 146–147.5° (acetone–ethyl acetate).

Alkylation of Vinylidenebisdimethylamine. With Methyl Iodide—To a solution of 4.56 g (0.040 mol) of vinylidenebisdimethylamine in 20 ml of dry acetonitrile was added 6.24 g (0.044 mol) of methyl iodide with cooling. After standing overnight, the acetonitrile was evaporated under vacuum and the solid recrystallized from dry acetone to afford 9.11 g (84%) of N,N,N′,N′-tetramethylpropionamidinium iodide (**2c**): mp 225–229°; nmr spectrum (in methylene chloride), (s) 6.67, (q) 7.13, J = 7.5 Hz, (t) 8.74, J = 7.5 Hz (12:2:3).

Anal. Calcd for $C_7H_{17}IN_2$: C, 32.81; H, 6.68; I, 49.51; N, 10.94. Found: C, 32.73; H, 6.80; I, 49.65; N, 10.83.

An authentic sample of the amidinium salt, mp 232–233°, prepared by addition of dry hydrogen iodide to propenylidenebisdimethylamine, had identical nmr and infrared spectra; mmp 230–231.5°.

With Benzyl Chloride.—A mixture of 6.4 g (0.05 mol) of benzyl chloride, 5.7 g (0.05 mol) of vinylidenebisdimethylamine, and 20 ml of acetonitrile was heated to reflux for 80 hr. The acetonitrile was evaporated under vacuum to give a viscous orange residue which was taken up in dry acetone and recrystallized to yield 10.6 g (86%) of N,N,N′,N′-tetramethyl-3-phenylpropionamidinium chloride (**2e**): mp 105–107°; nmr spectrum (methylene chloride), (s) 2.69, (s) 6.78, (m) 6.91 (5:12:4). Because of the extreme hygroscopicity of the salt, a satisfactory analysis could not be obtained. Addition of sodium hexafluorophosphate to an aqueous solution of the chloride salt afforded the hexafluorophosphate, recrystallized from acetone: mp 146–146.5°; mmp with authentic sample, 146.5–147.5°.

Anal. Calcd for $C_{13}H_{21}F_6N_2P$: C, 44.57; H, 6.04; N, 8.00. Found: C, 44.63; H, 6.08; N, 7.79.

N,N,N′,N′-Tetramethyl-3-phenylpropionamidinium chloride (8.0 g, 0.033 mol) was dissolved in 20 ml of 2 *N* sodium hydroxide and allowed to stand overnight. Extraction of the aqueous solution with ether, followed by distillation, afforded 3.3 g (56%) of N,N-dimethylhydrocinnamamide (**3e**): bp 102° (0.35 mm); $n^{25}D$ 1.5303. The nmr spectrum (in CCl_4) was identical with that of an authentic sample[11] with peaks at (s) 2.85, (s) 7.21, (m) 7.32 (5:6:4).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90; mol wt, 177. Found: C, 74.42; H, 8.64; N, 7.88; mol wt, 177.

With Allyl Bromide.—A solution of 3.6 g (0.03 mol) of allyl bromide, 3.4 g (0.03 mol) of vinylidenebisdimethylamine, and 10 ml of acetonitrile was heated to reflux for 24 hr. The acetonitrile was removed under vacuum and the resulting solid recrystallized from acetone to yield 5.45 g (77%) of N,N,N′,N′-tetramethyl-4-pentenamidinium bromide (**2g**): mp 153–154.5°; nmr spectrum (in $CDCl_3$), (m) ~4.25, (m) 4.83, (s) 6.62 (m) ~6.95, (t) 7.51 (1:2:12:2:2).

Anal. Calcd for $C_9C_{19}BrN_2$: C, 45.96; H, 8.14; Br, 33.98; N, 11.91. Found: C, 46.04; H, 8.14; Br, 33.80; N, 11.73.

Hydrolysis of 10.0 g (0.042 mol) of the amidinium bromide with 15 ml of 2 *N* sodium hydroxide afforded, after extraction with ether and distillation, 3.1 g (57%) of N,N-dimethyl-4-pentenamide (**3g**): bp 88° (10 mm); $n^{25}D$ 1.4605 [lit.[13] bp 88–89° (11 mm)]; nmr spectrum (in CCl_4), (m) 4.1, (m) 5.0, (s) 3.02, (s) 2.88, (m) 2.32 (1:2:3:3:4).

Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.02; mol wt, 127. Found: C, 65.80; H, 10.27; N, 11.27; mol wt, 127.

With Butyl Bromide.—A mixture of 5.7 g (0.05 mol) of vinylidenebisdimethylamine, 6.9 g (0.05 mol) of *n*-butyl bromide, and 20 ml of acetonitrile was heated to reflux for 3 days, or until the starting materials had disappeared as evidenced by nmr. The acetonitrile was evaporated under vacuum to afford 11.8 g of viscous residue. The viscous residue was treated overnight with 20 ml of 2 *N* sodium hydroxide and the mixture extracted with ether. Distillation afforded 2.4 g (33%) of N,N-dimethylhexanamide (**3i**): bp 50° (0.45 mm); $n^{25}D$ 1.4451 (lit.[14] bp 158° (100 mm); $n^{25}D$ 1.4430); nmr spectrum (in CCl_4), (s) 7.02, (s) 7.14, (m) 7.80, (m) 8.1–9.3 (3:3:2:9).

Anal. Calcd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78; mol wt, 143. Found: C, 66.98; H, 12.02; N, 9.80; mol wt, 143.

Vapor phase chromatographic examination of the aqueous sodium hydroxide solution after extraction indicated considerable quantities of N,N-dimethylacetamide along with several unidentified materials. It was estimated from nmr spectra that the aqueous mixture after hydrolysis but before extraction contained N,N-dimethylacetamide and N,N-dimethylhexanamide in the molar ratio of 1:2.

Alkylation of 2-Methylpropenylidenebisdimethylamine. With Methyl Iodide.—Methyl iodide, 15.6 g (0.11 mol), 2-methylpropenylidenebisdimethylamine, 14.2 g (0.10 mol), and 20 ml of dry acetonitrile were maintained at reflux for 24 hr. The mixture was chilled in ice, filtered, and the adduct salt washed with acetone to obtain 17.6 g (62%) of N,N,N′,N′,2,2-hexamethylpropionamidinium iodide (**2d**), sublimes at ~390°: nmr spectrum (in $CDCl_3$), (s) 6.55, (s) 8.40 (4:3).

Anal. Calcd for $C_9H_{21}IN_2$: C, 38.04; H, 7.45; I, 44.66; N, 9.86. Found: C, 37.83; H, 7.35; I, 44.87; N, 9.78.

With Benzyl Bromide.—A mixture of 7.1 g (0.05 mol) of 2-methylpropenylidenebisdimethylamine, 8.5 g (0.05 mol) of benzyl bromide, and 15 ml of dry acetonitrile was heated to reflux for 40 hr. The acetonitrile was evaporated under vacuum and the crude adduct salt (9.9 g, 63%) was recrystallized from acetone to give N,N,N′,N′,2,2-hexamethylhydrocinnamamidinium bromide (**2f**): mp 181–183°; nmr spectrum (in $CDCl_3$), (m) 2.7, (s) 6.70, (s) 6.88, (s) 8.35 (5:12:2:6).

Anal. Calcd for $C_{15}H_{25}BrN_2$: C, 57.51; H, 8.04; Br, 25.51; N, 8.94. Found: C, 57.24; H, 8.16; Br, 25.72; N, 8.94.

Hydrolysis of 9.5 g (0.033 mol) of the crude adduct salt in 10 ml of 2 *N* sodium hydroxide afforded 4.5 g (66%) of N,N,2,2-tetramethylhydrocinnamamide (**3f**): bp 108–110° (0.55 mm); $n^{25}D$ 1.5257; nmr spectrum (in CCl_4), (s) 2.80, (s) 7.08, (s) 7.11, (s) 8.81 (5:6:2:6).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82; mol wt, 205. Found: C, 75.94; H, 9.47; N, 6.80; mol wt, 205.

With Benzyl Chloride.—The reaction between 11.4 g (0.08 mol) of 2-methylpropenylidenebisdimethylamine and 11.2 g (0.09 mol) of benzyl chloride in 20 ml of acetonitrile required 8 days at reflux to reach completion. Evaporation of the acetonitrile under vacuum yielded a viscous residue which could not be made to crystallize. The viscous product was hydrolyzed in 2 *N* sodium hydroxide and the aqueous solution extracted with ether. Distillation yielded 0.6 g (6%) of N,N-dimethylbenzylamine, bp 30° (0.55 mm), identified by comparison of nmr spectra and vapor phase chromatographic retention times with an authentic sample, and 5.7 g (34%) of N,N,2,2-tetramethylhydrocinnamamide. The aqueous solution remaining from the hydrolysis was treated with sodium hexafluorophosphate to precipitate soluble salts as their hexafluorophosphates. These were collected by filtration and fractionally crystallized from acetone–ethyl acetate to yield two salts, mp 214–218 and 185–186.5° dec. The 214–218° salt, 5.3 g (18% yield based on 2-methylpropenylidenebisdimethylamine), was identified as dibenzyldimethylammonium hexafluorophosphate on the basis of its nmr spectrum and elemental analysis: nmr spectrum (in acetone-d_6), (m) 2.25, (s) 5.10, (s) 6.80 (5:2:3).

Anal. Calcd for $C_{16}H_{20}F_6NP$: C, 51.76; H, 5.43; N, 3.77. Found: C, 51.66; H, 5.48; N, 3.67.

The 185–186.5° salt, 2.0 g (13% based on 2-methylpropenylidenebisdimethylamine), was identified as 3-dimethylamino-N,N,N′,N′,2,2,4-heptamethyl-3-pentenamidinium hexafluorophosphate (**6**, X = PF_6): nmr spectrum (in CD_3CN), (s) 6.78 (s) 7.24, (s) 8.29, (s) 8.44, (s) 8.53 (4:2:1:2:1).

Anal. Calcd for $C_{14}H_{30}F_6N_3P$: C, 43.63; H, 7.85; N, 10.90. Found: C, 43.47; H, 7.80; N, 10.89.

A sample of the 185–186.5° salt, dissolved in chloroform, was treated with dry hydrogen chloride, whereupon crystals formed immediately. The crystals were collected by filtration: nmr spectrum (in CD_3CN), (s) 6.06, (s) 6.43, (s + m) 6.70, (s) 8.07, (d) 8.43, J = 7.5 Hz (3:3:13:6:6).

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With Allyl Bromide.—A solution of 11.4 g (0.08 mol) of 2-methylpropenylidenebisdimethylamine and 10.9 g (0.09 mol) of allyl bromide in 20 ml of dry acetonitrile was heated to reflux for 3 days. The acetonitrile was evaporated under vacuum to yield 20.5 g (92%) of crude adduct. Recrystallization from acetone gave N,N,N′,N′,2,2-hexamethyl-4-pentenamidinium bromide (**2h**): mp 212–213°; nmr spectrum (in $CDCl_3$), (m) ~4.2, (m) 4.7, (s) 6.52, (d) 7.37, J = 7.0 Hz, (s) 8.37 (1:2:12:2:6).

Anal. Calcd for $C_{11}H_{23}BrN_2$: C, 50.19; H, 8.81; Br, 30.26; N, 10.64. Found: C, 50.23; H, 8.94; Br, 30.13; N, 10.47.

Treatment of 17.1 g of the crude adduct salt with 20 ml of 2 *N* sodium hydroxide overnight yielded 5.3 g (51% based on 2-methylpropenylidenebisdimethylamine) of N,N,2,2-tetramethyl-4-pentenamide (**3h**): bp 75–80° (4 mm); $n^{25}D$ 1.4641; nmr spectrum (in CCl_4), (m) ~4.2, (m) ~5.0, (s) 6.99, (d) 7.64, J = 7.0 Hz, (s) 8.78 (1:2:6:2:6).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; mol wt, 155. Found: C, 69.53; H, 10.96; N, 9.16; mol wt, 155.

With Butyl Iodide.—A mixture of 8.5 g (0.06 mol) of 2-methylpropenylidenebisdimethylamine, 11.1 g (0.06 mol) of butyl iodide, and 20 ml of acetonitrile was heated to reflux for 11 days. The acetonitrile was removed under vacuum to give 15.2 g of yellow semisolid. Recrystallization afforded 0.5 g of crude N,N,N′,N′,2-pentamethylpropionamidinium iodide, whose nmr spectrum was identical with that of the bromide prepared by addition of dry hydrogen bromide to 2-methylpropenylidenebisdimethylamine. The bulk of the crude product could not be induced to crystallize. The crude product was dissolved in 15 ml of 2 *N* sodium hydroxide and allowed to stand overnight. The mixture was extracted with ether and the extract distilled to obtain 1.8 g (18%) of N,N,2,2-tetramethylhexanamide (**3j**): bp 61–62° (0.7 mm); $n^{25}D$ 1.4512; nmr spectrum (in CCl_4), (s) 7.02, (s) 8.81, (m) 8.70, (m) 9.05 (2:2:2:1).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18; mol wt, 171. Found: 69.92; H, 12.28; N, 8.18; mol wt, 171.

The aqueous layer remaining after ether extraction was filtered and the crystals so obtained were recrystallized from acetone–tetrahydrofuran to yield 0.6 g (5.4% yield based on 2-methylpropenylidenebisdimethylamine) of material identified as 3-dimethylamino-N,N,N′,N′,2,2,4-heptamethyl-3-pentenamidinium iodide (**6**, X = I): mp 189–191° dec; nmr spectrum (in $CDCl_3$), (s) 6.58, (s) 7.27, (s) 8.30, (s) 8.40, (s) 8.49 (4:2:1:2:1).

Anal. Calcd for $C_{14}H_{30}IN_3$: C, 45.78; H, 8.23; I, 34.55; N, 11.44. Found: C, 45.64; H, 8.27; I, 34.81; N, 11.28.

When butyl bromide was used in place of the iodide, 17 days were required for complete disappearance of the reactants. A total of 15.4 g (69%) of N,N,N′,N′,2-pentamethylpropionamidinium bromide, mp 263° dec, was recovered by crystallization from the reaction mixture. The nmr spectrum was identical with that of an authentic sample of the salt, mp 267° dec, prepared by addition of dry hydrogen bromide to 2-methylpropenylidenebisdimethylamine: mmp 266° dec; nmr spectrum (in CH_2Cl_2), (m) ~6.4, (s) 6.58, (d) 8.53, J = 7.2 Hz (12:6:1).

Anal. Calcd for $C_8H_{19}BrN_2$: C, 43.05; H, 8.58; Br, 35.81; N, 12.55. Found: C, 42.94; H, 8.67; Br, 35.94; N, 12.42.

The remainder of the reaction mixture was hydrolyzed in 2 *N* sodium hydroxide. Extraction with ether, followed by distillation of the extract, afforded less than 1% yield of crude N,N,2,2-tetramethylhexanamide.

Registry No.—N,N,N′,N′-Tetramethyl-3-phenylpropionamidinium hexafluorophosphate, 12260-64-9; 3-phenylpropenylidenebisdimethylamine, 16487-48-2; **2c**, 16487-49-3; **2d**, 16520-61-9; **2e**, 16487-50-6; **2f**, 16487-51-7; **2g**, 16487-52-8; **2h**, 16487-53-9; **3e**, 5830-31-9; **3f**, 16487-55-1; **3g**, 16487-56-2; **3h**, 16487-57-3; **3i**, 5830-30-8; **3j**, 16487-59-5; **6** (X = PF_6), 12260-65-0; **6** (X = I), 16487-60-8; dibenzyldimethylammonium hexafluorophosphate, 12260-70-7; N,N,N′,N′,2-pentamethylpropionamidinium bromide, 16487-61-9.

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Reductive Alkylation of Imines and Esters with Sodium in Ammonia

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Diphenyl- or pyridylketimines and pyridylaldimines were alkylated at carbon by the addition of sodium metal in liquid ammonia, followed by an organic halide. The same products were obtained by treating the corresponding amine with sodamide in liquid ammonia, followed by the halide. Similar reductive alkylations of methyl isonicotinate with benzyl chlorides gave the corresponding 4-pyridyl ketones.

Numerous reactions in organic synthesis involve the alkylation of carbanions. One route to such intermediates is the addition of electrons from alkali metals to an unsaturated center. The addition of the first electron gives a radical anion, which in the case of most double bonds is so reactive that it dimerizes or reacts with the solvent. In some instances, however, a second electron can be added to give a stable dianion. Schlenk[1] was first to show that a relatively stable dianion can be formed by treating diaryl ketones with sodium in ether and that this dianion can be alkylated with ethyl or methyl iodides. Later workers[2] showed that the dianions, formed from diaryl ketones with sodium in liquid ammonia, alkylated preferentially at carbon with a variety of alkylating agents, but aryl alkyl or dialkyl ketones would not alkylate under these conditions.

$$Ar_2C{=}O \xrightarrow[NH_3]{2Na} [Ar_2\overset{\ominus}{C}{-}\overset{\ominus}{O}]2Na^{\oplus} \xrightarrow{RX} Ar_2\underset{R}{C}{-}O^{\ominus}Na^{\oplus}$$

Kharasch[3] studied the reductive alkylation of esters and obtained 30–35% yields of ketones from the following esters and alkyl halides.

$$RCOOC_2H_5 \xrightarrow[NH_3]{2Na} [R\overset{\ominus}{C}{=}O]Na^{+} \xrightarrow{R'Br} RC{=}O \quad (R')$$

R = C_6H_5, *i*-Pr, *t*-Bu; R′ = *n*-Bu, Et

However, with benzyl chloride and ethyl benzoate, only a 5% yield of ketone was detected.

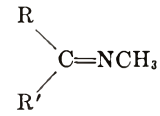
(1) W. Schlenk and T. Weikel, *Chem. Ber.*, **44**, 1182 (1911).

(2) (a) P. J. Hamrick and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959); (b) D. V. Ioffe, *Zh. Obshch. Khim.*, **34**, 703 (1964); **35**, 1851 (1965); (c) E. L. Anderson and J. E. Casey, Jr., *J. Org. Chem.*, **30**, 3960 (1965); (d) S. Selman and J. Eastham, *ibid.*, **30**, 3804 (1965); (e) J. A. Gautier, M. Miocque, C. Fauran, and M. D. D'Engenieres, *Bull. Soc. Chim. Fr.*, 3762 (1965).

(3) M. S. Kharasch, E. Sternfeld, and F. Mayo, *J. Org. Chem.*, **15**, 362 (1940).

TABLE I

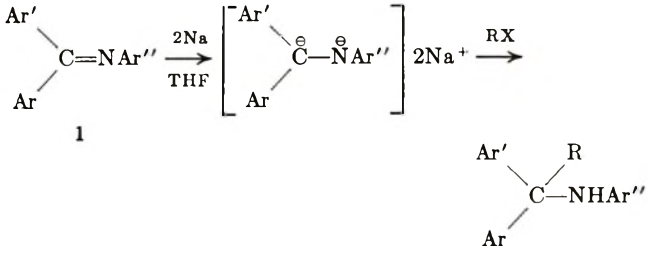
N-METHYLIMINES



No.	R	R′	Bp (mm) or mp, °C	Yield, %	Reaction conditions[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2a	C_6H_5	H[b]	183–185 (atm)	61	A, 15 hr, 25°	C_8H_9N	...	...	...	...	...	...
2b	C_6H_5	CH_3[c]	206–208 (atm)	82	B, 19 hr, 120°	$C_9H_{11}N$	...	...	...	...	...	...
2c	C_6H_5	C_6H_5[d]	147–148 (3.0)	97	B, 18 hr, 125°	$C_{14}H_{13}N$	86.12	6.71	7.17	86.24	6.65	7.13
2d	2-C_5H_4N	H	67–70 (8.0)	93	C, 2 hr, 25°	$C_7H_8N_2$	69.97	6.71	23.32	70.22	6.83	23.61
2e	3-C_5H_4N	H	70–75 (10.0)	91	C, 2 hr, 25°	$C_7H_8N_2$	69.97	6.71	23.32	69.98	6.98	23.30
2f	4-C_5H_4N	H	70–75 (10.0)	90	C, 2 hr, 25°	$C_7H_8N_2$	69.97	6.71	23.32	70.29	6.99	23.51
2g	2-C_5H_4N	CH_3	108–110 (30)	86	B, 5 hr, 90°	$C_8H_{10}N_2$	71.61	7.51	20.88	71.57	7.26	21.02
2h	3-C_5H_4N	CH_3	123–124 (20)	61	B, 24 hr, 120°	$C_8H_{10}N_2$	71.61	7.51	20.88	71.91	7.41	20.93
2i	4-C_5H_4N	CH_3	123–127 (20)	85	B, 6 hr, 95°	$C_8H_{10}N_2$	71.61	7.51	20.88	71.15	7.55	21.08
2j	4-C_5H_4N	C_6H_5	120–125 (0.2)	67	B, 8 hr, 90°	$C_{13}H_{12}N_2$	*e*					
2k	4-$O_2NC_6H_4$	H	105–107[f]	78	A, 1 hr, 60°	$C_8H_8N_2O_2$	...	...	...	...	...	...

[a] A, aqueous methylamine; B, liquid methylamine as solvent; C, methylamine in benzene. [b] N. Cromwell, R. Babson, and C. Harris, *J. Amer. Chem. Soc.*, **65**, 313 (1943). [c] W. Saunders and E. A. Caress, *ibid.*, **86**, 861 (1964). [d] C. Hauser, R. Manyik, W. Brasen, and P. Bayless, *J. Org. Chem.*, **20**, 1119 (1955). [e] Gas chromatography showed product to be 97% pure. [f] A. Burawoy and J. Critchley [*Tetrahedron*, **5**, 340 (1959)] reported mp 106°.

In the case of carbon–nitrogen double bonds, only N-arylimines of type **1** have been studied to date.[4] The latest paper by Smith and Veach establishes that carbon alkylation is the exclusive product with monohalides.



Gautier[5] recently showed that oximes derived from diaryl ketones, treated with 4 mol of sodium in ammonia followed by an organic halide, underwent reductive alkylation at carbon, giving good yields of amines.

Our investigation concerned the use of alkyl and unsubstituted imines in the reductive alkylation reaction (Scheme I).

Diaryl ketones readily give the dianion with sodium in liquid ammonia, but with imines one would not expect **3** to predominate if R″ is not aryl. Since anions of secondary and primary amines are of comparable basicity to the NH_2^- ion, the large excess of ammonia would insure a low concentration of **3** or **5**. Whether the predominant species is **4** or **6** clearly depends on the substituents, R and R′.

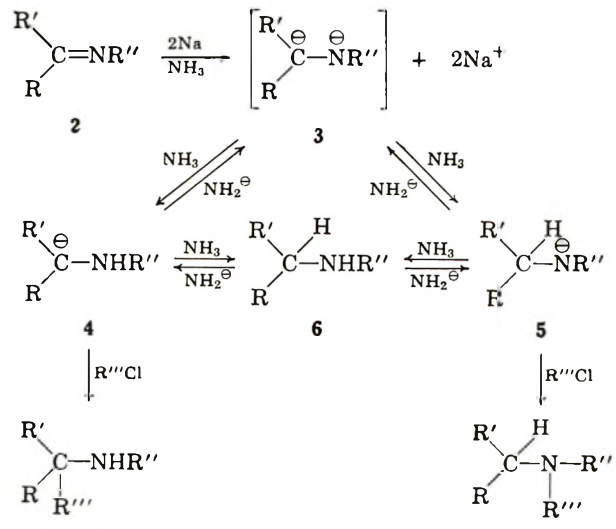
Results and Discussion

Preparation of Imines.—The N-methylimines were conveniently prepared by the reaction of the corresponding carbonyl compound with an excess of anhydrous methylamine. With aldehydes, the reaction was exothermic, but with aryl ketones, heating in an autoclave was necessary. Conditions and results are summarized in Table I.

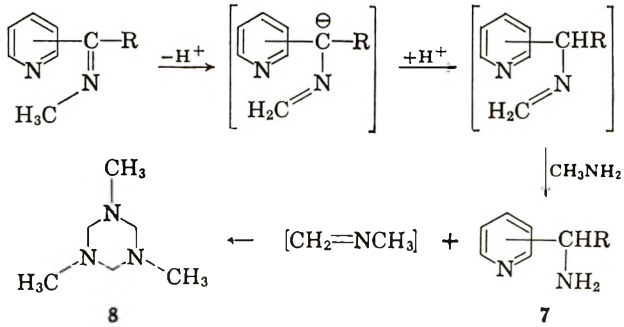
(4) (a) W. Schlenk and E. Bergmann, *Ann. Chem.*, **463**, 281 (1928); (b) B. M. Mikhailov and K. Kurdiumova, *J. Gen. Chem. USSR*, **25**, 1687 (1955); (c) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2245 (1966).

(5) J. A. Gautier, M. Miocque, C. Fauran, and A. Y. Cloarec, *Compt. Rend.*, **263**, 1164 (1966).

SCHEME I



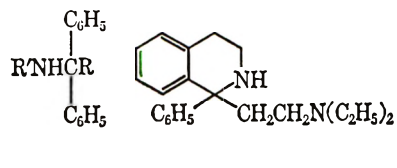
For the preparation of some of the pyridylketimines, the indicated reaction conditions are critical. Milder conditions gave unreacted ketone, and more vigorous conditions led to the production of the hydrotriazine (**8**) and the primary amine **7**. Their formation can be rationalized by the following sequence.



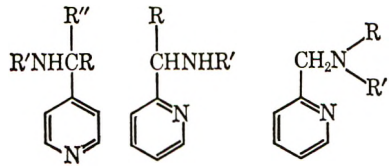
This side reaction is most serious in the 2-pyridyl, less so in the 4-pyridyl, and not detected at all in the 3-pyridyl series. With **7** (R = CH_3) the triazine **8** distilled at the same temperature as **7**, but with **7** (R = C_6H_5) they were easily separated. This per-

TABLE II

PRODUCTS FROM THE REDUCTIVE ALKYLATION OF IMINES WITH SODIUM AND ALKYL CHLORIDES[a]



16 17



18 19 20

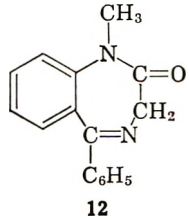
No.	R, R', R''	Yield, %	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
16a	$(C_2H_5)_2NCH_2CH_2$, H	78[b]	144–148 (0.5)[c]	$C_{19}H_{26}N_2$	80.80	9.28	9.92	80.67	9.16	9.98
16b	$(CH_3)_2NCH_2CH_2$, H	71	75–84[d]	$C_{17}H_{22}N_2$	80.27	8.72	11.01	80.18	8.67	10.99
16c	$(C_2H_5)_2NCH_2CH_2$, CH_3	70	69–70	$C_{20}H_{28}N_2$	81.03	9.25	9.45	81.11	9.60	9.31
16d	HC≡CCH$_2$, H	48	248–251[e]	$C_{16}H_{16}ClN$	74.20	6.22	5.43	74.37	6.24	5.61
16e	H, $(CH_3)_3Si$[f]	57	105–110 (0.1)	$C_{16}H_{21}NSi$	75.26	8.29	5.49	75.31	8.14	5.55
17		69	155–158 (0.3)	$C_{21}H_{28}N_2$	81.71	9.15	9.08	81.76	8.99	9.17
18a	$(C_2H_5)_2NCH_2CH_2$, CH_3, H	42	110–112 (0.3)	$C_{13}H_{23}N_3$	70.54	10.47	18.98	70.58	10.68	19.19
18b	HC≡CCH$_2$, CH_3 H	29	200–202[g]	$C_{10}H_{14}Cl_2N_2$	51.50	6.01	12.01	51.24	6.04	11.93
18c	$C_6H_5CH_2$, CH_3, H	50[h]	248–251[i]	$C_{14}H_{18}Cl_2N_2$	59.00	6.36	9.84	58.71	6.15	9.79
18d	4-$ClC_6H_4CH_2$, CH_3, H	11	260–263[j]	$C_{14}H_{17}Cl_3N_2$	52.40	5.37	8.98	52.31	5.49	9.18
18e	$(C_2H_5)_2NCH_2CH_2$, CH_3, CH_3	60	110–115 (0.2)	$C_{14}H_{25}N_3$	71.44	10.71	17.85	71.59	10.70	17.91
18f	$C_6H_5CH_2$, CH_3, CH_3	22	235–238[k]	$C_{15}H_{20}Cl_2N_2$	60.40	6.73	9.37	60.25	6.90	9.57
19a and 20	$(C_2H_5)_2NCH_2CH_2$, CH_3	24[l]	112–115 (0.8)	$C_{13}H_{23}N_3$	70.54	10.47	18.98	70.46	10.74	19.12

[a] All reactions were conducted in liquid ammonia unless otherwise specified. [b] Also carried out in DME giving a 54% yield. [c] Dihydrochloride, mp 268–269° (lit.[5] mp 251°). [d] Lit.[5] mp 75°. [e] Melting point of hydrochloride; free base, bp 118–123 (0.3 mm) (ref 5 reports melting point of maleate at 190°). [f] DME solvent. [g] Melting point of hydrochloride; free base, bp 78–80 (0.1 mm). [h] Yield by glpc; yield of pure salt 33%. [i] Melting point of hydrochloride; free base, bp 120–125° (0.2 mm). [j] Melting point of hydrochloride; free base, bp 150–160 (0.2 mm). [k] Melting point of hydrochloride; free base, bp 130–135° (0.2 mm). [l] Composed of 71% 20 and 29% 19a.

mitted the isolation of **7** (2- and 4-pyridyl, R = C_6H_5) in good yield when the appropriate reaction conditions were used (see Experimental Section).

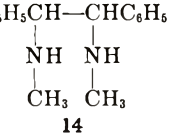
It is also interesting to note that while benzophenone gave a methylimine in excellent yield, dibenzo[*a*,*d*]cycloheptan-5-one failed to react appreciably (only 10% conversion) with methylamine even under more vigorous conditions (150°, 2 days). In contrast, fluorenone reacted readily, but the nmr spectrum of the product revealed a complex mixture of products, including the type of reaction encountered in the pyridine series. Ammonia, however, reacts normally to give fluoren-9-onimine (**9**).[6]

The following were prepared as starting materials by literature methods: **9**,[6] diphenylketimine (**10**),[7] 1-phenyl-3,4-dihydroisoquinoline (**11**),[8] and **12**.[9]



12

Reductive Alkylation.—Imines of type **2**, where R = R' = C_6H_5 or R = 4-pyridyl, R' = H, CH_3, or C_6H_5, and the cyclic imine **11** underwent reductive alkylation at carbon, using sodium in ammonia and a variety of organic chlorides. Good yields of amines **16**, **17**, and **18** were obtained (see Table II). When R was 3-pyridyl, only polymeric material was formed with 2-diethylaminoethyl chloride (**13**) as the alkylating agent. When R was 2-pyridyl, reductive alkylation with **13** gave tars plus a mixture of C- and N-alkylated amine, with N-alkylation predominating (70:30). With the methylimine from benzaldehyde no alkylation occurred. Only N-methylbenzylamine and the dimer **14** were isolated (presumably from radical ion intermediate). From the methylimine of acetophenone, only the reduced product resulted. Other starting materials which failed to give pure alkylated products were compounds **2h** (Table I), **9**, and **12**, as well as isoquinoline, acridine, and benzonitrile. Attempts to use dihalides to synthesize aziridines and azetidines of type **15** also were unsuccessful.



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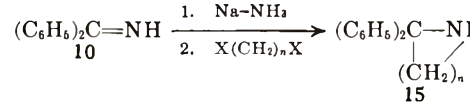


Using sodium dispersion in 1,2-dimethoxyethane (DME), **10** gave the same C-alkylated product with **13** as it did in ammonia but in lower yield. Trimethylsilyl chloride (which is too reactive for use in ammonia) reacted with the sodium adduct of **10** in DME to give the N-alkylated product, presumably because of steric hindrance to C-alkylation. Since DME is aprotic, it seems likely that the disodio derivative **3** (R = R' = C_6H_5, R'' = H) is the predominant species present in this solvent. Results of all successful reductive alkylations are summarized in Table II.

(6) L. Pinck and G. Hilbert, *J. Amer. Chem. Soc.*, **56**, 490 (1934).
(7) Moureu and Mignonac, *Compt. Rend.*, **56**, 1806 (1913).
(8) W. Whaley and W. Hartung, *J. Org. Chem.*, **14**, 650 (1949).
(9) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, S. Sach, G. Sancy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

TABLE III

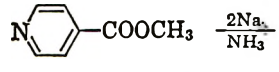
PRODUCTS FROM ALKYLATION OF AMINES WITH ALKYL CHLORIDES (RCl) USING SODIUM AMIDE IN LIQUID AMMONIA

No.[a]	R, R′, R″	Yield, %	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
16a	$(C_2H_5)_2NCH_2CH_2$, H	77	See Table II							
18c	$C_6H_5CH_2$, CH_3, H	57	See Table II							
19a and 20	$(C_2H_5)_2NCH_2CH_2$, CH_3	63[b]	See Table II 155–158 (0.1)							
18g	$(C_2H_5)_2NCH_2CH_2$, CH_3, C_6H_5	45	56–58	$C_{19}H_{27}N_3$	76.72	9.15	14.13	76.80	9.16	14.03
18h	$(C_2H_5)_2NCH_2CH_2$, H, H	54	205–210[c]	$C_{12}H_{24}Cl_3N_3$	45.53	7.63	13.26	43.26[d]	7.75	13.17
19b	$(C_2H_5)_2NCH_2CH_2$, H	55	120–122 (0.7)	$C_{12}H_{21}N_3$	69.52	10.21	20.27	69.44	10.22	20.43
19c	$HC{\equiv}CCH_2$, H	12	72–75 (0.5)	$C_9H_{10}N_2$	73.94	6.89	19.16	74.16	6.99	19.36
19d	$C_6H_5CH_2$, H	18	238–240[e]	$C_{13}H_{16}Cl_2N_2$	57.65	5.95	10.34	57.61	6.00	10.43

[a] See Table II for structures. [b] Composed of 52% 20 and 48% 19a. [c] Melting point of trihydrochloride; free base, bp 118–125° (0.3 mm). [d] *Anal.* Calcd for Cl: 33.35%. Found: 33.77%. [e] Melting point of dihydrochloride; free base, bp 130–135° (0.8 mm).

These results indicate that reductive alkylation occurs with only those imines, which, upon addition of sodium in liquid ammonia, afford carbanions that are weaker bases than sodium amide. One should then be able to get the same intermediates by treating the reduced imine (*i.e.*, the amine) with sodium amide in liquid ammonia. Subsequent alkylation would give identical products. This proved to be the case. Benzhydrylamine with sodium amide (1.3 mol) in liquid ammonia gave a dark red solution, also formed from the imine **10** when it was added to a sodium–ammonia solution. Alkylation with diethylaminoethyl chloride (**13**) gave the same product, **16a**, in comparable yield. This comparison also was extended to 4-pyridine aldehyde methylimine and its corresponding amine, using benzyl chloride as the alkylating agent. The same product, **18c**, resulted, and gas chromatography of the crude product showed it was contaminated with even the same impurities. However, comparison of 2-pyridine aldehyde methylimine and the corresponding amine, showed significant differences in the reaction with **13**. N-Alkylation predominated in both cases but the sodium amide method gave a higher yield (63 *vs.* 24%) of a mixture containing a higher proportion (48 *vs.* 29%) of the C-alkylated isomer. A number of sodium amide alkylations using 2- and 4-aminomethylpyridines were carried out and are summarized in Table III. With 2-aminomethylpyridine, only C-alkylation was observed while its N-methyl derivative gave 52% N-alkylation. One would have to know more about the relative acidities and reactivities of the carbanions and nitranions derived from them to explain these results.

In view of our promising results with 2- and 4-pyridylimines and Kharasch's[3] fair success in the reductive alkylation of simple esters, extension of the reactions to pyridyl esters seemed to be in order. Hopefully, Kharasch's supposed intermediate would acquire more resonance stabilization (*e.g.*, **22**) in the pyridine system.



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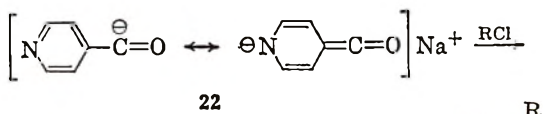

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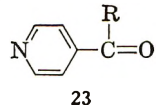

23

Reductive alkylation of **21** with benzyl- and *p*-chlorobenzyl chlorides gave 54 and 34% yields of **23** respectively. This is much better than Kharasch's 5% with benzyl chloride and ethyl benzoate. However, ethyl bromide, diethylaminoethyl chloride (**13**), and allyl chloride failed to give significant yields of ketone with **21**. Methyl picolinate also was used but, even with benzyl chloride, failed to give any benzyl 2-pyridyl ketone. It was suspected that benzyl sodium may be the reactive intermediate instead of **22** in the successful runs, but reversing the order of addition (adding the benzyl chloride to the sodium in ammonia, followed by the ester) gave only bibenzyl and no ketone in these cases.

Experimental Section

All compounds gave infrared and nmr spectra consistent with their assigned structures.

Preparation of N-Methylimines (2).—The conditions for the preparation of N-methylimines are listed in Table I. For aldehyde imines, 3 equiv of methylamine in the solvent listed were used for each equivalent of aldehyde. For the other imines, 0.2 mol of ketone was dissolved in 100 ml of liquid methylamine and heated in an autoclave at the temperature and for the time listed in the table. The methylamine was vented, and the residue was dissolved in ether, dried over potassium carbonate, and distilled.

4-(α-Methylaminobenzyl)pyridine (18, R = H; R′ = CH_3; R″ = C_6H_5).—The imine **21** (82.5 g) was hydrogenated in ethanol at 40 psi using a 5% platinum–charcoal catalyst. Distillation gave 68.0 g (82%) of product, bp 130–135° (0.2 mm). A small amount of higher boiling material was recovered which contained phenyl-4-pyridylmethanol. Treatment of the base with excess alcoholic hydrogen chloride gave the dihydrochloride, mp 238–240°.

Anal. Calcd for $C_{13}H_{16}Cl_2N_2$: C, 57.51; H, 5.91; N, 10.32. Found: C, 57.71; H, 6.10; N, 10.64.

4-α-Aminobenzylpyridine (18, R = C_6H_5; R′ = R″ = H).—4-Benzoylpyridine (55.0 g) was dissolved in 300 ml of methylamine and heated for 30 hr at 150° in an autoclave. The autoclave was cooled and vented. The residue was taken up in ether, dried over potassium carbonate, and distilled to give 3.40 g, bp 50–60° (0.8 mm), and 45.8 g, bp 130–140° (0.2 mm). The low boiling fraction was redistilled to give 2.52 g, bp 75–80° (10 mm). Its nmr spectrum showed it to be the triazine *8*.

Anal. Calcd for $C_6H_{15}N_3$: C, 55.78; H, 11.70; N, 32.52. Found: C, 55.83; H, 11.76; N, 32.73.

Gas chromatography of the higher boiling fraction indicated the presence of 67% of the primary amine **18** and 24% of the N-methylimine **2j**. (*Note:* Running the reaction for a longer period of time did not lower the percentage of **2j**.) The dihydrochloride was prepared with hydrogen chloride in 2-propanol. After two recrystallizations from ethanol–2-propanol, there was obtained 42.3 g (56%) of dihydrochloride, mp 231–234° (lit.[10] mp 234–236°).

(10) C. Lovell and K. Rorig, U. S. Patent 3,025,302 (1962); *Chem. Abstr.*, **57**, 11173b,c (1962).

2-α-Aminobenzylpyridine (19, R = C_6H_5; R′ = H).—2-Benzoylpyridine (55.0 g) was treated as in the foregoing procedure for 24 hr at 130°. The product [24.5 g, 45% yield, bp 135–140° (0.2 mm)] was at least 90% pure as indicated by nmr analysis. The dihydrochloride melted at 242–244° (lit.[11] mp 242–244°).

Reductive Alkylation with Sodium in Ammonia.—To 300 ml of liquid ammonia under a nitrogen atmosphere, and cooled in a Dry Ice–acetone bath, was added 5.17 g of sodium (0.225 g-atom). After all the sodium had dissolved (blue-black solution), a solution of 0.10 mol of the imine in 25 ml of dry ether was added dropwise over a 15-min period. This was stirred for 15 min, and then a solution of 0.11 mol of the halide in 25 ml of ether was added over another 15-min period. The dark-colored solution was stirred for 3–4 hr at the Dry Ice bath temperature under a nitrogen atmosphere. Then 10 ml of water was added slowly, the ammonia was evaporated on a warm water bath, and the residue was taken up in ether and 25 ml of water. The ether layer was separated and dried over anhydrous potassium carbonate. Removal of the drying agent by filtration and distillation of the filtrate gave the products listed in Table II.

1,2-Diphenyl-N,N′-dimethylethylenediamine (14).—When benzaldehyde methylimine was subjected to the foregoing conditions using diethylaminoethyl chloride as the alkylating agent, the color of the solution changed from blue-black to light yellow after less than half of the halide had been added. The mixture was worked up in the prescribed way to give N-methylbenzylamine and a 45% yield of **14** as a mixture of *meso* and *dl* isomers. The isomers could be partially separated into the solid *meso*, mp 115–124° (lit.[12] mp 135°) and the liquid *dl* form. The nmr spectra indicated that the liquid contained very little *meso*, and the solid contained about 80% *meso* form. The liquid was the major (80%) product in the mixture.

Anal (for liquid *dl*). Calcd for $C_{16}H_{20}N_2$: C, 79.83; H, 8.37. Found: C, 79.96; H, 8.39.

Use of Dimethoxyethane (DME) Solvent. N-Trimethylsilylbenzhydrylamine (16e).—To a suspension of 3.90 g of sodium dispersion in 110 ml of DME was added, dropwise with stirring in a nitrogen atmosphere, a solution of 9.0 g of diphenylketimine (**10**) in 30 ml of DME. A dark blue solution formed. After being stirred for 0.5 hr, the solution was cooled to −30° and 7.0 g of trimethylsilyl chloride dissolved in 30 ml of DME was added over a 15-min period. At the end of the addition the reaction mixture changed to a light pink color but on warming to room temperature it became dark red. Water (10 ml) was added to discharge the color, the DME was removed under reduced pressure, and the residue was treated with ether and water. The ether layer was separated, dried, and distilled. See Table II for the results.

Benzyl 4-Pyridyl Ketone (23, R = $C_6H_5CH_2$).—A solution of methyl isonicotinate (20.0 g) in 50 ml of ether was added over a 15-min period to a solution of 6.90 g of sodium in 250 ml of liquid ammonia kept under a nitrogen atmosphere and cooled in a Dry Ice–acetone bath. This was stirred for 5 min, and then 19.0 g of benzyl chloride dissolved in 40 ml of ether was added over a 20-min period. The Dry Ice–acetone bath was removed, and the mixture was stirred for 1.3 hr. Water (100 ml) was added slowly, the ammonia was evaporated on a warm water bath, and the residue was extracted with ether (50 ml) and then with chloroform (250 ml). (*Note*: The color of the solution changed from black to yellow on addition of chloroform.) Drying and removing the chloroform by distillation gave 15.6 g (54%) of ketone, mp 94–96° (chloroform–ether) (lit.[13] mp 96°). From the ether extract no ketone was obtainable.

***p*-Chlorobenzyl 4-Pyridyl Ketone (23, R = 4-$ClC_6H_4CH_2$).**—Substituting *p*-chlorobenzyl chloride for benzyl chloride in the foregoing procedure gave a 42% yield of the chloro ketone, mp 85–87° (chloroform—ether).

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.50; H, 4.35; N, 6.06. Found: C, 67.30; H, 4.38; N, 6.24.

Sodium Amide Alkylations.—To a suspension of 11.5 g (0.13 mol) of sodium amide in 300 ml of ammonia at −33° was added 0.10 mol of the amine. After being stirred for 20 min, the dark red solution was cooled in a Dry Ice–acetone bath. Then, under nitrogen, 0.10 mol of the halide dissolved in 30 ml of dry ether was added over a 15-min period. The reaction mixture was treated as specified above for the reductive alkylation. An exception was in the alkylation of 4-(α-methylaminobenzyl)pyridine. Here the reaction mixture was kept overnight in an autoclave at 15° instead of for 4 hr at −60°. Data are summarized in Table III.

Registry No.—**2d**, 7032-20-4; **2e**, 16273-54-4; **2f**, 16273-55-5; **2g**, 16273-56-6; **2h**, 16273-57-7; **2i**, 16273-58-8; **2j**, 16273-59-9; **16a**, 16273-85-1; **16c**, 16273-60-2; **16d**, 16273-61-3; **16d**·HCl, 16273-62-4; **16e**, 16273-86-2; **17**, 16273-63-5; **18a**, 16273-64-6; **18b**, 16273-65-7; **18b**·HCl, 16273-66-8; **18c**, 16273-67-9; **18c**·HCl, 16273-68-0; **18d**, 16273-69-1; **18d**·HCl, 16273-70-4; **18e**, 16273-71-5; **18f**, 16273-72-6; **18f**·HCl, 16273-73-7; **18g**, 16273-74-8; **18h**, 16273-75-9; **18h**·HCl, 16273-76-0; **18**(R = H; R′ = CH_3; R″ = C_6H_5)·2HCl, 16273-77-1; **19a**, 16273-78-2; **19b**, 16273-79-3; **19c**, 16273-80-6; **19d**, 16273-81-7; **19d**·2HCl, 16273-82-8; **20**, 16273-83-9; **23**, 16273-84-0; sodium, 7440-23-5; ammonia, 7664-41-7.

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The Isomeric Pyridopyrazines from the Reaction of Some Tetraaminopyridines with Pyruvaldehyde and Benzil[1]

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The major product obtained from the condensation of 2,3,4,6-tetraaminopyridine (**5**) with pyruvaldehyde under acidic conditions was identified as 6,8-diamino-3-methylpyrido[2,3-*b*]pyrazine (**1**). The condensation of ethyl 4,5,6-triamino-2-pyridinecarbamate (**18**) with benzil gave a 2:3 mixture of the pyrido[2,3-*b*]pyrazine (**19**) and pyrido[3,4-*b*]pyrazine (**20**) under neutral conditions, and mainly **20** containing a small amount of **19** under acidic conditions. These results were confirmed by the unambiguous synthesis of **19** and the ethoxy deamination of **20** to give ethyl 2,3-diphenyl-5-ethoxypyrido[3,4-*b*]pyrazine-7-carbamate (**24**). The isomeric carbamate (**23**) was obtained by a reaction sequence starting with 2,6-diamino-4-ethoxy-3-nitropyridine (**17**).

Previously the unambiguous syntheses of deaza analogs of methotrexate[2-4] was accomplished by modification of the multistep procedure of Boon and Leigh.[5] The successful preparation of 2,3,4,6-tetraaminopyridine (**5**), and availability of **2**[3] and **3**[4] for purposes of comparison, prompted the investigation of the more direct, one-step condensation of pyruvaldehyde with **5**. This reaction could theoretically give four isomeric deazapteridines (**1**–**4**) depending upon the relative nucleophilicities of the 2-, 3- and 4-amino groups of **5**. The condensation of **5** with pyruvaldehdye and of **18** with benzil under acidic conditions showed that the nucleophilicities of the amino groups are dependent on the pyridine substrate.

Reaction of diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (**13**)[4] with methanolic ammonia in a bomb at 138° not only replaced the chloro group, but cleaved the urethan groups to give 3-nitro-2,4,6-triaminopyridine (**9**). The latter was reduced with Raney nickel to give 2,3,4,6-tetraaminopyridine (**5**), isolated as the dihydrochloride. A complex reaction mixture resulted from the reaction of the unstable free amine of **5** with pyruvaldehyde under neutral conditions. The condensation of the dihydrochloride of **5**, however, with 30% aqueous pyruvaldehyde in 0.1 *N* hydrochloric acid under nitrogen gave a 58% yield of crude product, which was purified to give a 49% yield of one of the four possible isomers (**1**–**4**). A second fraction, which was obtained from this reaction in 6% yield, was shown to be either **3** or **4** by thin layer chromatography (see below). The mother liquor from the second fraction appeared to contain only **5** or its decomposition products. The ultraviolet spectrum of the purified product was more similar to that of **2** than that of **3**, and was tentatively assigned structure **1**. This assignment was substantiated by preparation of the isomeric 5,7-diamino-2-methylpyrido[3,4-*b*]pyrazine (**4**). The (diphenylmethyl)amino compound **6**[3] was treated with 10% hydrogen bromide in acetic acid to give the hydrobromide of the 4-aminopyridine **7**, which was converted into the free base with sodium acetate. The nitro group of **7** was hydrogenated in the presence of Raney nickel, and the resulting 3,4-diaminopyridine was condensed *in situ* with 30% aqueous pyruvaldehyde to give **8** in 56% yield. The urethan groups of **8** were hydrolyzed with potassium hydroxide in ethanol to give the 2-methylpyrido[3,4-*b*]pyrazine **4** in 79% yield.

A comparison of the properties of the four isomers (**1**–**4**) is presented in Table I. The pair of pyrido[2,3-*b*]pyrazines **1** and **2** were easily distinguished from the pair of pyrido[3,4-*b*]pyrazines **3** and **4** by the differences in their ultraviolet spectra and R_f values. In addition, potentiometric titrations indicated that the ionization constants (pK_a) of **1** and **2** were near **7**, while those of **3** and **4** were less than **5**. By comparison the constant of 2,4-diaminopteridine is reported to be 5.32.[6] The isomers of each pair, however, have very similar physical and chemical properties. The pyrido[2,3-*b*]pyrazines **1** and **2** have identical R_f values on silica gel plates, and similar ultraviolet and infrared spectra. Proton magnetic resonance (pmr) spectroscopy was found to be the only unequivocal method for differentiating between **1** and **2**. Spectra of the two isomers were obtained both separately and in a mixture to ensure that displacements of absorption peaks were not due to concentration effects. The similarities and differences noted in **1** and **2** were also found in the pyrido[3,4-*b*]pyrazines **3** and **4**.

In the condensation of **5**, and the 3,4-diaminopyridine resulting from **7**, with pyruvaldehyde, it is reasonable to assume that the initial reaction occurred between the 3-amino group and the aldehyde moiety to give the corresponding pyridine anil. In the anil from **5** the direction of cyclization is determined by the relative nucleophilicities of the 2- and 4-amino groups in acidic media. Since **1** is the major isomer formed, the 2-amino group must be more nucleophilic than the 4-amino group under the conditions employed. This conclusion is supported by the reaction of 2,3,4-triaminopyridine with polyglyoxal to give the pyrido[3,4-*b*]pyrazine system under neutral conditions and the pyrido[2,3-*b*]pyrazine system under acidic conditions.[7]

The 3,4-diaminopyridine resulting from the reduction of **7** as described above was also condensed with benzil to give the 2,3-diphenyl derivative **11**. Hydrolysis of the urethan groups of this compound gave an 84% yield of 5,7-diamino-2,3-diphenylpyrido[3,4-*b*]pyrazine (**12**).

The isomeric 2,3-diphenylpyrido[2,3-*b*]pyrazine **16**

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Center Institute, National Institutes of Health, Contract No. PH43-64-51.

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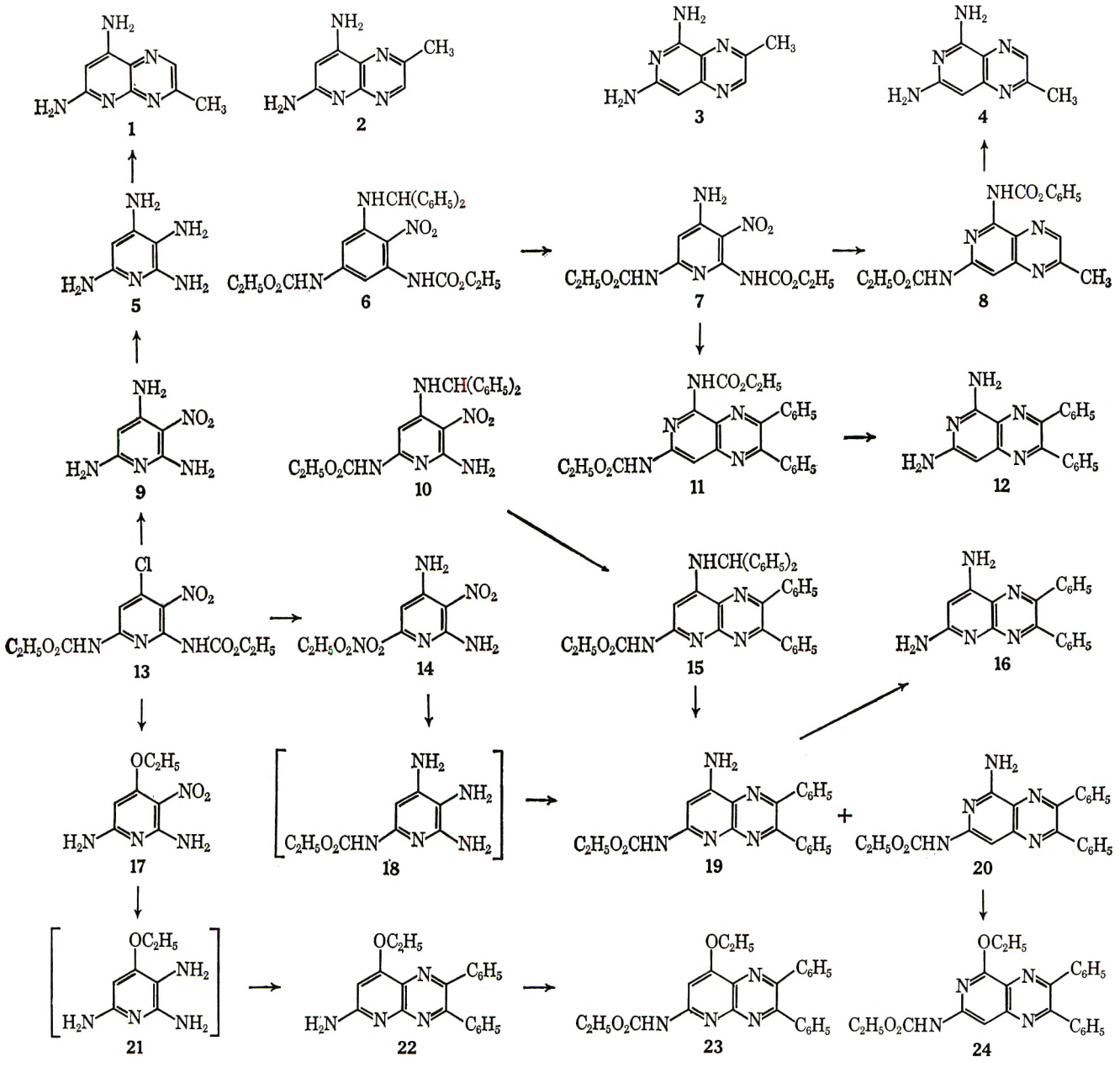

was prepared in three steps from the pyridine **10**[3]. The nitro group of **10** was reduced in the presence of a 30% palladium-on-charcoal catalyst, and the resulting 2,3-diaminopyridine was condensed *in situ* with benzil to give **15**. The diphenylmethyl group of **15** was removed with 15% hydrogen bromide in acetic acid to give **19**, and the urethan group of the latter was cleaved with ethanolic potassium hydroxide to give **16**. A comparison of the properties of **12** and **16** is also included in Table I.

To examine the reaction of a 2,3,4-triaminopyridine with benzil, the nitro group of **14**[3] was reduced with Raney nickel to give the intermediate ethyl 4,5,6-triamino-2-pyridinecarbamate (**18**). In contrast to the reaction of **5** with pyruvaldehyde, which gave the pyrido[2,3-*b*]pyrazine ring system, the condensation of **18** *in situ* with benzil under acidic conditions gave **20** containing a small amount of **19**. The latter was identified by comparison of a thin layer chromatogram of the reaction product with a chromatogram of the unambiguously prepared sample of **19** described above. However, **19** was undetected in the pmr spectrum of the reaction product in deuterated DMSO indicating that this sample probably contained less than 10% **19**. Under neutral conditions the condensation of **18** with benzil gave a greater amount of **19**. The reaction product was estimated from its pmr spectrum to be a 2:3 mixture of **19** and **20**. The change in the direction of cyclization in the condensation of **18** with benzil, when compared with the reaction of **5** with pyruvaldehyde, is attributed to a change in the nucleophilicities of the 2- and 4-amino groups in the intermediate pyridine anil resulting from the ethoxycarbonyl group on the 2-amino group.

Although **20** was not completely freed of **19** by recrystallization, the ethoxy deamination[8] of **20** containing about 30% of **19** with ethanolic isoamyl nitrite and hydrogen chloride in a sealed tube at 100° gave **24**. The isomeric ethoxy compound **23** was prepared from 2,6-diamino-4-ethoxy-3-nitropyridine (**17**). The latter was obtained by treatment of **13** with ethanolic potassium hydroxide. Reduction of the nitro group of **17** with Raney nickel gave **21**, which was condensed

(8) N. C. Hindley and J. A. Low, British Patent 588,806 (1947).

TABLE I

Compd	Tlc,[a] R_f	Ultraviolet absorption spectra, λ_{max} in mμ (ε × 10⁻³) 0.1 N HCl	pH 7	0.1 N NaOH	Infrared absorption spectra, 1700–1500 cm⁻¹	Pmr spectra assignments,[b] chemical shift, τ (ppm) $CH_3(C_6H_5)$	CH	NH_2
1[c]	0.66	221 (37.0)	221 (36.5)	259 (14.3)	1645, 1600, 1555,	7.34	3.87	1.95
		246 (sh) (6.63)	246 (sh) (6.82)	351 (12.1)	1517		1.37	1.83
		331 (18.0)	332 (17.1)					
2[c,d]	0.66	221 (36.9)	220 (33.7)	259 (15.9)	1650, 1630 (sh),	7.31	3.73	1.97
		334 (15.9)	255 (9.32)	354 (9.56)	1600 (sh), 1545		1.25	1.66
			341 (12.1)					
3[e]	0.79	244 (17.9)	265 (22.6)	266 (23.3)	1650, 1600, 1575 (sh),	7.48	4.03	4.20
		314 (16.8)	312 (7.3)	312 (7.3)	1535		1.46	3.23
4	0.79	248 (17.7)	267 (27.2)	267 (27.2)	1650 (sh), 1608, 1590,	7.51	4.14	4.14
		256 (sh) (17.1)	314 (6.36)	314 (6.36)	1550		1.93	3.25
		320 (15.7)						
12		233 (25.3)	237 (21.0)	237 (20.7)	1650 (sh), 1605	2.65	3.97	*ca.* 4.3
		338 (30.2)	305 (24.5)	305 (24.5)	1580 (sh), 1555 (sh),			*ca.* 2.6
					1515			
16		222 (36.0)	277 (20.6)	229 (25.4)	1618, 1575 (sh),	2.61	3.72	1.90
		273 (17.2)	371 (18.6)	279 (24.7)	1540, 1525			1.60
		366 (22.6)		378 (16.9)				

[a] The compounds were spotted on silica gel H (Brinkmann) plates, exposed to ammonia, and developed with ethyl acetate–methanol (1:1). [b] Spectra were obtained on DMSO-d_6 solutions (2–11% w/v) with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. [c] Hydrochloride. [d] See ref 3. [e] See ref 4.

in situ with benzil to give **22**. Then, reaction of **22** with ethyl chloroformate and pyridine in dioxane gave the corresponding urethan **23**.

Experimental Section

Melting points, unless otherwise indicated, were determined on a Kofler Heizbank and are corrected. The ultraviolet absorption spectral were determined in aqueous solution with a Cary Model 14 spectrophotometer (sh designates shoulder), whereas the infrared absorption spectra were determined in pressed potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers.

6,8-Diamino-3-methylpyrido[2,3-*b*]pyrazine (1).—The dihydrochloride of **5** (500 mg, 2.36 mmol) was dissolved in a stirred solution of 30% aqueous pyruvaldehyde (622 mg, 2.59 mmol) and 0.1 *N* HCl (4.4 ml) at 0° under N_2. The resulting solution remained at room temperature for 2 hr and at 4° for 1 hr. The orange crystalline precipitate of crude **1** hydrochloride (290 mg) was collected by filtration, washed with cold water (0.5 ml), and recrystallized (charcoal) from hot 0.2 *N* HCl (4 ml). The light tan crystals of **1** hydrochloride were collected by filtration and dried *in vacuo* over P_2O_5 to yield 245 mg (49%), mp >330° (Mel-Temp).

Anal. Calcd for $C_8H_9N_5 \cdot HCl$: C, 45.40; H, 4.76; N, 33.09. Found: C, 45.45; H, 4.88; N, 32.82.

Concentration of the reaction filtrate gave 29 mg (6%) of a precipitate that was identified as either **3** or **4** by thin layer chromatography.

5,7-Diamino-2-methylpyrido[3,4-*b*]pyrazine (4).—A solution of **8** (319 mg, 1.00 mmol) and KOH (701 mg, 12.5 mmol) in EtOH (5 ml) was refluxed under N_2 for 7 hr. The reaction mixture was cooled to room temperature, and the resulting orange-yellow precipitate was collected by filtration. A suspension of the precipitate in H_2O (2 ml) was neutralized with 3 *N* HCl to give an orange precipitate of **4** which was collected by filtration, washed with cold H_2O, and dried at 78° *in vacuo* over P_2O_5 to yield 138 mg (79%), mp 237° dec (taken rapidly to melting point).

Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.80; H, 5.43; N, 40.09.

2,3,4,6-Tetraaminopyridine (5).—A solution of **9** (800 mg, 4.73 mmol) in EtOH (80 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1.4 g, weighed wet with EtOH). The reaction mixture absorbed the theoretical amount of H_2 in 80 min. The resulting solution was filtered under N_2, treated with 6.1 *N* anhydrous HCl in ethanol (1.64 ml, 10 mmol), and refrigerated. The crystalline precipitate of **5** dihydrochloride was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5 to yield 900 mg (90%): mp >220° with slow decomposition; λ_{max} in mμ (ε × 10⁻³), pH 1—224 (47.1) and 293 (11.5), pH 7 (unstable)—225 and 301, pH 13 (unstable)—288; $\bar{\nu}$ in cm⁻¹, 3320 and 3190 (NH), 2850 and 2560 (acidic H), 1670 and 1640 (NH_2), 1570 and 1500 (ring stretching).

Anal. Calcd for $C_5H_{11}Cl_2N_5$: C, 28.32; H, 5.23; N, 33.02. Found: C, 28.50; H, 5.12; N, 32.95.

Diethyl 4-Amino-3-nitro-2,6-pyridinedicarbamate (7).—A solution of 6[3] (48.0 g, 0.100 mol) and phenol (5 g) in 10% HBr in AcOH (1.44 l.) was stirred at room temperature for 18 hr and diluted with ether (4.80 l.). The resulting yellow crystalline **7** hydrobromide was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5 to yield 33.8 g (86%): mp 153–156° dec; λ_{max} in mμ (ε × 10⁻³), pH 1—221 (34.4), 244 (23.0), 273 (18.7), and 325 (10.9), pH 7—219 (33.0), 246 (20.3), and 343 (13.3), pH 13—224 (26.0), 263 (16.1), and 361 (8.03); $\bar{\nu}$ in cm⁻¹, 3430 and 3270 (NH), 2980 and 2930 (CH), 1728 (C=O), 1655 (NH_2), 1605 (ring stretching), 1230 (C–O–C).

Anal. Calcd for $C_{11}H_{15}N_5O_6 \cdot HBr$: C, 33.51; H, 4.09; N, 17.77. Found: C, 33.27; H, 4.33; N, 17.47.

A mixture of the hydrobromide (30.0 g, 76.1 mmol) and NaOAc (6.24 g, 76.1 mmol) in H_2O (400 ml) was stirred for 18 hr. The free base (**7**) was collected by filtration, washed with H_2O, air dried, recrystallized from boiling EtOH (2 l.), and dried *in vacuo* over P_2O_5 at 78° to yield 18.8 g (79%): mp *ca* 190°; λ_{max} in mμ (ε × 10⁻³), pH 1—221 (33.8), 244 (22.9), 273 (18.9), and 324 (10.8), pH 7—219 (32.5), 246 (20.8), and 343 (12.9), pH 13—226 (26.2), 263 (16.7), and 362 (6.92); $\bar{\nu}$ in cm⁻¹, 3460, 3435, 3340, 3315, and 3200 (NH), 3070, 2980, 2935, and 2905 (CH), 1745, 1735, and 1713 (C=O), 1620 (NH), 1590, 1530, and 1490 (ring stretching), 1200 (C–O–C).

Anal. Calcd for $C_{11}H_{15}N_5O_6$: C, 42.17; H, 4.83; N, 22.36. Found: C, 42.08; H, 4.80; N, 22.52.

Diethyl 2-Methylpyrido[3,4-*b*]pyrazine-5,7-dicarbamate (8).—A solution of **7** (1.00 g, 319 mmol) in Me_2CO (20 ml) and H_2O (1 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1 g weighed wet with EtOH). The H_2 uptake was complete in 2 hr. The resulting solution was filtered under N_2 and treated with a solution of 30% pyruvaldehyde (843 mg, 3.51 mmol) in H_2O (2 ml). The reaction mixture (under N_2) was allowed to stand at room temperature for 16 hr, then at 4° for 24 hr. The crystalline **8** that deposited was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5 at 78° to yield 570 mg (56%): mp 199°; λ_{max} in mμ (ε × 10⁻³), pH 1—219 (19.8), 240 (29.4), 257 (sh) (22.1), 263 (22.5), 304 (12.6), and 378 (3.16), pH 7—258 (36.5), 292 (4.88), and 366 (5.47), pH 13—262 (29.1) and 388 (3.11); $\bar{\nu}$ in cm⁻¹, 3385, 3255, and 3160 (NH), 3080, 2980, 2930, and 2910 (CH), 1762 (sh), 1750, 1732, and 1721 (sh) (C=O), 1610 (NH), 1588, 1540, and 1510 (ring stretching), 1220 and 1200 (C–O–C).

Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.73; H, 5.41; N, 21.94.

3-Nitro-2,4,6,triaminopyridine (9).—A solution of **13**[4] (3.00 g, 9.02 mmol) in MeOH (90 ml) saturated with NH_3 at 0° was heated in a Parr bomb at 138° for 23 hr. The residue that was obtained by evaporation of the reaction mixture was recrystallized from a boiling EtOH–H_2O mixture (1:3). The product which crystallized as long orange needles was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to yield 1.26 g (83%): mp 261°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—216 (31.4), 274 (9.50), and 347 (8.95), pH 7—212 (26.2), 257 (11.0), and 349 (13.6), pH 13—256 (11.3) and 349 (13.9); $\bar{\nu}$ in cm^{-1}, 3475, 3440, 3395, and 3350 (NH), 3080 (CH), 1650 (NH_2), 1580 and 1550 (sh) (ring stretching).

Anal. Calcd for $C_5H_7N_5O_2$: C, 35.50; H, 4.17; N, 41.41. Found: C, 35.50; H, 4.18; N, 41.23.

Diethyl 2,3-Diphenylpyrido[3,4-*b*]pyrazine-5,7-dicarbamate (11).—A solution of **7** (2.00 g, 6.38 mmol) in Me_2CO (40 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1.7 g, weighed wet with EtOH). The theoretical quantity of H_2 was absorbed in 2 hr. The catalyst was removed by filtration and benzil (1.48 g, 7.02 mmol) was added to the filtrate. After 4 days at room temperature the solution was evaporated to dryness, and the resulting residue was recrystallized from EtOH (10 ml). The yellow crystalline product that deposited was collected by filtration, washed with EtOH, and dried at 100° *in vacuo* over P_2O_5 to yield 2.60 g (81%): mp 170° with softening from 100°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1 (unstable)—239 and 315, pH 7 (unstable)—257 and 312, pH 13—252 (24.9) and 307 (27.2); $\bar{\nu}$ in cm^{-1}, 3380 and 3250 (NH), 3060, 2977, 2930, and 2905 (CH), 1758 and 1730 (C=O), 1610 (NH), 1575, 1525, 1505, and 1496 (ring stretching), 1187 (C–O–C), 740 and 694 (monosubstituted phenyl).

Anal. Calcd for $C_{25}H_{23}N_5O_4$: C, 65.63; H, 5.07; N, 15.31. Found: C, 65.72; H, 5.13; N, 15.14.

5,7-Diamino-2,3-diphenylpyrido[3,4-*b*]pyrazine (12).—A mixture of **11** (458 mg, 1.00 mmol), KOH (1.40 g, 24.9 mmol), and EtOH (20 ml) was stirred at reflux under N_2 for 7 hr and cooled in an ice bath. The resulting orange crystalline precipitate was collected by filtration, suspended in H_2O (2 ml), and neutralized with 3 *N* HCl. The precipitate of orange product was collected by filtration, washed with cold H_2O, and dried *in vacuo* at 100° over P_2O_5 to yield 271 mg (84%), mp *ca.* 131° dec.

Anal. Calcd for $C_{19}H_{15}N_5 \cdot {}^1/_2H_2O$: C, 70.79; H, 5.00; N, 21.73. Found: C, 71.04; H, 4.93; N, 21.96.

Ethyl 2,3-Diphenyl-8-[(diphenylmethyl)amino]pyrido[2,3-*b*]pyrazine-6-carbamate (15).—A suspension of **10**[3] (1.00 g, 2.45 mmol) in EtOH (100 ml) was stirred with 30% palladium on charcoal (700 mg) in the presence of H_2 at atmospheric pressure and room temperature for 7 hr. The catalyst was removed by filtration and benzil (567 mg, 2.70 mmol) was added to the filtrate. After standing for 18 hr at room temperature, the resulting mixture containing white crystals was cooled at −25° for 1 hr, and the product was collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.24 g (92%), mp 205–215°. The analytical sample, mp *ca.* 225°, was obtained by recrystallization of a portion of the product from EtOH: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—243 (31.6), 273 (20.9), and 360 (22.4), pH 7 and 13 (cloudy)—242 (sh), 300, and 368; $\bar{\nu}$ in cm^{-1}, 3428 and 3400 (NH), 3062, 3030, 2980, 2928, and 2910 (CH), 1745 (C=O), 1595, 1569, 1540, 1510, and 1490 (ring stretching), 1193 (C–O–C), 740 and 690 (monosubstituted phenyl).

Anal. Calcd for $C_{35}N_5O_2$: C, 76.20; H, 5.30; N, 12.70. Found: C, 76.30; H, 5.23; N, 12.85.

6,8-Diamino-2,3-diphenylpyrido[2,3-*b*]pyrazine (16).—A solution of **19** (385 mg, 1.00 mmol) and KOH (2.00 g, 35.7 mmol) in EtOH (30 ml) was refluxed under N_2 for 7 hr. The solution was made slightly acidic with 6 *N* HCl and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH, and the extract was diluted with Et_2O to precipitate the hydrochloride of **16**. A mixture of the hydrochloride (270 mg, 0.772 mmol) and 1 *N* NaOH solution (0.772 ml, 0.772 mmol) in water (4 ml) was stirred for 1 hr and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH (10 ml), and the extract was refrigerated. The yellow needles that deposited were collected by filtration, washed with cold EtOH, and dried at 100° *in vacuo* over P_2O_5 to yield 173 mg (55%): mp *ca.* 148–153° (Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (36.0), 273 (17.2), and 366 (22.6), pH 7—277 (20.6) and 371 (18.6), pH 13—229 (25.4), 279 (24.7), and 378 (16.9); $\bar{\nu}$ in cm^{-1}, 3450, 3375, and 3160 (NH), 3050 (CH), 1618, 1575 (sh), 1540, 1525, and 1495 (NH_2, ring stretching), 739 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.82; H, 4.83; N, 22.35. Found: C, 72.37; H, 4.95; N, 22.55.

2,6-Diamino-4-ethoxy-3-nitropyridine (17).—A filtered solution of **13**[4] (5.00 g, 15.0 mmol) and KOH (15.0 g, 268 mmol) in EtOH (200 ml) was heated at reflux temperature for 3 hr. The yellow-orange precipitate was collected by filtration. Additional precipitate was obtained by concentration of the mother liquor *in vacuo*. The crops were combined, triturated with H_2O (5 ml), and dissolved in boiling water (380 ml). The hot solution after charcoal treatment and refrigeration deposited pure **17** as yellow needles which were collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.18 g (40%): mp 186–189°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—225 (sh) (10.3), 288 (3.29), and 360 (12.4), pH 7 and 13—222 (9.10), 257 (8.08), 311 (6.15), and 386 (13.3); $\bar{\nu}$ in cm^{-1}, 3441, 3419, 3348, 3230, and 3145 (NH), 2990, 2935, 2930, and 2885 (CH), 1650 and 1622 (NH_2), 1583 and 1550 (ring stretching), 1250 (C–O–C).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.46; H, 5.32; N, 28.39.

Ethyl 8-Amino-2,3-diphenylpyrido[2,3-*b*]pyrazine-6-carbamate (19).—A solution of **15** (500 mg, 0.907 mmol) in 15% HBr in AcOH (50 ml) was stirred for 18 hr at room temperature and evaporated to dryness at 40° (1 mm). The gummy residue was triturated with C_6H_6 (3 ml), collected by filtration under N_2, washed with C_6H_6 (3 ml), and dried *in vacuo* over P_2O_5 to yield 316 mg (68%): mp *ca.* 235–237° dec (Mel-Temp). The analytical sample, mp *ca.* 245–248° dec, was obtained by two recrystallizations of the crude hydrobromide from EtOH–Et_2O: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (30.4), 240 (sh), (26.1), 271 (20.5), and 360 (20.1), pH 7 (unstable)—221, 289, and 362, pH 13—221 (26.4), 288 (21.0), and 362 (11.6); $\bar{\nu}$ in cm^{-1}, 3600–2400 (NH, CH), 1740 (C=O), 1630 (NH_2), 1590, 1560, 1543, and 1505 (ring stretching), 1213 (C–O–C), 737 and 692 (monosubstituted phenyl).

Anal. Calcd for $C_{22}H_{19}N_5O_2 \cdot HBr$: C, 56.66; H, 4.32; N, 15.02. Found: C, 56.90; H, 4.52; N, 14.72.

A suspension of the crude hydrobromide (242 mg, 0.519 mmol) in 1.00 *N* NaOH solution (0.545 ml. 0.545 mmol) and H_2O (2 ml) was stirred at room temperature for 4 days. The free amine **19** was collected by filtration, washed with H_2O, dried *in vacuo* over P_2O_5, and recrystallized twice from EtOH–H_2O (3:1) to yield 140 mg (70%): mp >280°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (31.9), 238 (sh) (28.3), 272 (22.1), and 362 (21.3), pH 7 (unstable)—222, 287 and 363, pH 13—289 (24.3) and 367 (14.4); $\bar{\nu}$ in cm^{-1}, 3470, 3430, 3280, and 3150 (NH), 3050 and 2975 (CH), 1720 (C=O), 1620 (NH_2), 1580, 1560, 1535, and 1510 (ring stretching), 1200 (C–O–C), 738 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.30; H, 4.89; N, 17.98.

The Preparation of 19 and 20. A.—A solution of **14**[3] (1.43 g, 5.93 mmol) in EtOH (35 ml) was stirred with Raney nickel (600 mg, weighed wet with EtOH) in the presence of H_2 at room temperature and atmospheric pressure for 4.5 hr to give **18**. The catalyst was removed by filtration and benzil (1.25 g, 5.93 mmol) was added to the filtrate. After standing for 18 hr at room temperature, the solution deposited yellow crystals, which were collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.73 g (76%), mp 162° dec. A thin layer chromatogram and pmr spectrum showed that this solid was a 2:3 mixture of **19** and **20** (see discussion). Three recrystallizations of the mixture from EtOH afforded 650 mg (28%) of **20**, which was still contaminated with about 30% **19**, mp 255° dec.

Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.69; H, 4.89; N, 18.09.

B.—A solution of **14**[3] (500 mg, 2.07 mmol) in ethanol (15 ml) was hydrogenated as above and filtered under N_2 into 0.2 *N* HCl (15 ml). The resulting solution was treated with benzil (436 mg, 2.07 mmol) and stirred for 18 hr at room temperature and 15 min at reflux temperature. The yellow crystalline product which formed upon cooling the solution to room temperature was collected by filtration and dried *in vacuo* over P_2O_5 to yield 390 mg, mp 145–147° (Mel-Temp). A thin layer chromatogram of this crude product showed the presence of **20** and a trace of **19**. Only isomer **20** could be detected in a pmr spectrum of the product. Recrystallization of the solid from ethanol did not eliminate the trace of **19**.

6-Amino-2,3-diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine (22).—A solution of **17** (200 mg, 1.01 mmol) in EtOH (10 ml) was stirred with Raney nickel (300 mg, weighed wet with ethanol) in the presence of H_2 at atmospheric pressure and room temperature for 1.5 hr. The resulting colorless solution of **21** was carefully filtered under N_2 and treated with benzil (247 mg, 1.18 mmol). After standing for 18 hr under N_2 this solution deposited pale green crystals which were collected by filtration, washed with EtOH, and dried *in vacuo* over P_2O_5 to yield 318 mg (92%), mp 266–268° (Mel-Temp). The analytical sample, mp 268°, was obtained by recrystallization of a portion of the product from EtOH: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—227 (32.1), 265 (sh) (17.6), and 370 (24.7), pH 7—228 (26.3), 266 (sh) (22.9), and 380 (20.6), pH 13—228 (27.7), 266 (23.8), and 380 (20.7); $\bar{\nu}$ in cm^{-1}, 3600–2800 (NH, CH), 1630 (NH_2), 1604, 1550, and 1533 (ring stretching), 1205 (C–O–C), 740 and 696 (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.41; H, 5.40; N, 16.15.

Ethyl 2,3-Diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine-6-carbamate (23).—Ethyl chloroformate (1 ml) was added dropwise to a stirred solution of **22** (100 mg, 0.292 mmol) in pyridine (2 ml) and dioxane (10 ml). After the exothermic reaction had ceased, the solution was refluxed for 30 min. The cooled reaction mixture was treated dropwise with additional ethyl chloroformate (1 ml), refluxed for 1.5 hr, and evaporated to dryness under reduced pressure. The residue was triturated with H_2O (5 ml), collected by filtration, air dried, and crystallized two times from EtOH–H_2O. The crystalline product was collected by filtration and dried at 100° *in vacuo* over P_2O_5 for 3 days to yield 63 mg (52%): mp 111–114° (soft at 108°, Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—241 (34.2), 269 (23.8) and 373 (25.5), pH 7—223 (sh) (24.8), 254 (36.6), and 368 (22.9), pH 13—231 (27.2), 258 (30.0), 275 (sh) (27.8), and 382 (22.5); $\bar{\nu}$ in cm^{-1}, 3450 and 3120 (NH), 3055, 2975, and 2930 (CH), 1739 (C=O), 1604 (sh), 1596, 1539, and 1508 (ring stretching), 1195 (C–O–C), 740 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.46; H, 5.55; N, 13.67.

Ethyl 2,3-Diphenyl-5-ethoxypyrido[3,4-*b*]pyrazine-7-carbamate (24).—A sealed glass tube containing **20** (contaminated with **19**) (300 mg, 0.779 mmol), isoamyl nitrite (183 mg, 1.56 mmol), anhydrous HCl (28.4 mg, 0.779 mmol), and EtOH (20 ml) was refrigerated overnight and heated in a H_2O bath at 100° for 35 min. The solution was cooled to room temperature, filtered, and evaporated to dryness under reduced pressure. The residue was crystallized first from 1:1 EtOH–H_2O (3 ml) and then from propanol (5 ml) to give a yellow crystalline product which was collected by filtration and dried *in vacuo* over P_2O_5 to yield 70 mg (22%): mp 205°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—256 (18.0), 304 (25.2), and 390 (8.0), pH 7—256 (17.8), 304 (21.3), and 391 (10.4), pH 13—256 (18.6), 305 (23.2), and 390 (9.0); $\bar{\nu}$ in cm^{-1}, 3440 and 3230 (NH), 3057, 2980, 2930, 2900, and 2860 (CH), 1720 (C=O), 1608, 1570, 1530, and 1490 (ring stretching), 1218 and 1195 (C–O–C), 742 and 692 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.67; H, 5.41; N, 13.25.

Registry No.—Pyruvaldehyde, 78-98-8; benzil, 134-81-6; **1** HCl, 16335-89-0; **4**, 16335-90-3; **5**, 16335-91-4; **7**, 16335-92-5; **7** HBr, 16335-93-6; **8**, 16335-94-7; **9**, 16335-95-8; **11**, 16335-96-9; **12**, 16335-97-0; **15**, 16335-98-1; **16**, 16335-99-2; **17**, 16336-00-8; **19**, 16336-01-9; **19** HBr, 16336-02-0; **20**, 16336-03-1; **22**, 16336-04-2; **23**, 16336-05-3; **24**, 16336-06-4.

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The Quaternization of Isoxazoles with Alcohols and Perchloric Acid

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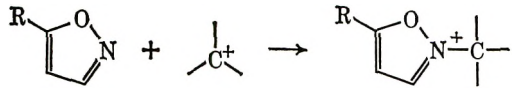
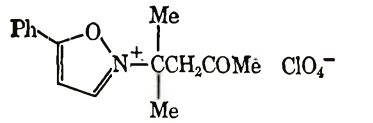
The reaction of isoxazoles and perchloric acid with alcohols which are efficient sources of carbonium ions has general utility as a method for the preparation of isoxazolium salts with branched quaternizing groups. The rate of reaction increases with the relative stability of the intermediate carbonium ion, while the equilibrium becomes less favorable for the formation of 3,5-dimethylisoxazolium cations as the bulk of the N-alkyl substituent is made greater.

In 1963, Eugster, Leichner, and Jenny, postulated[1] that combination of *t*-alkyl carbonium ions and unprotonated, 3-unsubstituted isoxazoles (**1**) gave isoxazolium salts (**2**) as reactive intermediates in sulfuric acid.



1 **2**

Subsequently, isolation of the perchlorate **3** from the reaction of 5-phenylisoxazole and mesityl oxide under the same conditions confirmed that this novel isoxazole quaternization had taken place, and it was found that 5-substituted N-*t*-butylisoxazolium salts (**4**) could conveniently be prepared simply by mixing *t*-butyl alcohol and the isoxazole with 70% perchloric acid.[2]



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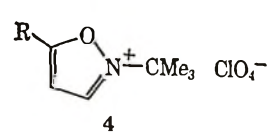

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A further study of the quaternization method was undertaken, because of the potential importance of the SN1 process as a general synthetic route to isoxazolium salts with branched groups on nitrogen. Such cations cannot be obtained with the normal SN2 alkylating agents,[3] and 3-unsubstituted isoxazolium salts with bulky nitrogen substituents have special significance as reagents for the preparation of stable enol ester acylating agents in peptide synthesis.[4–6] In addition it was

(1) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 1963).

(2) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).

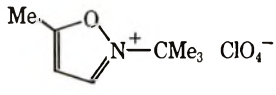
(3) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3**, 2 (1964).

(4) R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron Suppl.*, **8**, 321 (1966).

(5) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(6) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **90**, 1371 (1968).

of interest to determine if the alkylation technique would be applicable to isoxazoles substituted in the 3 position, because a substantial steric repulsion might be anticipated between the 3-alkyl group and bulky quaternizing substituent in the derived isoxazolium cation. It had earlier been found that the N^+–R bond of the relatively unhindered N-*t*-butyl-5-methylisoxazolium perchlorate (**5**) was sufficiently labile that **5** served as a carbonium ion donor in the catalysis of the isomerization of N-*t*-butylacetylketenimine (**6**) to β-*t*-butoxycrotononitrile (**7**).[7] It was considered possible, then, that the unfavorable steric interaction might cause 3-substituted N-*t*-butylisoxazolium salts to be still less stable than **5** and perhaps preclude their formation.



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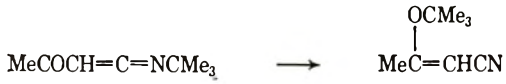
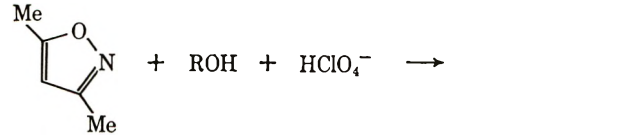


6 **7**

That *t*-butylation in fact is successful with 3-substituted isoxazoles was established using 3,5-dimethylisoxazole (**8**). Nmr assay of a mixture of equivalents of **8**, *t*-butyl alcohol, and 70% perchloric acid revealed that the alkylation was 20% complete within 0.5 hr, and there was no change in the composition of the mixture after 70% conversion, achieved within 1 week.

Next the effect of alcohol structure on the quaternization of **8** was investigated. In accord with the proposed[1] SN1 mechanism,[8] nmr assay of neat reaction mixtures revealed that alkylation was less rapid with benzyl alcohol (20% reaction within 2 months), and no reaction was observed with isopropyl alcohol. Spectral monitoring of neat mixtures with alcohols which provide carbonium ions of greater stability was complicated by product precipitation, but the problem was overcome when it was found that the reaction proceeded equally well in nitromethane solution. In further spectral tests in nitromethane, as expected, the rates increased through the series *t*-butyl alcohol (7% at 5 min), α-methylbenzyl alcohol (19% at 5 min), and α,α-dimethylbenzyl alcohol and benzhydrol (both near 70% at 5 min). However, the only reaction observed with 1,1-diphenylethanol was elimination to the stable alkene and the spectrum of a solution of **8** and perchloric acid with triphenylmethanol also showed no isoxazolium salt.

The quaternization is sufficiently rapid at room temperature for preparative convenience in the series of alcohols from *t*-butyl alcohol[10] through benzhydrol, either neat or in nitromethane solution. The products **10**–**13** are readily precipitated after 1 or 2 days in 50–90% yield, and other 3-unsubstituted isoxazoles have been found to give comparable results. The new types of isoxazolium perchlorates are nicely crystalline salts and may be stored without protection from light or atmospheric moisture.[11] However, the stability of **12** is marginal, and it decomposes completely within a few days in nonnucleophilic solvents. The product nmr spectrum shows the isoxazole **8** and complex signals presumably owing to the decomposition of α-methylstyrene in the acidic medium.



9, R = CH_2Ph
10, R = CMe_3
11, R = CHMePh
12, R = CMe_2Ph
13, R = $CHPh_2$

Although the repulsion between the 3-substituted isoxazole ring and N-*t*-butyl substituent is not so serious as had been feared, the importance of steric factors is evident from a comparison of the equilibrium constants K for the formation of the cations (assuming K = [isoxazole R^+][H_2O]/[isoxazole H^+][ROH]). The final compositions from the earlier test quaternization reactions were checked with spectral tests of the hydrolysis of the isoxazolium salts in nitromethane containing water. Immediate partial hydrolysis was observed with both **12** and **13**, with **10** hydrolysis proceeded very slowly for several days, and no change was observed with **11**. Composition data from both approaches to equilibrium indicate that K is of the order of magnitude of 100 for both **13** and **10**. A smaller value of K (30) was estimated[12] for **12**, while in the case of **11** K must be considerably greater than 100. Although the estimates of the equilibrium constants are relatively crude, a qualitative trend in K for the isoxazolium salts (**11** > **13** ~ **10** > **12**) is established which does not correlate with the polar effects of the quaternizing groups.[13] However, these results are in accord with a predominant steric influence on the equilibrium. Increasing the bulk of the N-alkyl substituent by replacing a methyl group with the larger phenyl group[14] makes the equilibrium less favorable for formation of **12** relative to **10** and for **13** relative to **11**. The effect of increasing the bulk still more with 1,1-diphenylethanol cannot be assessed because of the special stability of the derived alkene, but the equilibrium is clearly unfavorable with the trityl group.

(7) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

(8) Assuming that under the reaction conditions a phenyl group stabilizes a carbonium ion relative to the carbinol to a somewhat greater extent than do two methyl groups.[9]

(9) A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 43.

(10) The N-benzyl salt **9** was isolated in 29% yield from the neat test reaction mixture after 10 months.

(11) It should be noted that some isoxazolium perchlorates have been found to be impact sensitive explosives: B. D. Wilson and D. M. Burness, *J. Org. Chem.*, **31**, 1565 (1966). None of the salts prepared to date have detonated when small samples were subjected to mechanical shock.

(12) The extent of irreversible decomposition with this system at the time of the initial spectral assay, as judged by the rate of change in subsequent spectra, is not great enough to produce a major error in the estimate of K.

(13) The σ^* values[14] for R of B–R^+ are in the order **10** (−0.300) > **12** (estd 0.0) > **11** (0.105) > **13** (0.405).

(14) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

Experimental Section[15]

Spectral Tests.—Assay of the composition of test reaction mixtures was based on the integration of the methyl signals of the isoxazolium salts *vs.* those of the isoxazole at 10–20 cps higher field. Wherever possible integration data for other strong signals was checked against these results. Tests of the preparation of the isoxazolium salts in nitromethane (spectral quality) were conducted with approximately 0.5 *M* concentrations of each reactant, as were hydrolysis tests. With 10, 11, and 12 the hydrolysis results were also checked with 0.25 *M* solutions of the isoxazolium salt in nitromethane about 1.1 *M* in water.

N-Benzyl-3,5-dimethylisoxazolium Perchlorate (9).—After 10 months the benzyl alcohol spectral test reaction mixture (45% complete by nmr assay) gave 29% of 9 as a gummy solid on dilution with acetone and ether. The pure salt, mp 120–122°, was obtained after several precipitations. The nmr spectrum consisted of signals at τ 7.43 (s, 3.1), 7.30 (s, 3.0), 4.28 (s, 1.9), 3.15 (s, 1.0), and 2.61 (s, 5.0). The ultraviolet spectrum showed absorption at $\lambda_{max}^{H_2O}$ 232 mμ (ϵ 9200) and showed no significant change after 3 days.

Anal. Calcd for $C_{12}H_{14}ClNO_5$: C, 50.09; H, 4.91; Cl, 12.31; N, 4.87; O, 27.81. Found: C, 50.23; H, 4.98; Cl, 12.34; N, 5.02; O, 27.74.

N-*t*-Butyl-3,5-dimethylisoxazolium Perchlorate (10).—The standard procedure for the preparation of the isoxazolium salts is to add the alcohol (10% excess) and then 70% perchloric acid (10% excess) to the isoxazole slowly with stirring at 0°. On a 50-mmol scale, *t*-butyl alcohol gave 60% of 10 after 2 days upon dilution with acetone followed by a large volume of ether. One precipitation from acetone with ether provided 57% of the pure compound, mp 118–120° dec. The nmr spectrum consisted of signals at τ 8.17 (s, 9.2), 7.38 (broad, 2.9), 7.22 (s, 2.9), and 3.26 (broad, 1.0). The ultraviolet spectrum had an absorption at $\lambda_{max}^{H_2O}$ 231 mμ (ϵ 9100) and showed no change within 1 hr.

Anal. Calcd for $C_9H_{16}ClNO_5$: C, 42.61; H, 6.36; Cl, 13.98; N, 5.52; O, 31.54. Found: C, 42.55; H, 6.28; Cl, 13.88; N, 5.50; O, 31.44.

N-α-Methylbenzyl-3,5-dimethylisoxazolium Perchlorate (11).—The standard procedure with α-methylbenzyl alcohol resulted in a cloudy mixture which partially solidified when stirred overnight. Dilution with acetone and ether the following day gave an 86% yield of 11. One precipitation provided 82% of the pure compound, mp 83.5–84.5°. The nmr spectrum consists of signals at τ 7.95 (d, J = 7 Hz, 3.1), 7.36 (s, 5.9); 3.90 (m, J = 7 Hz, 0.9), 3.18 (s, 0.9), and 2.68 (s, 5.1).

Anal. Calcd for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; Cl, 11.75; N, 4.64; O, 26.51. Found: C, 51.76; H, 5.27; Cl, 11.61; N, 4.66; O, 26.72.

N-α,α-Dimethylbenzyl-3,5-dimethylisoxazolium Perchlorate (12).—With α,α-dimethylbenzyl alcohol the standard procedure gave a cloudy mixture which solidified when stirred. After 2 days addition of 1:1 acetone–nitromethane rapidly followed by ether gave 54% of 12. One precipitation provided 49% of the pure compound, mp 82–83°. The major nmr signals attributable to 12 in a freshly prepared solution were τ 7.93 (s, 3), 7.85 (s, 6), 7.25 (s, 3), 3.16 (s, 1), and 2.56 (s, 5). The abnormally high-field (τ 7.93) methyl singlet is assigned to the 3 substituent, shielded by the benzene ring of the quaternizing group.

Anal. Calcd for $C_{14}H_{18}ClNO_5$: C, 53.25; H, 5.75; Cl, 11.23; N, 4.44; O, 25.34. Found: C, 53.45; H, 5.73; Cl, 11.10; N, 4.53; O, 25.54.

N-Benzhydryl-3,5-dimethylisoxazolium Perchlorate (13).—The standard procedure with enough nitromethane to bring the benzhydrol into solution gave a mixture which partially solidified on standing overnight, and dilution with nitromethane and ether gave 70% of 13. Precipitation gave 63% of the pure compound, mp 160° dec.

Anal. Calcd for $C_{18}H_{18}ClNO_5$: C, 59.42; H, 4.99; Cl, 9.75; N, 3.85; O, 21.99. Found: C, 59.17; H, 5.22; Cl, 9.76; N, 3.93; O, 21.72.

(15) Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra (Varian A-60 spectrometer) of **9–12** were recorded in deuteriochloroform solution; chemical shifts are reported in τ values relative to tetramethylsilane as an internal standard (τ 10.00 ppm). Analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

Registry No.—**9**, 16404-24-3; **10**, 16315-65-4; **11**, 16315-66-5; **12**, 16315-67-6; **13**, 16315-68-7.

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Synthesis of Certain Naturally Occurring 2-Pyrones *via* 3,5-Diketo Acids[1]

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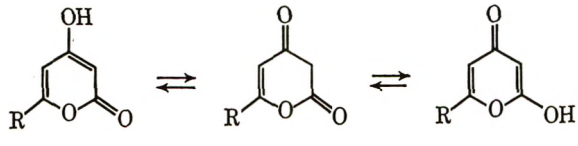
Two naturally occurring 4-methoxy-2-pyrones, 4-methoxyparacotoin and yangonin, were prepared by a three-step procedure involving carboxylation of disodio β-diketones, cyclization of the resulting diketo acids to 4-hydroxy-2-pyrones through the use of acetic anhydride, and O-methylation of the 4-hydroxy-2-pyrones at the 4 position. A partial synthesis of the hydroxypyrone, hispidin, was achieved. The synthesis of anibine was unsuccessful.

A number of 4-hydroxy-2-pyrones[2] and their methyl ethers have been isolated from natural sources.[3] Early interest in these compounds arose from their medicinal properties. In 1953, Birch and Donovan suggested that the 4-hydroxy-2-pyrones are biosynthesized by condensation of two acetate units with appropriate carboxylic acids to give diketo acids which subsequently lactonize.[4] Current interest has stemmed from the



(1) This work was supported by the National Institutes of Health, U. S. Public Health Service (Research Grant GM-12848).

(2) 4-Hydroxy-2-pyrones are in equilibrium with the tautomeric 2-hydroxy-4-pyrones and dihydropyran-2,4-diones. Spectroscopic evidence indicates that the 4-hydroxy-2-pyrone tautomer usually predominates; see F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, Chapter 4.

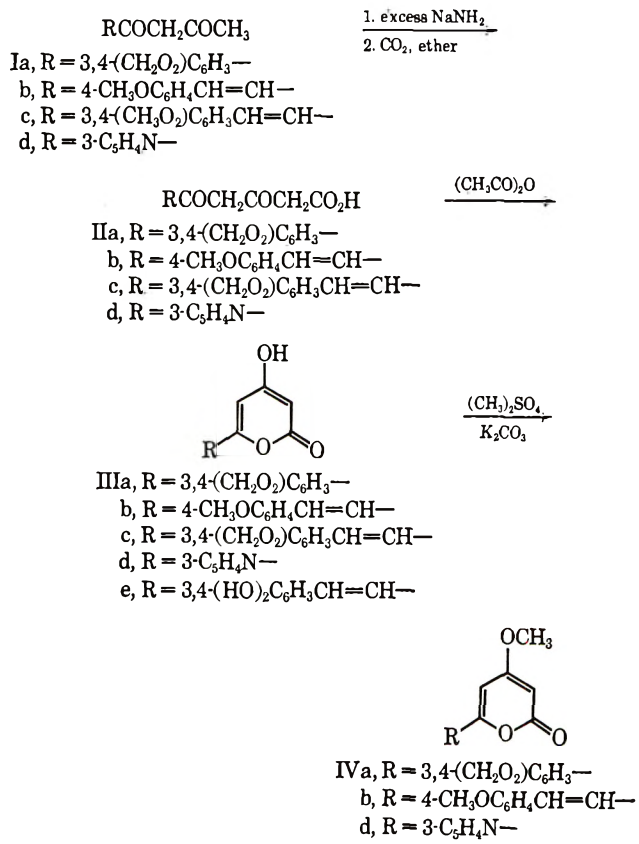
(3) For leading references, see (a) W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **79**, 4507 (1957); (b) O. R. Gottlieb and W. B. Mors, *J. Org. Chem.*, **24**, 17 (1959); (c) R. L. Edwards, D. G. Lewis, and D. V. Wilson, *J. Chem. Soc.*, 4995 (1961); (d) A. Penttila and J. Sundman, *Acta Chem. Scand.*, **15**, 839 (1961); (e) P. E. Brenneisen, T. E. Acker, and S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **86**, 1264 (1964); (f) A. K. Ganguly, T. R. Govindachari, and P. A. Mohamed, *Tetrahedron*, **21**, 93 (1965); (g) T. M. Harris, C. M. Harris, and R. J. Light, *Biochim. Biophys. Acta*, **121**, 420 (1966); (h) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 676 (1967).

(4) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **6**, 360 (1953).

possible relationship of the pyrones to the biosynthesis of fatty acids, phenols, and tropolones.[5]

A convenient method was described recently for the preparation of 4-hydroxy-2-pyrones.[6] β-Diketones were converted into dianions by reaction with 2 equiv of sodium amide in liquid ammonia. Treatment with carbon dioxide gave carboxylation at the γ position. The 3,5-diketo acids were converted into 4-hydroxy-2-pyrones by treatment with anhydrous, liquid hydrogen fluoride. The cyclizations can also be effected by polyphosphoric acid.[7] The application of this method to the synthesis of certain naturally occurring 2-pyrones has now been investigated (see Scheme I). The compounds chosen for study were 4-methoxyparacotoin (IVa), yangonin (IVb), anibine (IVd), and hispidin (IIIe).

SCHEME I



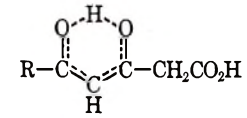
β-Diketones Ia–d were synthesized by conventional methods. The unsaturated diketones Ib and Ic were prepared by acylation of acetone with the phenyl esters of the appropriate cinnamic acids. The procedure has previously been demonstrated to be an excellent method for the preparation of similar unsaturated diketones; the use of phenyl esters minimizes β attack on cinnamate.[8]

The condensation of acetone with phenyl 3-piperonylacrylate afforded diketone Ic having a substantially lower melting point than material reported previously by Lampe and coworkers, which was prepared by acylation of ethyl acetoacetate with 3-piperonylacrylyl chloride followed by hydrolysis and decarboxylation.[9] The material obtained in the present reaction had a sharp melting point and gave satisfactory elemental analyses. The infrared spectrum was consistent with the proposed structure; intense absorption at 1610 cm^{-1} resulted from the enolized β-diketone. The nmr spectrum showed a large coupling constant (J = 16 cps) for the ethylenic hydrogens indicating that the *trans* isomer had been prepared.

The diketones were added to excess sodium amide in liquid ammonia to form the disodio salts. The ammonia was replaced with ether and the resulting suspension was treated with Dry Ice. By this procedure diketo acids IIa–c were isolated in yields of 30–61%. The method was not suitable for the preparation of pyridyl acid IId. Mors and coworkers have reported that alkaline hydrolysis of anibine (IVd) gave the salt of diketo acid IId but that spontaneous decarboxylation occurred on neutralization.[3a] Amine catalysis of the decarboxylation of another diketo acid has been observed,[10] and it seems probable that self-catalysis of decarboxylation occurred during the attempted isolation of diketo acid IId.

Diketo acid IIc has not been reported previously. The material gave a satisfactory elemental analysis. The infrared spectrum showed the presence of a carboxylic acid (1730 cm^{-1}) and an enolized β-diketone (1570 cm^{-1}). The nmr spectrum indicated that the *trans* olefinic structure ($J_{CH=CH}$ = 16 cps) had been retained. Diketo acids IIa–b had been prepared previously by alkaline hydrolysis of the corresponding 4-hydroxy-2-pyrones.[3a,11]

The 3,5-diketo acids II existed mainly as monoenols V in potassium bromide pellets and in solution. This assignment is made on the basis of the infrared spectra (KBr) that indicated the presence of unconjugated carboxyl and enolized β-dicarbonyl groups. The nmr spectra showed that the principal tautomer present in solution contained one methylene group between electronegative groups and one vinyl hydrogen of an enolized diketone.



V

The use of hydrogen fluoride for cyclization of diketo acid IIa was unsatisfactory; none of the desired pyrone was obtained and at least two other products were formed but these were not identified. It seems likely that the methylenedioxy group is attacked under the strongly acidic conditions. Borsche and Bodenstein reported that treatment of diketo acid IIb with refluxing acetic anhydride afforded the corresponding 2-acetoxy-4-pyrone, which can be hydrolyzed to give 4-hydroxy-2-pyrone IIIb.[11] In the present study the

(5) (a) G. Ehrensvard, *Exp. Cell Res., Suppl.*, **3**, 102 (1955); (b) R. Bressler and S. J. Wakil, *J. Biol. Chem.*, **237**, 1441 (1962); (c) J. D. Brodie, G. Wasson, and J. W. Porter, *ibid.*, **239**, 1346 (1964); (d) T. E. Acker, P. E. Brenneisen, and S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **88**, 834 (1966); (e) R. J. Light, T. M. Harris, and C. M. Harris, *Biochemistry*, **5**, 4037 (1966); (f) D. J. H. Brock and K. Bloch, *Biochem. Biophys. Res. Comm.*, **23**, 775 (1966); (g) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 681 (1967).

(6) T. M. Harris and C. M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).

(7) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

(8) C. R. Hauser, R. S. Yost, and B. I. Ringler, *J. Org. Chem.*, **14**, 261 (1949).

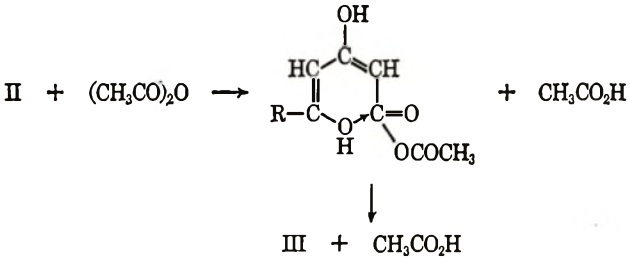
(9) W. Lampe, Z. Buczkowska, J. Frenkl, E. Gliksman-Korngold, M. Tokarska-Kozlowska, R. Nelken, and C. Sieradzka, *Rocz. Chem.*, **9**, 444 (1929); *Chem. Abstr.*, **23**, 4210 (1929).

(10) R. F. Witter and E. Stotz, *J. Biol. Chem.*, **176**, 485 (1948).

(11) W. Borsche and C. K. Bodenstein, *Ber.*, **62**, 2515 (1929).

use of acetic anhydride with IIa at ambient temperature was found to give cyclization directly to IIIa without appreciable O-acetylation and without attack on the methylenedioxy group. The method was employed similarly with IIb and IIc. Pyrones IIIa–c were obtained in yields of 63–79%. The piperonyl pyrones IIIa and IIIc are new compounds. The mechanism of these cyclizations probably involves the initial formation of a mixed carboxylic anhydride between the diketo acid and acetic acid. Cyclization occurs by acylation of the enol (or keto) group at the 5 position (see Scheme II).[12]

SCHEME II



4-Hydroxy-2-pyrones IIIa and IIIb were converted into 4-methoxyparacotoin (IVa) and yangonin (IVb), respectively, in yields of 69 and 89% by treatment with methyl sulfate and potassium carbonate. The product melting points were identical with ones of natural materials. This procedure for methylation of 4-hydroxy-2-pyrones III has been reported to form selectively the 4-methoxy derivatives.[13] Treatment of hydroxypyrones III with diazomethane has given mixtures of 4-methoxy-2-pyrones IV and the isomeric 2-methoxy-4-pyrones.[13a,14]

Previous syntheses of 4-methoxyparacotoin include (a) the condensation of diethyl phenylmercaptomalonate with 3,4-methylenedioxyacetophenone to give a pyrone from which thiophenol was cleaved with Raney nickel and (b) cyclization of 1-aryl-5,5-dichloropent-4-en-1-yn-3-one by means of hydrochloric acid.[15] Yangonin has been synthesized by two routes. One involves a condensation between *p*-methoxycinnamoyl chloride and diethyl 3-oxoglutarate[11] and the other a condensation of *p*-methoxybenzaldehyde with 4-methoxy-6-methyl-2-pyrone.[13a]

The conversion of IIIc into hispidin (IIIe) requires removal of the methylene bridge of the piperonyl system. In our hands a satisfactory procedure could not be found. The dioxole ring must be opened without disturbing the pyrone and the released formaldehyde must not recondense with the product. It is concluded that a more labile blocking group should be employed and preferably one that does not liberate formaldehyde. Edwards and Wilson have reported the successful use of methoxymethyl groups in a synthesis of hispidin.[16]

In summary, although the described method for synthesis of 4-hydroxy- and 4-methoxy-2-pyrones is not completely general, it nevertheless provides a direct method for the preparation of many of these compounds.

Experimental Section[17]

β-Diketones I. 1-(3,4-Methylenedioxyphenyl)-1,3-butanedione (Ia).—A mixture of 9.0 g (0.05 mol) of methyl piperonylate, 3.2 g (0.055 mol) of acetone, and 3.0 g (0.125 mol) of sodium hydride in 100 ml of tetrahydrofuran was refluxed for 2.5 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether and water. The aqueous layer was separated, acidified, and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, dried, and evaporated to afford 3.7 g (36% yield) of diketone Ia, mp 89.5–91° (lit.[3a] mp 91–92°).

6-(*p*-Methoxyphenyl)-5-hexene-2,4-dione (Ib).—A mixture of 2.54 g (0.010 mol) of phenyl *p*-methoxycinnamate,[18] 0.70 g (0.012 mol) of acetone, and 0.026 mol of sodium amide (prepared from 0.60 g of sodium in liquid ammonia) was refluxed in ether for 3 hr. The mixture was extracted with water and the aqueous solution was treated with carbon dioxide to precipitate the diketone. Recrystallization from methanol–water gave 0.44 g (20% yield) of diketone Ib, mp 88–89° (lit.[19] mp 93°).

6-(3,4-Methylenedioxyphenyl)-5-hexene-2,4-dione (Ic).—Condensation of phenyl 3,4-methylenedioxycinnamate[20] and acetone effected by sodium amide gave after recrystallization from methanol 24% of diketone Ic: mp 95.5–96.2° (lit.[9] mp 123–125°); ν_{max} 1640, 1610, 1450, and 1260 cm^{-1}; δ_{CDCl_3} 2.15 (CH_3), 5.62 (4-CH), 6.00 ($-OCH_2O-$), 6.15 and 6.41 (2-CH), and 7.40 and 7.67 ppm (1-CH).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.34; H, 5.40.

1-(3-Pyridyl)-1,3-butanedione (Id) was prepared by the method of Kuick and Adkins.[21]

3,5-Diketo Acids II.[6] 5-(3,4-Methylenedioxyphenyl)-3,5-dioxopentanoic Acid (IIa).—To a stirred suspension of 0.035 mol of sodium amide (prepared from 0.81 g of sodium) in 200 ml of liquid ammonia was added 2.06 g (0.010 mol) of diketone Ia. After 30 min, the ammonia was evaporated on the steam bath as an equal volume of ether was added. The ether was refluxed for several minutes to ensure complete removal of ammonia. Dry Ice was added to the suspension. The reaction mixture was poured into a mixture of ice and 30 ml of 12 *N* hydrochloric acid. The resulting ethereal solution was extracted with cold, 5% sodium bicarbonate solution. The aqueous extract was immediately acidified and extracted with ether. The ethereal solution was dried and evaporated under reduced pressure to give 0.75 g (30% yield) of diketo acid IIa, mp 128–129°. Recrystallization from chloroform gave mp 134–135° dec (lit.[3a] mp 125–130°); ν_{max} 1720, 1635, 1610, 1270, 1035, and 910 cm^{-1}; $\delta_{acetone\text{-}d_6}$ 3.52 (2-CH_2), 6.2 ($-OCH_2O-$), and 6.53 ppm (4-CH).

7-(*p*-Methoxyphenyl)-3,5-dioxo-6-heptenoic Acid (IIb).—The dianion of 0.436 g (0.0020 mol) of diketone Ib was carboxylated to give 0.321 g (61% yield) of diketo acid IIb, mp 125–126°. Recrystallization from chloroform–hexane gave mp 132–133° dec (lit.[11] mp 126–127°); ν_{max} 1710, 1640, 1575–1610, 1270, 1180, and 980 cm^{-1}; $\delta_{acetone}$ 3.50 (2-CH_2), 3.88 (*p*-CH_3O), 5.95 (4-CH), 6.50 and 6.77 (6-CH), and 7.52 and 7.78 ppm (7-CH).

(12) The use of this method for the selective lactonization of 3,5,7-triketo acids will be described in a subsequent paper. Under suitable conditions triketo acids can also be cyclized to form γ-pyrones, β-resorcylic acids, and acylphloroglucinols; see K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965), and T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **89**, 6734 (1967).

(13) (a) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); (b) H. Nakata, *Bull. Chem. Soc. Jap.*, **33**, 1693 (1960).

(14) D. Herbst, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959); H. Nakata, *Bull. Chem. Soc. Jap.*, **33**, 1688 (1960); I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik, and K. Pitakowska, *Tetrahedron*, **4**, 36 (1958).

(15) A. Lefeuvre and C. Mentzer, *Bull. Soc. Chim. Fr.*, 623 (1964); M. Julia and C. Binet du Jassonneix, *Compt. Rend.*, **253**, 872 (1961).

(16) R. L. Edwards and D. V. Wilson, *J. Chem. Soc.*, 5003 (1961).

(17) Melting points below 200° were determined in open capillaries using a silicone oil bath. Higher melting points were determined with a Kofler hot stage. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined by the potassium bromide pellet method using a Beckman IR-10 spectrometer. Nmr spectra were determined with a Varian A-60 spectrometer. Tetramethylsilane was employed as an internal standard.

(18) P. A. Foote, *J. Amer. Pharm. Soc.*, **17**, 958 (1928).

(19) W. Borsche and C. Walter, *Ber.*, **60**, 2112 (1927).

(20) D. H. R. Barton and D. W. Jones, *J. Chem. Soc.*, 3563 (1965). The nmr spectrum indicated that the ester had *trans* configuration: δ_{CDCl_3} 6.02 ($-OCH_2O-$), 6.32 and 6.58 (2-CH), and 7.67 and 7.93 ppm (3-CH, J_{CH-CH} = 16 cps).

(21) L. F. Kuick and H. Adkins, *J. Amer. Chem. Soc.*, **57**, 143 (1935).

7-(3,4-Methylenedioxyphenyl)-3,5-dioxo-6-heptenoic Acid (IIc).—The dianion of 0.348 g (0.0015 mol) of diketone Ic was carboxylated to give 0.208 g (50% yield) of diketo acid IIc, mp 118–120°. Recrystallization from chloroform gave mp 122–123° dec; ν_{max} 1730, 1630, 1610, 1540–1580, and 1130 cm^{-1}; $\delta_{acetone\text{-}d_6}$ 3.48 (2-CH_2), 5.93 (4-CH), 6.10 (-OCH_2O-), 6.48 and 6.75 (6-CH), and 7.45 and 7.72 ppm (7-CH).

Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.63; H, 4.19.

5-(3-Pyridyl)-3,5-dioxopentanoic Acid (IId).—Treatment of the disodium salt of diketone Id with Dry Ice gave an ether-insoluble, tan salt. Acidification afforded only unaltered diketone. Moreover, addition of the salt directly to anhydrous, liquid hydrogen fluoride gave no apparent formation of pyrone.

6-Substituted 4-Hydroxy-2-pyrones III. 4-Hydroxy-6-(3,4-methylenedioxyphenyl)-2-pyrone (IIIa).—Treatment of diketo acid IIa with anhydrous, liquid hydrogen fluoride apparently affected adversely the piperonyl ring system. As an alternative, the diketo acid (0.100 g, 0.00040 mol) was added to 10 ml of acetic anhydride. Initially the mixture was homogeneous; however, after 1 hr white crystals began to appear. After 16 hr the mixture was cooled and the crystals were separated by filtration, washed with water, and dried. Recrystallization from 95% ethanol gave 0.068 g (73% yield) of pyrone IIIa, mp 257–258° (lit.[22] mp 255–257°).

4-Hydroxy-6-(*p*-methoxystyryl)-2-pyrone (IIIb).—Treatment of 0.262 g (0.0010 mol) of diketo acid IIb with acetic anhydride afforded after recrystallization from methanol 0.155 g (63% yield) of pyrone IIIb, mp 235–237° (lit.[11] mp 238°).

4-Hydroxy-6-(3,4-methylenedioxystyryl)-2-pyrone (IIIc).—Diketo acid IIc (0.097 g, 0.00035 mol) and acetic anhydride gave 0.077 g (79% yield) of the monohydrate of pyrone IIIc: mp 230–234°, mp 233–236° after recrystallization from ethanol; ν_{max} 1620–1670 and 3300–3500 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}O_5 \cdot H_2O$: C, 60.87; H, 4.38. Found: C, 60.68; H, 4.50.

6-Substituted 4-Methoxy-2-pyrones IV. 4-Methoxyparacotoin (IVa).—A mixture of 0.0348 g (0.00015 mol) of pyrone IIIa, 2 g of potassium carbonate, and 1 ml of methyl sulfate in acetone was refluxed for 1.5 hr and allowed to stand at ambient temperature for 18 hr. Salts were removed by filtration and the solution was concentrated to give a partially crystalline mixture. The crystals were washed with ether, with 5% sodium hydroxide solution, and with water to give 0.0255 g (69% yield) of pyrone IVa, mp 221–222°. Recrystallization from methanol gave mp 223–224° (lit.[3c] mp 222–224°).

Yangonin (IVb).—Methylation of 0.122 g (0.00050 mol) of pyrone IIIb afforded 0.115 g (89% yield) of yangonin, mp 152.5–154°. Recrystallization from methanol gave mp 154–155° (lit.[11] mp 153–154°).

Registry No.—Ic, 16526-73-1; IIc, 16526-74-2; IIIc, 16526-75-3; IVa, 6969-80-8; IVb, 500-62-9.

(22) A. Resplandy, *Bull. Soc. Chim. Fr.*, 1332 (1962).

The Reaction of Some Keto Acids with Anthranilic Acid Anthranilamides, Orthanilamides, and Salicylamide[1]

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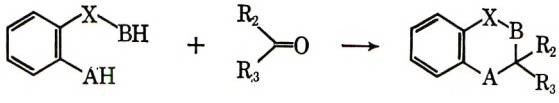
Sandoz Pharmaceuticals, Hanover, New Jersey 07936

Received November 20, 1967

The reaction of 2-acyl- and 2-aroylbenzoic acids and 3- and 4-oxoalkanoic acids with anthranilic acid, anthranilamides, salicylamide, and orthanilamides has been demonstrated to be a useful technique for preparing heterocyclic systems containing nitrogen, oxygen, and sulfur heteroatoms.

The reaction of an aldehyde or ketone (**2**) with an anthranilic acid (**1a**), anthranilamide (**1b**), salicylamide (**1c**), or orthanilamide (**1d**) has found general synthetic application in the synthesis of a variety of 1,2-dihydro-4H-3,1-benzoxazin-4-ones[2] (**3a**), 1,2,3,4-tetrahydroquinazolin-4-ones[3] (**3b**), 2,3-dihydro-4H-1,3-benzoxazin-4-ones[2,4] (**3c**), and 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides[5] (**3d**).



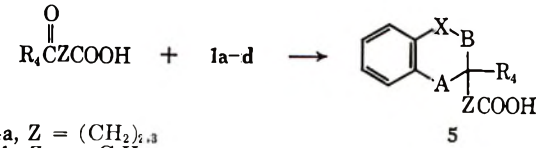
1a, X = CO; A = NH; B = O
b, X = CO; A = NR; B = NR_1
c, X = CO; A = O; B = NH
d, X = SO_2; A = NH; B = NR_1

R, R_1 = H, alkyl, etc.

2, R_2, R_3 = H, alkyl, etc.

3a, X = CO; A = NH; B = O
b, X = CO; A = NR; B = NR_1
c, X = CO; A = O; B = NH
d, X = SO_2; A = NH; B = NR_1

Extension of the carbonyl component (**2**) of this reaction to include ω-acylcarboxylic acids (**4a**) and *o*-acylbenzoic acids (**4b**) suggests that intermediates such as **5** could be formed. Further cyclization of the free carboxy group in **5** with an available nitrogen atom (A or B) could then lead to a variety of tricyclic or tetracyclic systems.



4a, Z = $(CH_2)_{2,3}$
b, Z = *o*-C_6H_4

5

R_4 = alkyl, aryl

Selleri and Caldini[6] and more recently Kratzl and Weinstock[7a] have reported that the reaction of phthaldehydic acids (**6**) with 2-aminobenzenesulfonamides (**7**) gave 6,6a-dihydro-11H-isoindolo[1,2-*c*][1,2,4]benzo-

(1) Portions of this paper were presented at the American Chemical Society Metropolitan Regional Meeting, Stevens Institute of Technology, Hoboken, N. J., Feb 1965.

(2) R. L. McKee in "The Chemistry of Heterocyclic Compounds, Five- and Six-Membered Compounds with Nitrogen and Oxygen," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1962, Chapter XIV, pp 341–375.

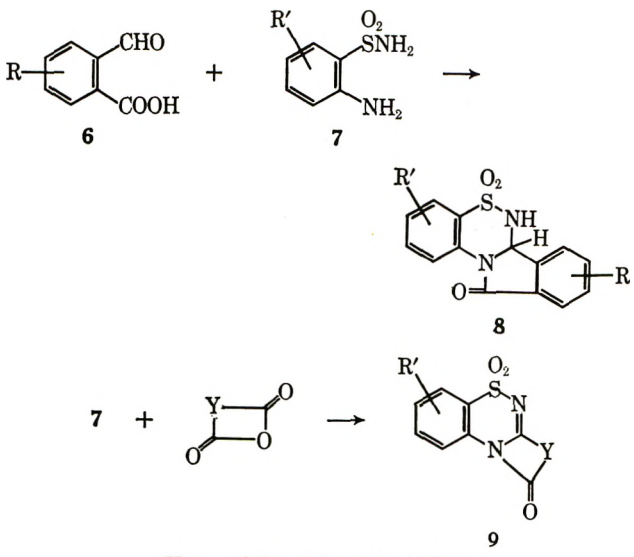
(3) F. Russo and M. Ghelardoni, *Ann. Chim.* (Rome), **56**, 839 (1966); K. H. Hauptmann, *Arzneim.-Forsch.*, **15**, 610 (1965); C. H. Boehringer Sohn, Netherlands Patent Appl. 302,479 (Oct 25, 1966) [*Chem. Abstr.*, **64**, 9743 (1966)]; J. W. Bolger, U. S. Patent 3,257,397 (June 21, 1966) [*Chem. Abstr.*, **65**, 8933 (1966)]; E. S. Schipper, U. S. Patent 3,265,697 (Aug 9, 1966) [*Chem. Abstr.*, **65**, 15399 (1966)].

(4) J. Maillard, M. Vincent, P. Delaunay, V.-V. Tri, and R. Jolly, *Bull. Soc. Chim. Fr.*, 2525 (1966); U. M. Teotino, L. P. Friz, A. Gandini, and D. Della Bella, *J. Med. Chem.*, **6**, 248 (1966).

(5) Numerous examples of this system are reported in "Diuretics," G. De-Stevens, Academic Press Inc., New York, N. Y., 1963.

(6) R. Selleri and O. Caldini, *Boll. Chim. Farm.*, **100**, 323 (1961).

(7) (a) K. Kratzl, R. Weinstock, and H. Ruis, *Oesterr. Chem.-Ztg.* **66**, 315 (1965); (b) R. Weinstock and K. Kratzl, *Monatsh. Chem.*, **96**, 1586 (1965); K. Kratzl, R. Weinstock, and H. Ruis, *ibid.*, **96**, 1592 (1965); (c) K. Kratzl and H. Ruis, *ibid.*, **96**, 1596, 1603 (1965).

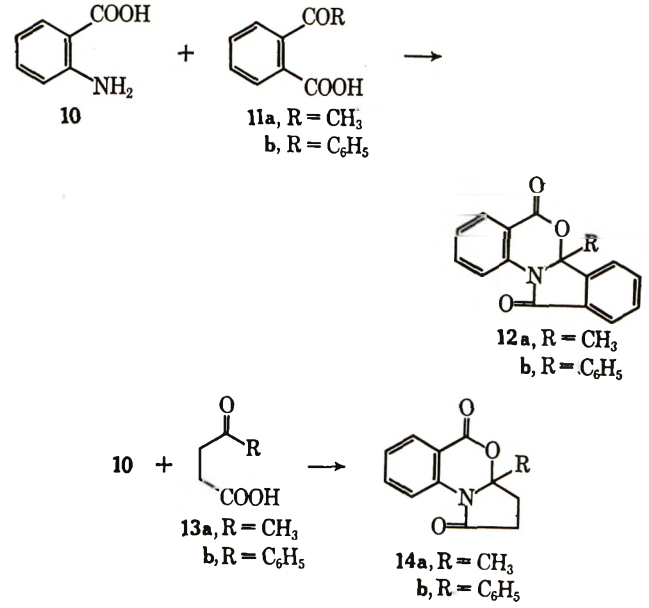


Y = o-C_6H_4, CH=CH, $(CH_2)_{2,3}$

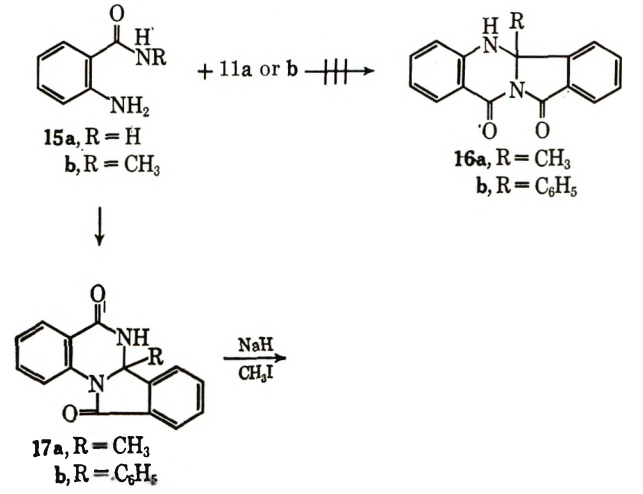
thiadiazin-11-one 5,5-dioxides (**8**). The same ring system has also been obtained by condensing **7** with phthalic acid[7a-c] or phthalic anhydride to form **9** (Y = o-C_6H_4). Borohydride reduction of **9** (Y = o-C_6H_4) gave **8**. From **7** and maleic,[7c,8] succinic,[8] and glutaric[7c,8] anhydride the closely related ring systems **9** [Y = CH=CH, $(CH_2)_{2,3}$] were also prepared.

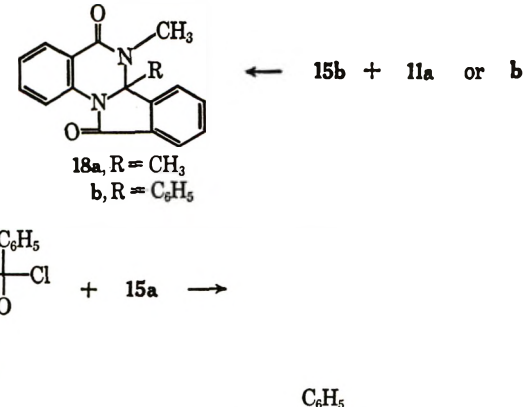
In the present work the authors wish to report that the reaction of an anthranilic acid, anthranilamide, salicylamide, or orthanilamide with an aromatic or aliphatic keto acid offers a convenient synthetic route for obtaining a variety of heterocyclic systems.

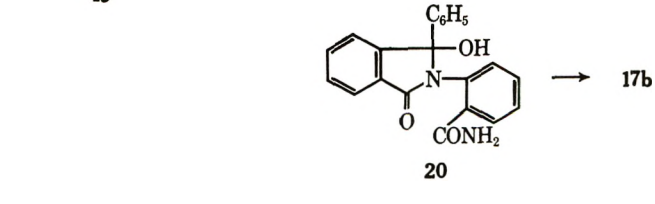
When anthranilic acid (**10**) was allowed to react with 2-acetylbenzoic acid[9] (**11a**) in refluxing dichlorobenzene, compound **12a** was obtained. This substance was shown to be 6a-methyl-6a,11-dihydro-5H-isoindolo-[2,1-a][3,1]benzoxazine-5,11-dione by comparing it with an authentic sample[10] obtained by treating anthranilic acid with 3-oxo-$\Delta^{1,2}$-phthalanacetic acid in refluxing acetic acid. The corresponding 6a-phenyl analog[11] (**12b**) was obtained by reaction of anthranilic acid and 2-benzoylbenzoic acid. Extension of this reaction to 4-oxopentanoic (**13a**) and 3-benzoylpropionic acid (**13b**) gave the related 3a-methyl- and 3a-phenyl-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a][3,1]-benzoxazine-1,5-dione (**14a** and **b**). The supporting infrared, ultraviolet, and nmr data are given in Table I.



The reaction of anthranilamide (**15a**) with 2-acetylbenzoic acid in refluxing dichlorobenzene resulted in the formation of a compound analyzing for the combination of **11a** and **15a** less 2 mol of water. From a consideration of the cyclization pathway this compound could have either of the tetracyclic structures **16a** or **17a**. To distinguish these structures a dimethylformamide solution of the sodium salt of **16a** or **17a** was

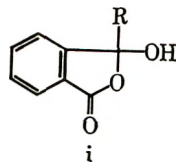






(8) S. C. Bell, P. H. L. Wei, and S. J. Childress, *J. Org. Chem.*, **29**, 3206 (1964).

(9) It is known that 2-acyl- or 2-aroylbenzoic acids can exist in a tautomeric mixture of the open form (**11a** or **b**) or a cyclic form i. The 4- and



5-oxoalkonaic acids (**13a**, **b**; **22a**, **b**) exist only in the open structure. (a) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959); (b) I. S. Trubnikov, R. B. Teplinskaya, Yu. A. Pentin, N. P. Shusherina, and R. Ya. Levina, *J. Gen. Chem. USSR* (Eng. Transl.), **33**, 1186 (1963); (c) M. V. Bhatt and K. M. Kamath, *Tetrahedron Lett.*, 3885 (1966).

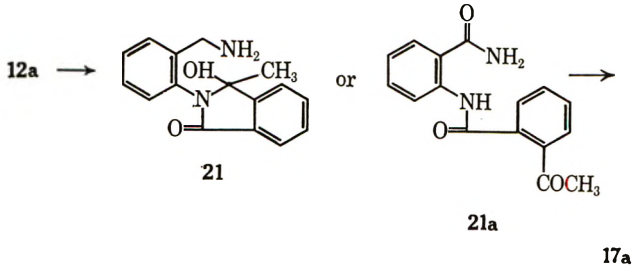
(10) J. Honzl, *Chem. Listy.*, **49**, 1671 (1955); J. Honzl, *Collect. Czech. Chem. Commun.*, **21**, 725 (1965).

(11) After our work had been completed, it was reported that a mixture of methyl anthranilate and 2-benzoylbenzoic acid when heated to 250° gave **12b**: E. Abramowitz and M. Lachen, *J. Chem. Soc.*, 2165 (1965).

treated with methyl iodide to give a monomethyl derivative. The same methyl compound was obtained when N-methylanthranilamide (**15b**) was treated with 2-acetylbenzoic acid. This then established the methyl group on the amide nitrogen, and therefore the monomethyl derivative is 6,6a-dimethyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (**18a**) and 6a-methyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (**17a**) rather than **16a** is the product from anthranilamide and 2-acetylbenzoic acid. When anthranilamide was treated with 2-benzoylbenzoic acid, the corresponding 6-phenyl analog **17b** was obtained. The ring system in **17b** was also established by forming the monomethyl derivative (**18b**) and then forming the same compound from N-methylanthranilamide and 2-benzoylbenzoic acid. Spectral and analytical data (Table I) were in agreement with the structural assignments.

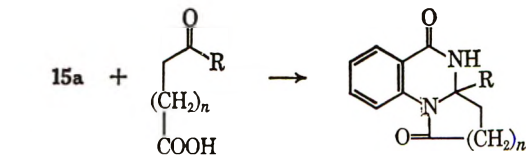
The structure of 9a-phenyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (**17b**) was additionally established by its synthesis from the acid chloride of 2-benzoylbenzoic acid (**19**)[12] and anthranilamide (**15a**) in dimethylformamide. Several unsuccessful attempts were made to isolate **20**, the probable intermediate in this reaction.

Honzl[10] had reported that 6a-methyl-6a,11-dihydro-5H-isoindolo[2.1-*a*][3,1]benzoxazine-5,11-dione (**12a**) on treatment with alcoholic ammonia at room temperature gave an amide which he postulated as being either 2-(*o*-carbamoylphenyl)-3-hydroxy-3-methylphthalimidine (**21**) or 2-(2-acetylbenzamido)benzamide (**21a**). Subsequent treatment of this amide in refluxing acetic acid gave a compound that Honzl postulated as being identical with **17a** prepared in the present work. This work has been repeated here and it was found that the structure (**17a**) postulated by Honzl is correct.



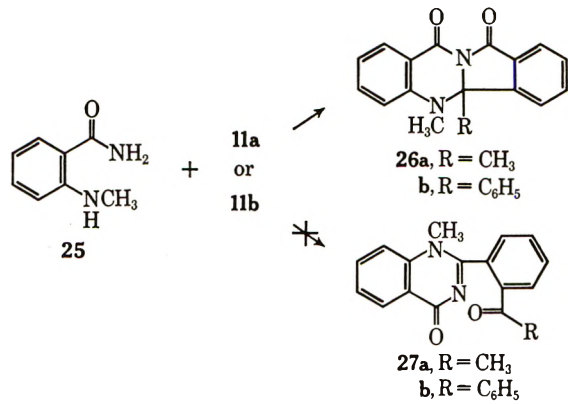
When anthranilamide (**15a**) was treated with the aliphatic acids, 4-oxopentanoic (**13a**), or 3-benzoylpropionic (**13b**), in refluxing dichlorobenzene, condensation occurred to give 3a-methyl- and 3a-phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (**22a** and **b**). The homologous 4a-methyl- and 4a-phenyl-1,2,-3,4,5,6-hexahydro-4aH-pyrido[1,2-*a*]quinazoline-1,6-diones (**24a** and **b**) were obtained from anthranilamide and 5-oxohexanoic (**23a**) or 4-benzoylbutyric acids (**23b**), respectively. The structural assignment of these compounds is based on spectral data (Table I) and the cyclization pathway established above for anthranilamide with 2-acylbenzoic acids.

(12) Physical measurements have shown that this compound exists mainly in the ring tautomer or pseudo-form **19** but can give rise to products which come from either **19** or the open-chain form 2-benzoylbenzoyl chloride. See ref 9a for some examples.



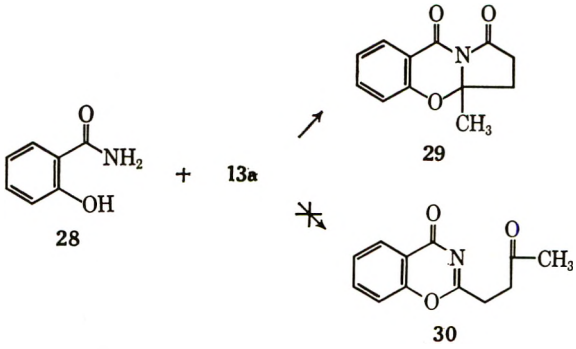
13a, R = CH_3; n = 1 — **22a**, R = CH_3; n = 1
b, R = C_6H_5; n = 1 — **b**, R = C_6H_5; n = 1
23a, R = CH_3; n = 2 — **24a**, R = CH_3; n = 2
b, R = C_6H_5; n = 2 — **b**, R = C_6H_5; n = 2

The reaction of 2-methylaminobenzamide (**25**) with 2-acetyl- or 2-benzoylbenzoic acid gave condensation products analyzing for the expected cyclization products **26a** and **b** or the quinazolones **27a** and **b**. The



latter ring system could form by the condensation of the methylamino and amide nitrogen of 2-methylaminobenzamide with the carboxy group of the starting acids. The spectral evidence is in agreement with assigning these compounds as 5,5a-dimethyl- and 5-methyl-5a-phenyl-5,5a,10-12-tetrahydroisoindolo[1,2-*b*]quinazoline-10,12-dione (**26a** and **b**). The ultraviolet spectrum (Table I) of both compounds are almost identical and quite dissimilar from that reported for a quinazolone system.[13] The similarity of the spectra is in accord with a common chromophoric system being present in both compounds. In the quinazolone structures **27a** and **b** this does not occur since **27a** contains a 2-acetylphenyl chromophore while **27b** contains a 2-benzoylphenyl system. In addition lack of a characteristic C=N infrared band[13,14] rules out the quinazolone system.

From the reaction of salicylamide (**28**) with 4-oxopentanoic acid (**13a**) there was obtained a compound that agreed with the expected product **29** or the benz-



(13) The ultraviolet spectrum of 2-hydroxymethyl- and 2-(1-hydroxethyl)-1-methyl-4(1H)quinazolinone are reported to have maxima at 230, 267–269, 276–277, 306–307, and 314–317 mμ. The carbonyl frequencies are 6.04–6.05 μ, and the C=N bands are 6.23–6.24 μ. M. Uskoković, J. Iacobelli, V. Toome, and W. Wenner, *J. Org. Chem.*, **29**, 582 (1964).

(14) H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 4834 (1952).

TABLE I

PHYSICAL PROPERTIES AND ANALYTICAL DATA[17]

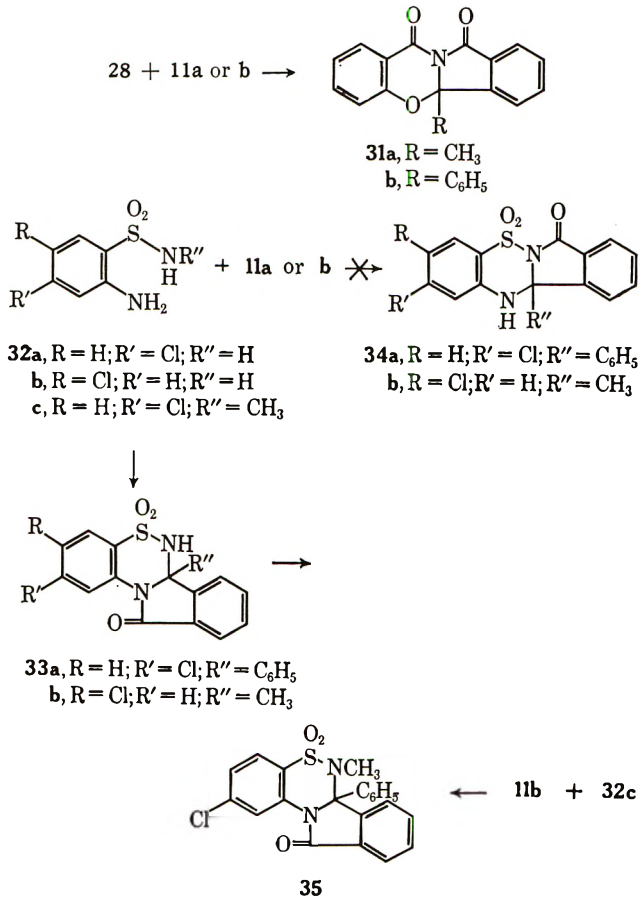
Compd no.	Yield, %	Mp, °C (crystn solvent)[a]	Infrared[b] μ	Infrared[b] Band	Ultraviolet[c] mμ	Ultraviolet[c] ε	Emperical formula	Elemental analysis Calcd., % C	H	N	O	Found, % C	H	N	O
12a	50	149–151[d] (A)	5.77	COO	222	28,270	$C_{16}H_{11}NO_3$[e]	...	...	...	...	...	...	...	...
				CON	243	16,600		...	...	...	...	...	...	...	...
					267	6,860		...	...	...	...	...	...	...	...
					314	5,415		...	...	...	...	...	...	...	...
12b	37	184–184.5[f] (B)	5.77	COO	225	35,330	$C_{21}H_{13}NO_3$	77.1	4.0	4.3	14.7	77.3	4.2	4.4	14.7
				CON	316	5,450									
14a	53	118–120 (B)	5.69	COO	221	24,550	$C_{12}H_{11}NO_3$[g]	66.4	5.1	6.4	22.2	66.8	5.3	6.4	22.1
			5.78	CON	250	8,915									
					306	3,165									
14b	16	136–138 (B)	5.73	COO	224	22,885	$C_{17}H_{13}NO_3$[h]	73.0	4.9	5.0	17.1	72.9	5.0		17.0
			5.83	CON	251	8,070									
					308	2,935									
17a	75	214–215[i] (A)	3.16	NH	221	26,840	$C_{16}H_{12}N_2O_2$[j]	72.7	4.6	10.6	12.1	72.5	4.5	10.7	
			5.82	CON	274	8,800									
			5.98	CONH	316	4,400									
17b	91	>300 (C)	3.17	NH	211	36,080	$C_{21}H_{14}N_2O_2$	77.6	4.0	8.6	9.8	77.3	4.2	8.4	10.0
			5.82	CON	276	7,105									
			5.98	CONH	311	4,950									
18a	54	185–186 (D)	5.84	CON	225	20,745	$C_{17}H_{14}N_2O_2$[k]	73.4	5.1	10.1	11.5	73.6	5.3	10.1	11.4
			6.05	$CONCH_3$	303	5,395									
18b	73	226–227 (E)	5.82	CON	221	34,000	$C_{22}H_{16}N_2O_2$[l]	77.6	4.7	8.2	9.4	77.8	5.1	8.3	9.3
			6.05	$CONCH_3$	306	4,705									
22a	47	179–180 (A)	3.14	NH	232	26,920	$C_{12}H_{12}N_2O_2$[m]	66.7	5.6	13.0	14.8	66.6	5.8	13.3	14.9
			5.79	CON	301	2,755									
			5.94	CONH											
22b	73	>290 (E)	3.14	NH	275	6,490	$C_{17}H_{14}N_2O_2$	73.4	5.1	10.0	11.5	74.0	4.9		11.3
			5.78	CON	310	4,635									
			5.96	CONH											
24a	27	205–206 (A)	3.12	NH	221	22,910	$C_{13}H_{14}N_2O_2$[n]	67.8	6.1	12.2	13.9	68.0	6.4	11.9	13.9
			5.91	CON	245	9,775									
			6.03	CONH	294	2,140									
24b	49	242–243 (A)	3.05	NH	215	24,975	$C_{18}H_{16}N_2O_2$[o]	74.0	5.5	9.6	10.9	73.8	5.8	9.5	11.0
			5.90	CON	245	10,370									
			6.02	CONH	295	2,190									
26a	59	194–195 (E)	5.70	CON (5)	236	32,900	$C_{17}H_{14}N_2O_2$[p]	73.4	5.1	10.1	11.5	73.2	5.4	9.8	11.8
			5.99	CON (6)	253	21,315									
					370	2,415									
26b	40	228–229 (E)	5.70	CON (5)	232	30,220	$C_{22}H_{16}N_2O_2$[q]	77.6	4.7	8.2	9.4	77.4	5.1	8.1	9.9
			6.01	CON (6)	254	20,020									
					369	1,310									
29	52	121 (A)	5.64	CON (5)	250	12,600	$C_{12}H_{11}NO_3$[r]	66.4	5.1	6.4	22.1	66.4	5.3	6.5	22.0
			5.94	CON (6)	310	3,005									
31a	49	169–170 (A)	5.63	CON (5)	255	20,140	$C_{16}H_{11}NO_3$	72.4	4.2	5.3	18.0	72.5	4.2	5.1	17.8
			5.83	CON (6)	311	2,650									
31b	45	214–215 (F)	5.65	CON (5)	254	18,700	$C_{21}H_{13}NO_3$	76.9	4.2	4.3	14.6	76.9	4.0	4.7	14.7
			5.95	CON (6)	308	2,430									
33a	68	>325 (E)	3.13	NH	225	28,450	$C_{20}H_{13}ClN_2O_3S$[s]	60.5	3.3	7.1	12.0	60.1	3.0		
			5.88	CON	277	10,500									
			7.45, 8.48	SO_2											
33b	23	280–283 (E)	3.13	NH	228	26,015	$C_{16}H_{11}ClN_2O_3S$	53.8	3.3	8.4	14.3	54.1	3.6	8.2	14.5
			5.88	CON	274	11,880									
			7.45, 8.48	SO_2											
35	30	247–248 (E)	5.80	CON	226	29,770	$C_{21}H_{15}ClN_2O_3S$	60.5	3.3	7.1	12.1	60.8	3.5	6.8	
			7.47, 8.52	SO_2	280	9,550									

[a] Recrystallization from the following solvents: A, isopropyl alcohol; B, ethanol; C, methanol–water; D, methanol; E, isopropyl alcohol–dimethylformamide; F, ethanol–dimethylformamide. [b] The numbers 5 and 6 found next to the assignment refer to the ring size containing the C=O group. The assignments were based on values reported in ref 9a–c and L. J. Bellamy, "The infrared Spectra of Complex Organic Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958. [c] All spectra were determined in 95% ethanol. [d] Lit.[10] mp 150°. [e] Nmr analysis showed δ 1.91 (s, C–CH_3). [f] Lit.[11] mp 181–182°. [g] Nmr analysis showed 0.77 (s, C–CH_3), 1.81 (A_2B_2, 4 H, CH_2CH_2). [h] Nmr analysis showed a complex multiplet at 2.20–3.00. [i] Lit.[10] mp 215°. [j] Nmr analysis showed 1.81 (s, CH_3). [k] Nmr analysis showed 0.67 (s, C–CH_3), 2.22 (s, N–CH_3). [l] Nmr analysis showed 3.12 (s, N–CH_3). [m] Nmr analysis showed 0.73 (s, C–CH_3), 1.69 (A_2B_2, 4 H, CH_2CH_2). [n] Nmr analysis showed 0.71 (s, C–CH_3), 0.83–1.53 (m, 4 H, 1.81 [t, J = 12.0 cps, 2 H]. [o] Nmr analysis showed 1.88 (m, 2 H), 2.38 (m, 2 H), 2.78 (m, 2 H). [p] Nmr analysis showed 0.85 (s, C–CH_3), 2.12 (s, N–CH_3). [q] Nmr analysis showed 2.17 (s, N–CH_3). [r] Nmr analysis showed 0.75 (s, C–CH_3), 1.68 (m, 4 H, CH_2CH_2). [s] Calcd: Cl, 8.9; S, 8.1. Found: Cl, 8.6; S, 8.0.

oxazinone **30**. The benzoxazine system could form by the condensation of the amino and hydroxyl groups in salicylamide with the carboxyl group of 4-oxopentanoic acid. The nmr of the product gave a methyl singlet at 0.75 ppm and a four-proton complex centered at 1.68 ppm. The high-field position of the methyl signal[15] and the complex signals for the CH_2CH_2 grouping agree with structure **29**. The methyl[16] signal in **30** would be expected in the 2.1–2.4-ppm region. The absence of a C=N[14] band in the infrared spectrum is also in agreement with **29**.

The condensation of salicylamide (**28**) with 2-acetyl- or 2-benzoylbenzoic acid proceeded by the same pathway as 4-oxopentanoic acid to give the related ring derivatives 5a-methyl- and 5a-phenyl-11,12-dihydro-5H-isoindolo[1,2-*b*][1,3]benzoxazine-10,12-dione (**31a** and **b**). Supporting spectral data are listed in Table I.

The reaction of 2-amino-4-chlorobenzenesulfonamide (**32a**) with 2-benzoylbenzoic acid gave 2-chloro-6a-phenyl-6,6a-dihydro-11H-isoindolo[1,2-*c*][1,2,4]benzothiadiazin-11-one 5,5-dioxide (**33a**). By analogy with the cyclization of anthranilamide and 2-benzoylbenzoic



acid the tetracyclic system **34a** has to be considered as an alternate structure for this compound. To distinguish these structures the sodium salt of the condensation product was treated with methyl iodide to give a monomethyl derivative. The same monomethyl derivative was obtained from the condensation of 2-amino-4-chloro-N-methylbenzenesulfonamide (**32c**) with 2-benzoylbenzoic acid. This interconversion establishes the methyl derivative as 2-chloro-6-methyl-6a-phenyl-6,6a-dihydro-11H-isoindolo[1,2-*c*][1,2,4]benzothiadiazin-11-one 5,5-dioxide (**35**) and rules out structure **34a**. Reaction of 2-acetylbenzoic acid with 2-amino-5-chlorobenzenesulfonamide (**32b**) gave 3-chloro-6a-methyl-6,6a-dihydro-11H-isoindolo[1,2-*c*][1,2,4]benzothiadiazin-11-one 5,5-dioxide (**33b**) rather than the tetracyclic system **34b**. Supporting spectral data are given in Table I.

(15) The C–CH_3 group in the closely related compounds **14a**, **22a**, and **24a** also exhibit high-field signals at 0.77, 0.71, and 0.73 ppm, respectively (Table I).

(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 33.

Experimental Section[17]

General Conditions for Cyclization.—To a flask equipped with a magnetic stirring and heating mantle there was added 0.05–0.10 mol of the anthranilic acid, anthranilamide, salicylamide, or orthanilamide, 0.10–0.05 mol of the oxo acid, 100–250 ml of technical (85%) *o*-dichlorobenzene, and 0.5 mol of *p*-toluenesulfonic acid monohydrate. The flask was fitted with an extractor packed with beryl saddles or glass chips and a reflux condenser. The mixture was then stirred and refluxed until water ceased (6–24 hr) to separate in the condensate. The solvent was removed *in vacuo* on a rotary evaporator, and the residue was crystallized from an appropriate solvent system. If necessary the compound was treated with charcoal during the crystallization procedure.

The compounds prepared by the above procedure together with infrared, ultraviolet, and nuclear magnetic resonance data are given in Table I.

6a-Methyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,-11-dione (17a).—A mixture of **12a** (1.0 g) and 25 ml of isopropyl alcohol saturated with anhydrous ammonia was stirred at room temperature for 72 hr. The resultant solid was filtered off and recrystallized from isopropyl alcohol to give 0.92 g of **20** as a solid: mp 209–210° (lit.[10] mp 205°); infrared (KBr, μ) 2.98 and 3.13 (NH_2; OH), 5.91 and 6.03 (C=O for CONH, $CONH_2$, and $COCH_3$); ultraviolet, λ_{EtOH}^{infl} 257 mμ (ϵ 5950) and 286 (2820).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.1; H, 5.0; N, 9.9; O, 17.0. Found: N, 9.8; O, 17.1.

A solution of **20** (0.60 g) and 10 ml of acetic acid was stirred and refluxed for 6 hr. The solvent was removed *in vacuo* and the residue crystallized from isopropyl alcohol–dimethylformamide gave 0.42 g of solid, mp 213–214°. Comparison of the R_f value and infrared and ultraviolet spectra of this compound with those of **17a** showed them to be identical.

6a-Phenyl-5,6,6a-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (17b).—A solution of 2-benzoylbenzoic acid chloride[12] (15.0 g, 0.06 mol), anthranilamide (10 g, 0.07 mol), pyridine (5.0 ml), and anhydrous dimethylformamide (100 ml) was maintained at 60° for 48 hr. The solvent was removed *in vacuo* on a rotary evaporator and the residue crystallized from methanol–water. There was obtained 16.3 g (84%) of **17b**, mp >300°. Comparison of the R_f value and the infrared and ultraviolet spectrum of this substance with **17b** prepared from anthranilamide and 2-benzoylbenzoic acid showed them to be identical.

6,6a-Dimethyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (18a).—To a stirred solution of **17a** (5.4 g, 0.02 mol) in anhydrous dimethylformamide (200 ml) there was added 50% sodium hydride–mineral oil dispersion (1.06 g, 0.02 mol as NaH). The solution was maintained at 40° until hydrogen evolution had ceased. After cooling to room temperature the solution was treated with methyl iodide (2.15 g, 0.035 mol) and allowed to stir for about 20 hr at room temperature. The solvent was removed *in vacuo*, and the residue was crystallized from methanol–methylene chloride to give 4.5 g (81%) of solid material, mp 184–186°. Comparison of the mixture melting point, R_f value, and infrared and ultraviolet spectrum with those of **18a** showed them to be identical.

(17) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were determined as pyridine solutions on a Varian Associates A-60 spectrometer and are recorded in parts per million (δ) downfield from an internal tetramethylsilane standard. Infrared spectra were determined as potassium bromide pellets using a Perkin-Elmer Model 421 spectrometer or an Infracord. The ultraviolet spectra were obtained on a Beckman Model DB spectrophotometer attached to a Sargent SRL recorder or on a Cary Model 15 spectrophotometer.

2-Chloro-6-methyl-6,6a-dihydro-11H-isoindolo[1,2-c][1,2,4]-benzothiadiazin-11-one 5,5-Dioxide (35).—A mixture of **33a** (3.97 g, 0.01 mol), 50% sodium hydride–mineral oil dispersion (0.72 g, 0.015 mol as NaH), anhydrous dimethylformamide (100 ml), and methyl iodide (2.85 g, 0.02 mol) was allowed to react as in the preparation of **18a**. There was obtained 3.8 g of solid, mp 246–247°. Comparison of the infrared and ultraviolet spectra of this compound with those of **35** showed them to be identical.

Registry No.—**1c**, 65-45-2; **10**, 118-92-3; **12a**, 16240-89-4; **12b**, 801-48-9; **14a**, 16240-91-8; **14b**, 16240-92-9; **17a**, 16240-93-0; **17b**, 16214-87-2; **18a**, 16240-77-0; **18b**, 16214-88-3; **22a**, 16240-78-1; **22b**, 16240-79-2; **24a**, 16240-80-5; **24b**, 16240-94-1; **26a**, 16240-95-2; **26b**, 16240-96-3; **29**, 16240-97-4; **31a**, 16240-98-5; **31b**, 16240-99-6; **33a**, 16214-90-7; **33b**, 16241-00-2; **35**, 16241-01-3.

Acknowledgments.—The authors wish to thank Mr. Urs Stoeckli and his associates for obtaining the analytical and instrumental data reported in this paper.

Oxidation with Metal Oxides. III. Oxidation of Diamines and Hydrazines with Manganese Dioxide

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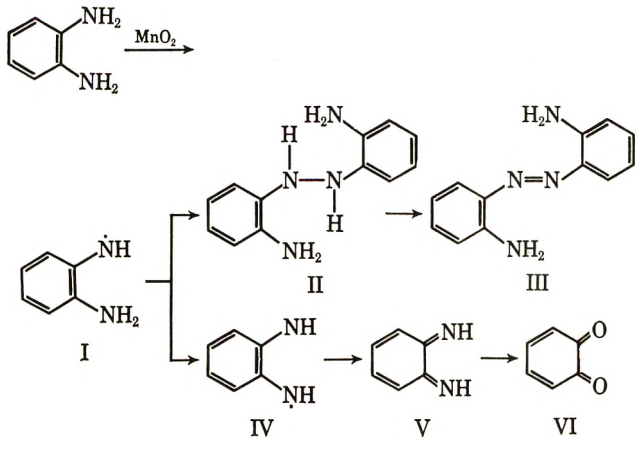
o-Phenylenediamine and *p*-phenylenediamine, on oxidation with manganese dioxide, gave the corresponding diaminoazo compounds. Under similar conditions, 2,2′-diaminobiphenyl gave dibenzopyridazine, whereas *o,o*′-diaminobiphenyl sulfide gave a linear azo compound. The oxidation of N-phenyl-*p*-phenylenediamine and N,N′-diphenyl-*p*-phenylenediamine gave N-phenyl-*p*-benzoquinone monoimine and N,N′-diphenyl-*p*-phenylenediimine, respectively. N,N′-Dibenzenesulfonyl-*p*-benzoquinone imine, benzenesulfonamide, and *p*-benzoquinone were formed from N,N′-dibenzenesulfonyl-*p*-phenylenediamine, whereas, both benzophenone and azobenzene were formed from the oxidation of benzophenone anil. Manganese dioxide oxidation of phenylhydrazine gave biphenyl and azobenzene. *p*-Nitrophenylhydrazine and 2,4,6-trichlorophenylhydrazine gave the corresponding substituted biphenyls, under similar conditions. Oxidation of N-aminopiperidine, N-aminohomopiperidine, N-aminomorpholine, and N,N-diphenylhydrazine gave the corresponding tetrazenes, whereas N,N-dibenzylhydrazine gave mainly bibenzyl.

In previous communications[2,3] we have reported the oxidation of several aldehyde and ketone phenylhydrazones, chalcone phenylhydrazones, pyrazolines, *o*-aminobenzylidine anils, and *o*-hydroxybenzylidine anils, with manganese dioxide. Chalcone phenylhydrazones, for example, give rise to pyrazoles, when oxidized with manganese dioxide in a neutral solvent like benzene. Under similar conditions, *o*-aminobenzylidine anils and *o*-hydroxybenzylidene anils give the corresponding benzimidazoles and benzoxazoles, respectively. The oxidation of aldehyde phenylhydrazones, on the other hand, give a mixture of several oxidative dimers, triazoles and biphenyl, depending on the reaction conditions. During the course of the present investigation, we have examined the oxidation of several aromatic diamines and hydrazines, employing active manganese dioxide.

The oxidation of *o*-phenylenediamine has been reported to give rise to different products, depending on the nature of the oxidizing agent and the reaction conditions. Thus, the oxidation of *o*-phenylenediamine with nickel peroxide[4] or lead tetraacetate[5] gives *cis,cis*-1,4-dicyano-1,3-butadiene, whereas the oxidation with lead peroxide[6] or silver oxide[6] gives a mixture of *o,o*′-diaminoazobenzene and 3,4-diaminophenazine. The formation of these products has been explained in terms of an *o*-quinone imine intermediate. We have examined the oxidation of *o*-phenylenediamine, employing manganese dioxide. When the reaction was carried out in benzene at room temperature, we were able to isolate a 13% yield of *o,o*′-diaminoazobenzene. No other product, including 1,4-dicyano-1,3-butadiene could be obtained from this run. The same reaction has been tried both in refluxing benzene, and also in the absence of any solvent by heating the mixture to around 110°, with a view to detecting the presence of other products which might be formed under these conditions. Considerable amount of ammonia was evolved during these reactions and, from both cases, only *o,o*′-diaminoazobenzene was isolated, but the yields were somewhat higher, compared with that of the room temperature reaction. In a typical run, involving the reaction of *o*-phenylenediamine with manganese dioxide in refluxing benzene, the amount of ammonia liberated was found to be around 21%. A probable mechanism for the formation of *o,o*′-diminoazobenzene is indicated in Scheme I. In this scheme, we assume that manganese dioxide effects the cleavage of one of the N–H bond of the amine

SCHEME I



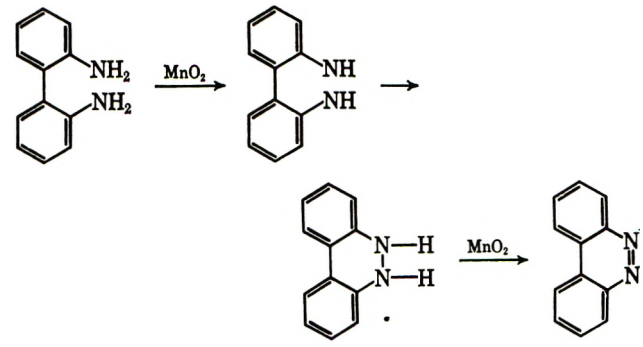
(1) To whom enquiries should be addressed.
(2) I. Bhatnagar and M. V. George, *J. Org. Chem.*, **32**, 2252 (1967).
(3) I. Bhatnagar and M. V. George, *Tetrahedron*, **24**, 1293 (1968).
(4) K. Nakagawa, H. Onoue, *Tetrahedron Lett.*, **20**, 1433 (1965).
(5) K. Nakagawa and H. Onoue, *Chem. Commun.*, **16**, 396 (1965).
(6) R. Wilstätter and A. Pfannenstiel, *Ber.*, **38**, 2348 (1905).

to generate the radical I which dimerizes to the hydrazine II. Oxidation of II to *o,o'*-diaminoazobenzene (III) will be quite facile in presence of manganese dioxide. The formation of III from *o*-phenylenediamine is analogous to the formation of azobenzene from aniline.[7] However, the evolution of ammonia and the poor yield of III strongly suggests that other pathways are also important for this oxidation. One such possibility is the conversion of the intermediate radical I into the diradical IV which can isomerize to *o*-quinone diimine (V). The quinone diimine V will suffer ready hydrolysis under the experimental conditions, giving rise to *o*-quinone (VI) which is easily polymerized. The actual isolation of a small amount of *p*-benzoquinone in the oxidation of *p*-phenylenediamine supports the postulated mechanism. When *p*-phenylenediamine was oxidized with active manganese dioxide in benzene at room temperature, a 30% yield of *p,p'*-diaminoazobenzene was formed. In addition, a small quantity of benzoquinone (2%) and polymeric material could be isolated. It was not possible to detect the presence of any *p*-benzoquinone diimine; one would expect this compound to be easily hydrolyzed [8,9] during the reaction. With a view to isolating stable quinone imine intermediates from these reactions, we have examined the oxidation of both N-phenyl-*p*-phenylenediamine (VII) and N,N'-diphenyl-*p*-phenylenediamine (VIII). Treatment of VII with manganese dioxide gave a 70% yield of N-phenyl-*p*-benzoquinone monoimine (IX), whereas VIII under the same conditions gave a 91% yield of N,N'-diphenyl-*p*-benzoquinone imine (X). Ammonia gas was evolved during the oxidation of VII, but not in the reaction of VIII. The isolation of such quinone imines as IX and X strongly supports the mechanism (Scheme I) that has been suggested for amine oxidation.

Lithium aluminium hydride reduction of 2,2'-dinitrobiphenyl is reported to give rise to dibenzopyridazine.[10] Under similar conditions, 2,2'-dinitrobiphenyl ether and 2,2'-dinitrobiphenyl sulfide give the corresponding cyclic, seven-membered azo compounds.[11] We have examined the reactions of 2,2'-diaminobiphenyl and 2,2'-diaminobiphenyl sulfide with manganese dioxide, with a view to finding out whether these reactions would lead to the formation of the corresponding cyclic azo compounds. The oxidation of 2,2'-diaminobiphenyl with manganese dioxide gave a 55% yield of dibenzopyridazine and a probable pathway is indicated in Scheme II. 2,2'-Diaminobiphenyl sulfide, on the other hand, gave a 20% yield of 2,2'-bis(*o*-aminothiophenoxy)azobenzene (XI) and none of the cyclic azo compound.

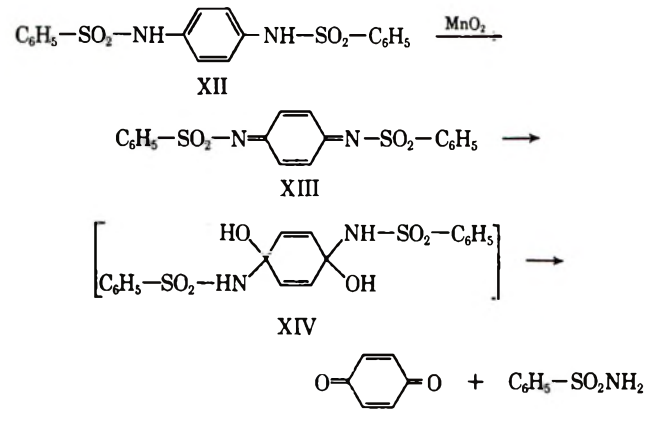
N,N'-Dibenzenesulfonyl-*p*-phenylenediamine (XII) is oxidized to *p*-benzoquinonebenzenesulfonimide by reagents like silver oxide, sodium chromate, and lead tetraacetate.[9] In the present investigation, we have studied the oxidation of XII using active manganese dioxide. When this oxidation was carried out at room temperature in acetone medium, a 32% yield of N,N'-

Scheme II



dibenzenesulfonyl-*p*-benzoquinone imine (XIII) was isolated. The same reaction, in refluxing benzene gave a 37% yield of benzenesulfonamide and a small quantity of benzoquinone. It is apparent that both benzenesulfonamide and benzoquinone are formed from XIII, the initial oxidation product of XII. However, a simple mode of hydrolysis for the conversion of XIII into benzenesulfonamide and benzoquinone is ruled out since XIII is reported to be quite resistant to hydrolysis, both under acid and basic conditions.[9] A more probable pathway would be the hydroxylation of XIII by manganese dioxide (which invariably contains some water) to give the intermediate XIV which is then cleaved to the products as shown in Scheme III. The

Scheme III



formation of similar hydroxylated intermediates have been postulated in the oxidation of substituted amines using manganese dioxide.[12]

If we assume that the oxidation of XII is proceeding through the hydroxylated intermediate XIV, then one would expect that anils will also be oxidized by manganese dioxide by a similar route. In this connection, we have examined the oxidation of benzophenone anil with manganese dioxide which led to benzophenone (50%) and azobenzene (55%). It is pertinent to observe that benzophenone anil is not hydrolyzed by refluxing with water for few hours. Also, the oxidation of benzophenone anil could not be achieved by treatment with dry manganese dioxide from which all water has been removed. We therefore assume that the active manganese dioxide containing small amounts of moisture is actually responsible for this type of oxidation. The reported oxidation of azines to give alde-

(7) (a) O. Wheeler and D. Gonzalez, *Tetrahedron*, **20**, 189 (1964); (b) O. Wheeler, *Chem. Ind.* (London), 1769 (1965).

(8) R. Willstätter, *Ber.*, **37**, 1499 (1904).

(9) R. Adams and A. S. Nagarkatti, *J. Amer. Chem. Soc.*, **72**, 4601 (1950).

(10) G. M. Badger and J. H. Seidler, *J. Chem. Soc.*, 3207 (1951).

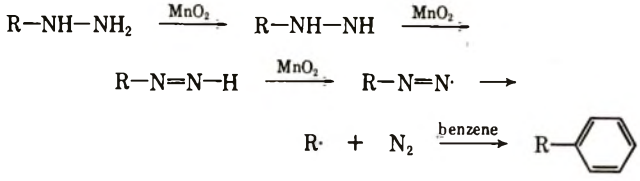
(11) N. L. Allinger and G. A. Youngdales, *J. Amer. Chem. Soc.*, **84**, 1020 (1962).

(12) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).

hydes and ketones[13] may also be proceeding through a similar mechanism.

In continuation of our studies, we have examined the reaction of different substituted hydrazines with manganese dioxide. The oxidation of phenylhydrazine, for example, gave a 26% yield of biphenyl, when the reaction was carried out in benzene. Similarly, the oxidation of *p*-nitrophenylhydrazine and 2,4,6-trichlorophenylhydrazine gave *p*-nitrobiphenyl (50%) and 2,4,6-trichlorobiphenyl (39%), respectively. A probable route for this oxidation involves the stepwise removal of hydrogen atoms from the hydrazines by manganese dioxide giving rise to radical intermediates which finally yield aryl radicals by the loss of nitrogen. These aryl radicals can combine with the solvent to give biphenyls (Scheme IV). The formation of bi-

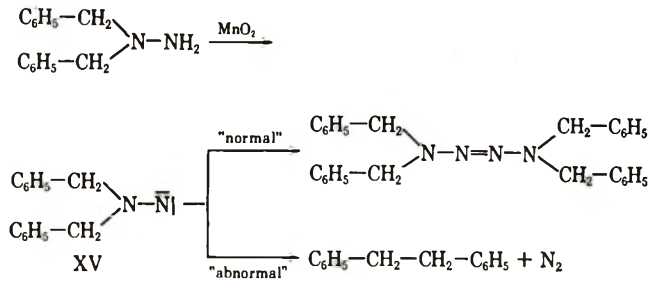
SCHEME IV



phenyls in the oxidation of phenylhydrazines have also been observed earlier, when either silver oxide or mercuric oxide have been employed.[14]

Several 1,1-disubstituted hydrazines have been oxidized with different oxidizing agents such as potassium permanganate, bromine, ferric chloride, quinone, and mercuric oxide[15] to give tetrazenes as major products. Report has also been made of the anomalous type of oxidation of 1,1-disubstituted hydrazines giving rise to symmetrical, substituted bibenzyls and nitrogen.[16] A detailed study of the oxidation of 1,1-disubstituted hydrazine derivatives has been done by several workers.[17] They have observed that if the oxidation is carried out under conditions in which the hydrazine is present in relatively high concentration, *e.g.*, by rapid addition of hydrazine to the oxidizing agent or by the rapid addition of the solid oxidizing agent to the solution of hydrazine, the aminoimido intermediate formed initially dimerizes to the tetrazene in the so-called "normal" manner. If the nitrogen atom in the aminoimido intermediate is lost to yield a stabilized radical, then an alternative "abnormal" pathway is possible, giving rise to fragmentation and recombination of products. For example, the oxidation of 1,1-dibenzylhydrazine gives rise to mainly bibenzyl and nitrogen and an intramolecular process has been suggested as shown in Scheme V. The formation of the tetrazene is explained in terms of the dimerization of the aminoimido inter-

SCHEME V



mediate XV or by its reaction with another molecule of unchanged hydrazine to give a tetrazane which is subsequently oxidized to tetrazene.[18] In the present study, the oxidation of several disubstituted hydrazines have been tried using manganese dioxide. Thus, the oxidation of N-aminopiperidine in benzene at room temperature gave a 76% yield of 1,4-bispentamethylenetetrazene (XVI). Similarly, N-aminohomopiperidine and N-aminomorpholine gave the corresponding tetrazenes XVII and XVIII in 86 and 80% yields, respectively. It is assumed on the basis of analogy, that the oxidation of these hydrazines is proceeding through the aminoimido intermediates which dimerize to the tetrazenes. The loss of nitrogen is not facile in view of the unstable nature of the resultant radicals.

The oxidation of N,N-diphenylhydrazine with manganese dioxide gave a 76% yield of 1,1,4,4-tetraphenyltetrazene and a small quantity of biphenyl. N,N-Dibenzylhydrazine on the other hand, when oxidized at room temperature in chloroform solution gave a 10% yield of 1,1,4,4-tetrabenzyltetrazene and a 20% yield of bibenzyl. When the same reaction was carried out in refluxing ethanol and with the gradual addition of manganese dioxide to the hydrazine, a 40% yield of bibenzyl was isolated. The formation of bibenzyl could arise from an intramolecular loss of nitrogen from the aminoimido intermediate XV as postulated earlier.

Experimental Section

All melting points are uncorrected and were determined in a Thomas–Hoover melting point apparatus. Infrared spectra were determined on a Perkin-Elmer Infracord spectrometer and uv spectra were obtained on a Cary 14-R spectrophotometer.

Starting Materials.—Active manganese dioxide was prepared by using manganese sulfate dihydrate (280 g) and potassium permanganate (320 g) according to reported procedure.[19] N,N-Diphenyl hydrazine[20] and N-aminomorpholine[21] were prepared by the reduction of N-nitrosodiphenylamine and N-nitrosomorpholine, respectively, using zinc and acetic acid. Dibenzylhydrazine[22] was prepared by the lithium aluminum hydride reduction of N-nitrosodibenzylhydrazine, whereas N-aminopiperidine[23] was prepared by reducing N-nitrosopiperidine employing aluminum amalgam in absolute ethanol. 2,2′-Diaminobiphenyl[24] was prepared by the reduction of the corre-

(13) G. Mair and U. Heep, *Angew. Chem. Intern. Ed. Engl.*, **4**, 956 (1965).
(14) L. Hardie and R. H. Thomas, *J. Chem. Soc.*, 2512 (1957).
(15) For some of these oxidations, see, (a) E. Fischer, *Ann.*, **190**, 67 (1877); (b) E. Fischer, *ibid.*, **199**, 281 (1879); (c) E. Renouf, *Ber.*, **13**, 2169 (1880); (d) T. Curtius and H. Franzer, *ibid.*, **34**, 552 (1901); H. Wieland and H. Fressel, *Ann.*, **392**, 133 (1912).
(16) See (a) M. Busch and B. Weiss, *Ber.*, **33**, 2701 (1900); (b) H. Duval, *Bull. Soc. Chim. Fr.*, **7**, 728 (1910); (c) J. Kenner and J. Wilson, *J. Chem. Soc.*, 1108 (1927).
(17) For some of these studies, see (a) D. M. Lemal, T. W. Rave, and S. D. McGregor, *J. Amer. Chem. Soc.*, **85**, 194 (1963); (b) C. G. Overberger, *Rec. Chem. Progr.*, **21**, 21 (1960); (c) C. G. Overberger and L. P. Herin, *J. Org. Chem.*, **27**, 417 (1962); (d) C. G. Overberger and B. S. Marks, *J. Amer. Chem. Soc.*, **77**, 4097, 4104 (1955); (e) C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *ibid.*, **77**, 4100 (1955).
(18) See, for example (a) R. L. Hinnman and K. L. Hamm, *ibid.*, **81**, 3294 (1959); (b) C. G. Overberger and L. P. Herin, *J. Org. Chem.*, **21**, 2423 (1962); (c) C. G. Overberger, J. Kesselin, and P. T. Huang, *J. Amer. Chem. Soc.*, **81**, 3779 (1959); (d) C. G. Overberger, J. G. Lombardino and R. G. Hiske, *J. Amer. Chem. Soc.*, **80**, 6430 (1958); (e) ref 16b–d.
(19) E. F. Pratt and T. McGovern, *J. Org. Chem.*, **29**, 1540 (1964).
(20) E. Fischer, *Ann.*, **190**, 175 (1877).
(21) I. V. Podgornaya and I. Ya. Postovskii, *Zh. Obshch. Khim.*, **34** (1), 33 (1964); *Chem. Abstr.*, **60**, 10676 (1964).
(22) C. G. Overgerger, *J. Amer. Chem. Soc.*, **77**, 4100 (1955).
(23) H. G. Kazmirowski and H. Goldhahn, East German Patent, 23,001 (1962); *Chem. Abstr.*, **58**, 6746 (1963).
(24) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **75**, 6335 (1953).

sponding dinitro compound using Raney nickel as catalyst. 2,2′-Diaminobiphenylsulfide,[11] on the other hand, was prepared by the reduction of 2,2′-dinitrobiphenylsulfide using zinc and calcium chloride in ethanol. *p*-Benzoquinonesulfonimide[9] was prepared by lead tetraacetate oxidation of *p*-phenylenedibenzenesulfonamide. All other starting materials were obtained commercially.

Oxidation of *o*-Phenylenediamine.—A mixture of *o*-phenylenediamine (2 g, 0.009 mol) and manganese dioxide (10 g) was refluxed in dry benzene (150 ml) for 4 hr. Ammonia gas was evolved during the course of the reaction which was identified by the usual qualitative tests. Removal of the unchanged manganese dioxide and the solvent gave a residue which was chromatographed on alumina. Elution with benzene gave 0.7 g (35%) of 2,2′-diaminoazobenzene (III) which melted at 134°, after recrystallization from a mixture (1:1) of benzene and petroleum ether (bp 60–80°). The identity of this compound was confirmed by a mixture melting point with an authentic sample,[6] and also by comparison of the ir spectra. The ultraviolet spectrum of this compound in methanol showed the following absorption maxima: 245 mμ (ε 30,750), 312 (12,000), and 442 (11,500). Further elution of the alumina column with a mixture of benzene and ethanol gave a dark red polymeric material, which on treatment with dilute hydrochloric acid, followed by treatment with sodium hydroxide, gave a further yield (0.3 g, 15%) of 2,2′-diaminoazobenzene (III). No other identifiable product could be obtained from this material.

In a repeat experiment, a solution of 2 g (0.009 mol) of *o*-phenylenediamine in 250 ml of benzene was gradually added to a stirred suspension of manganese dioxide (10 g) in benzene (200 ml), over a period of 12 hr. Removal of the solvent and unchanged manganese dioxide gave a dark red polymeric material which showed a C=O band absorption at 1675 cm^{-1}. Work-up of this mixture, employing chromatography over alumina, gave 0.25 g (13%) of 2,2′-diaminoazobenzene, mmp 134°.

In a repeat run, employing the same quantities of starting materials, but carrying out the reaction in refluxing benzene, a 21% yield of ammonia was evolved, as measured by absorption in a standard solution of hydrochloric acid.

In a different run, 2 g (0.009 mol) of *o*-phenylenediamine and manganese dioxide (10 g) were heated at *ca.* 110° in the absence of any solvent. Vigorous evolution of ammonia was observed during the reaction. Work-up of the mixture by treatment with benzene and chromatography of the benzene extract over alumina gave 0.45 g (22%) of 2,2′-diaminoazobenzene, mmp 134°.

Oxidation of *p*-Phenylenediamine.—A mixture of *p*-phenylenediamine (2 g, 0.009 mol) and manganese dioxide (10 g) in dry benzene (175 ml) was stirred for 6 hr. Evolution of ammonia could be detected during the reaction. Removal of the solvent and unchanged manganese dioxide gave an impure product, which on fractional crystallization from a mixture (1:1) of benzene and ethanol gave 0.8 g of impure *p,p′*-diaminoazobenzene, mp 246–250°. Chromatography over alumina, employing a mixture (1:1) of benzene and ethyl acetate gave a pure sample (0.6 g, 30%) of *p,p′*-diaminoazobenzene, mmp 250–251°. The identity of this compound was further confirmed by a comparison of its ir and uv spectra with those of an authentic sample.[25,26]

From the mother liquor 0.04 g (2%) of *p*-benzoquinone was isolated which melted at 114–115° (mixture melting point). Its ir and uv spectra were identical with those of an authentic sample.

In a repeat run, employing the same quantities of starting materials, but carrying out the reaction in refluxing benzene, a 25% (0.5 g) yield of *p,p′*-diaminoazobenzene was obtained. Vigorous evolution of ammonia was observed during the reaction. No other product could be isolated from this run.

Oxidation of N-Phenyl-*p*-phenylenediamine.—A mixture of N-phenyl-*p*-phenylenediamine (VII) (2 g, 0.01 mol) and manganese dioxide (8 g) was refluxed in benzene for 4 hr. Unchanged manganese dioxide was removed and the organic matter was chromatographed on alumina to give 1.4 g (70%) of N-phenyl-*p*-benzoquinone monoimine (IX): mp 99–100° after recrystallization from benzene; uv spectrum (methanol), λ_{max} 264 mμ (ε 18,000), 288 (16,000) and 450 (3100); ir spectrum (KBr), ν_{max} 1660 cm^{-1} (C=O).

The melting point and uv data are in agreement with those reported for this compound in the literature.[27,28]

Anal. Calcd for $C_{12}H_9NO$: C, 78.8; H, 4.9; N, 7.6. Found: C, 79.3; H, 5.2; N, 7.6.

Oxidation of N,N′-Diphenyl-*p*-phenylenediamine.—Treatment of a mixture of N,N′-diphenyl-*p*-phenylenediamine (0.5 g, 0.0018 mol) with manganese dioxide (2.5 g) in refluxing benzene (50 ml) for 3 hr and work-up in the usual manner, employing chromatography on alumina, gave 0.45 g (91%) of N,N′-diphenyl-*p*-benzoquinone imine (X), mp 187°.[29]

Oxidation of 2,2′-Diaminobiphenyl.—A mixture of 2,2′-diaminobiphenyl (2 g, 0.01 mol) and manganese dioxide (16 g) was refluxed in benzene (125 ml) for 4 hr. Removal of the solvent and unchanged manganese dioxide gave a red-brown viscous mass, which was chromatographed on alumina. Elution with a mixture (3:1) of benzene and petroleum ether (bp 60–80°) gave 0.5 g of unchanged 2,2′-diaminobiphenyl, mmp 78°. Further elution of the column with benzene gave 0.8 g (55%) of dibenzopyridazine, which melted at 157° after recrystallization from benzene. The identity of this compound was established by a mixture melting point determination and also by a comparison of its ir spectrum with that of an authentic sample.[10]

Oxidation of 2,2′-Diaminobiphenyl Sulfide.—Treatment of a mixture of 2,2′-diaminobiphenyl sulfide (1 g, 0.0047 mol) and manganese dioxide (5 g) in refluxing benzene (75 ml) for 6 hr and work-up in the usual manner gave a deep red, viscous material. Chromatography over alumina, employing benzene gave 0.2 g (20%) of *o,o′*-bis(*o*-aminothiophenoxy)azobenzene (XI): mp 202° dec after recrystallization from benzene; uv spectrum (methanol), λ_{max} 240 mμ (ε 47,000) and 315 (21,000) and 420 (12,500); ir spectrum (KBr), ν_{max} 3480, 3400 cm^{-1} (NH_2).

Anal. Calcd for $C_{24}H_{20}N_4S_2$: C, 67.3; H, 4.6; N, 13.1. Found: C, 67.79; H, 4.6; N, 12.7.

Oxidation of N,N′-Dibenzenesulfonyl-*p*-phenylenediamine (XII).—A solution of XII (2 g, 0.005 mol) in dry acetone (175 ml) was stirred with manganese dioxide (12 g) for 5 hr. Removal of the solvent and excess of manganese dioxide gave a greenish yellow viscous mass which showed the presence of a C=O absorption band at 1675 cm^{-1} in the infrared spectrum. Extraction with hot benzene and fractional crystallization from the same solvent gave 0.6 g (32%) of N,N′-dibenzenesulfonyl-*p*-benzoquinone imine, mmp 178°.

In a repeat experiment, 2 g (0.005 mol) of XII and 16 g of manganese dioxide were refluxed in 200 ml of benzene for 6 hr. Work-up of the mixture as in the previous case, gave 0.6 g (37%) of benzenesulfonamide, mmp 151°, and 0.3 g (50%) of benzoquinone, identified through its infrared spectrum.

Oxidation of N,N′-Dibenzenesulfonyl-*p*-benzoquinone Imine (XIII).—Refluxing a mixture of XIII (0.5 g, 0.005 mol) and manganese dioxide (5 g) in dry benzene (100 ml) for 4 hr and work-up in the usual manner gave 0.1 g (25%) of benzenesulfonamide, mmp 151°. A brown polymeric material which showed a sharp carbonyl peak at 1675 cm^{-1} was isolated from the mother liquor.

Oxidation of Benzophenone Anil.—A mixture of benzophenone anil (1 g, 0.004 mol) and active manganese dioxide (30 g) was refluxed in benzene (150 ml) for 8 hr. Water formed during the reaction was collected in a Dean–Stark water separator. Removal of the unchanged manganese dioxide and solvent gave an orange red solid, which was chromatographed over alumina. Elution with petroleum ether (bp 60–80°) gave 0.19 g (55%) of azobenzene, mmp 65°. Further elution with benzene gave 0.3 g of unchanged benzophenone anil, mmp 113°. Elution with ethanol gave a product which on treatment with 2,4-dinitrophenylhydrazine gave 0.71 g of benzophenone 2,4-dinitrophenylhydrazone, mmp 230°.

In a second experiment, a mixture of benzophenone anil (1 g, 0.004 mol) and dry manganese dioxide[30] (30 g) was refluxed in dry benzene (200 ml) for 6 hr. Work-up of the mixture gave 0.9 g (90%) of unchanged benzophenone anil, mmp 113°.

Oxidation of Phenylhydrazines.—In a typical run, 2 g of the hydrazine and 5 g of active manganese dioxide was stirred in refluxing benzene (50 ml) for 4 hr. After removal of the inorganic

(25) O. N. Witt and E. Koptshni, *Ber.* **45**, 1136 (1912).

(26) W. R. Brode and I. L. Seldini, *J. Amer. Chem. Soc.*, **77**, 2762 (1955).

(27) R. Wilstätter and C. L. Moore, *Ber.*, **40**, 668 (1907).

(28) C. J. Podersen, *J. Amer. Chem. Soc.*, **79**, 5014 (1957).

(29) W. L. Semon, U. S. Patent, 2,118,826 (1938); *Chem. Abstr.*, **32**, 5411 (1938).

(30) Dry manganese dioxide was prepared by refluxing the hydrated form of active manganese dioxide in toluene for 12 hr and removing the water in a Dean–Stark separator.

material and the solvent, the product formed in each case was recrystallized from suitable solvents.

Oxidation of phenylhydrazine (2 g, 0.019 mol) gave a mixture of biphenyl (0.75 g, 26%), mp 70°, and azobenzene (40 mg, 3%), mp 65°.

p-Nitrophenylhydrazine (2 g, 0.013 mol) gave *p*-nitrobiphenyl (1.3 g, 50%), mp 113°, after recrystallization from ethanol.

2,4,6-Trichlorophenylhydrazine (2 g, 0.009 mol) on oxidation gave 2,4,6-trichlorobiphenyl (0.9 g, 39%), mmp 62°[31] after recrystallization from dilute acetic acid.

Oxidation of Hydrazines.—In a typical experiment a mixture of the hydrazine and manganese dioxide (1:2.5) in 75 ml of dry benzene was stirred at room temperature for 1 hr. The products were purified by chromatography over alumina using benzene and by recrystallization from suitable solvents.

N-Aminopiperidine (2.5 g, 0.025 mol) gave 1.9 g (76%) of 1,4-bispentamethylenetetrazene (XVI): mp 44° after recrystallization from dilute ethanol; uv spectrum of XVI (cyclohexane), λ_{max} 288 mμ (ε, 11,630); ir spectrum (KBr), ν_{max} 2930, 2800, 1460, 1442, 1365, 1320, 1290, 1265, 1160, 1125, 1082, 1066, 1030, 1025, 986, 970, 925, 868, 770, and 695 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_4$: C, 61.2; H, 10.2; N, 28.5. Found: C, 60.8; H, 10.6; N, 28.4.

Oxidation of N-aminohomopiperidine (3 g, 0.026 mol) gave 2.5 g (86%) of 1,4-bishexamethylenetetrazene (XVII), which melted at 62–63° after recrystallization from ethanol: uv spectrum of XVII (cyclohexane), λ_{max} 290 mμ (ε 12,610); ir spectrum (KBr), ν_{max} 2930, 2850, 1460, 1442, 1365, 1280, 1240, 1200, 1120, 1110, 1070, 1060, 1005, 986, 965, 912, 885, 865, 820, and 715 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}N_4$: C, 64.28; H, 10.7; N, 25.0. Found: C, 64.06; H, 10.30; N, 25.14.

N-Aminomorpholine (2 g, 0.019 mol) of oxidation gave 1.6 g (80%) of 1,4-bis(3-oxapentamethylenetetrazene (XVIII): mp 157° after recrystallization from ethanol: uv spectrum of XVIII (cyclohexane), λ_{max} 284 mμ (ε 10,150); ir spectrum (KBr), ν_{max} 3000, 2910, 1460, 1400, 1380, 1275, 1220, 1190, 1140, 1120, 1100, 1080, 1020, 990, 935, 870, and 779 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_2N_4$: C, 48.0; H, 8.0; N, 28.0. Found: C, 48.04; H, 8.2; N, 28.09.

N,N-Diphenylhydrazine (0.6 g, 0.003 mol) gave 0.45 g (76%) of 1,1,4,4-tetraphenyltetrazene: mp 123° dec (lit.[32] mp 123°); uv spectrum (cyclohexane), λ_{max} 285 mμ (ε 13,900), 304 (15,140) and 360 (14,860); ir spectrum (KBr), ν_{max} 3010, 1590, 1490, 1450, 1345, 1325, 1295, 1090, 1280, 1010, 1100, 1065, 1020, 995, 938, and 890 cm^{-1}.

Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.1; H, 5.9; N, 15.3. Found: C, 79.29; H, 5.6; N, 15.0.

Oxidation of N,N-Dibenzylhydrazine.—N,N-Dibenzylhydrazine (0.5 g, 0.0024 mol) was treated with manganese dioxide (2.2 g) in chloroform (50 ml) at room temperature for 1 hr. Removal of the unchanged manganese dioxide gave a product which was chromatographed over alumina. Elution with petroleum ether (bp 60–80°) and recrystallization from ether gave 15 mg (10%) of 1,1,4,4-tetrabenzyltetrazene, mmp 99°. Further elution of the alumina column with a mixture of benzene and petroleum ether gave 85 mg (20%) of bibenzyl, mmp 52°.

In a second experiment, a mixture (0.5 g, 0.0024 mol) of N,N-dibenzylhydrazine and 1.8 g of manganese dioxide was refluxed in absolute ethanol (70 ml) for 1 hr. Work-up of the mixture in the usual manner gave 0.21 g (49%) of bibenzyl, mmp 52°. None of the tetrazene could be isolated from this run.

Registry No.—Manganese dioxide, 1313-13-9; *o*-phenylenediamine, 95-54-5; *p*-phenylenediamine, 106-50-3; N-phenyl-*p*-phenylenediamine, 101-54-2; N,N′-diphenyl-*p*-phenylenediamine, 74-31-7; 2,2′-diaminobiphenyl, 1454-80-4; 2,2′-diaminobiphenyl sulfide, 5873-51-8; XI, 16504-18-0; XII, 16504-19-1; XIII, 1050-82-4; benzophenone anil, 574-45-8; phenylhydrazine, 100-63-0; *p*-nitrophenylhydrazine, 100-16-3; 2,4,6-trichlorophenylhydrazine, 5329-12-4; N-aminopiperidine, 2213-43-6; XVI, 2081-14-3; N-aminohomopiperidine, 5906-35-4; XVII, 16504-24-8; N-aminomorpholine, 4319-49-7; XVIII, 16504-26-0; N,N-diphenylhydrazine, 530-50-7; 1,1,4,4-tetraphenyltetrazene, 16504-27-1; N,N-dibenzylamine, 5802-60-8.

Acknowledgment.—The authors thank Mr. A. H. Siddiqui for his help in microanalysis.

(31) P. J. Bain, E. J. Blackman, and W. Cummings, *Proc. Chem. Soc.*, 186 (1962).

(32) H. Wieland and E. Wecker, *Ber.*, **43**, 3265 (1910).

Some Aspects of Vinyl Azide Chemistry. Thermally Induced Reactions

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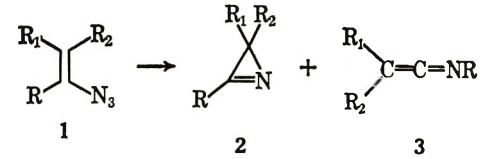
A comparison of the chemistry of terminal and internal vinyl azides is presented. On decomposition, internal vinyl azides formed azirines while terminal vinyl azides did not. The nature of the products from the latter azides depended upon the substituents on the carbon β to the azido group. In solvents other than ethanol, 9-(azidomethylene)fluorene gave 9-(N,N-fluorenylideneaminomethylene)fluorene, while 2-azido-1,1-diphenylethylene and 1-azido-2-phenylpropene formed indole derivatives. The latter two compounds when decomposed in ethanol produced dihydropyrazines at the expense of indole formation. Possible mechanisms for these reactions are considered. In addition, the geminal vinyl diazide, 9-diazidomethylenefluorene, was found to form 9-azido-9-fluorenecarbonitrile while the vicinal diazide, 2,3-diazido(N-phenyl)maleimide, gave N,N-bis(cyanocarbonyl)aniline.

The decomposition of vinyl azides has been the subject of several recent investigations.[1] The majority of these studies has dealt exclusively with internal[2] vinyl azides **1**. It was found that on photolysis or thermolysis this type of azide consistently lost nitrogen and



1 **2** **3**

rearranged to azirines **2** in good yield usually accompanied by small amounts of iminoketenes **3**.[1a-c]

(1) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962); (b) A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, in press; (c) G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966); (d) S. Maiorana, *Ann. Chim.* (Rome), **56**, 1531 (1966); (e) J. H. Boyer, W. E. Krueger, G. J. Mikol, *J. Amer. Chem. Soc.*, **89**, 5504 (1967); (f) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **32**, 985 (1968).

(2) By internal, we mean vinyl azides in which a substituent other than hydrogen is bonded to the carbon bearing the azide group. When a hydrogen atom is bonded to the azide bearing carbon, we will refer to the compound as a terminal vinyl azide.

The few previous studies on the decomposition of terminal vinyl azides indicated that the products of these reactions were not so easily predicted. Some evidence was obtained for the intermediacy of an azirine (**2**, R = R_1 = H; R_2 = tosyl) in the photodecomposition of β-azidovinyl *p*-tosyl sulfone (**4**, R = tosyl).[1f] However, thermal decomposition of the three terminal vinyl azides **4** was reported to yield nitriles **5** with no accompanying azirine formation.[1d-f]

In the present study we have prepared and thermally decomposed a number of terminal vinyl azides (see Chart I). Whenever possible we have also prepared a corresponding internal vinyl azide derivative for comparison. We found, as did the other workers,[1] that internal vinyl azides always produced azirines. On the other hand, the terminal compounds did not, but instead a variety of products resulted depending on the constitution of the molecule. For example, heating 9-(azidomethylene)fluorene (**6**) in benzene for several hours produced about 25% of a high melting, red crystalline material having the formula $C_{27}H_{17}N$ along with a considerable amount of tar. A high resolution mass spectrometric analysis of this red material suggested to us that it was 9-(N,N-fluorenylidenaminomethylene)fluorene (**7**). This compound was synthesized by bromine oxidation of the condensation product of 9-aminofluorene and 9-fluorenecarboxaldehyde and found to be identical with the red reaction product. In contrast with the results for decomposition of the terminal azide **6**, the corresponding internal azide, 9-(1-azidoethylidene)fluorene (**8**), produced the expected azirine, 2-2-(2,2′-biphenylene)-3-methyl-2H-azirine (**9**).

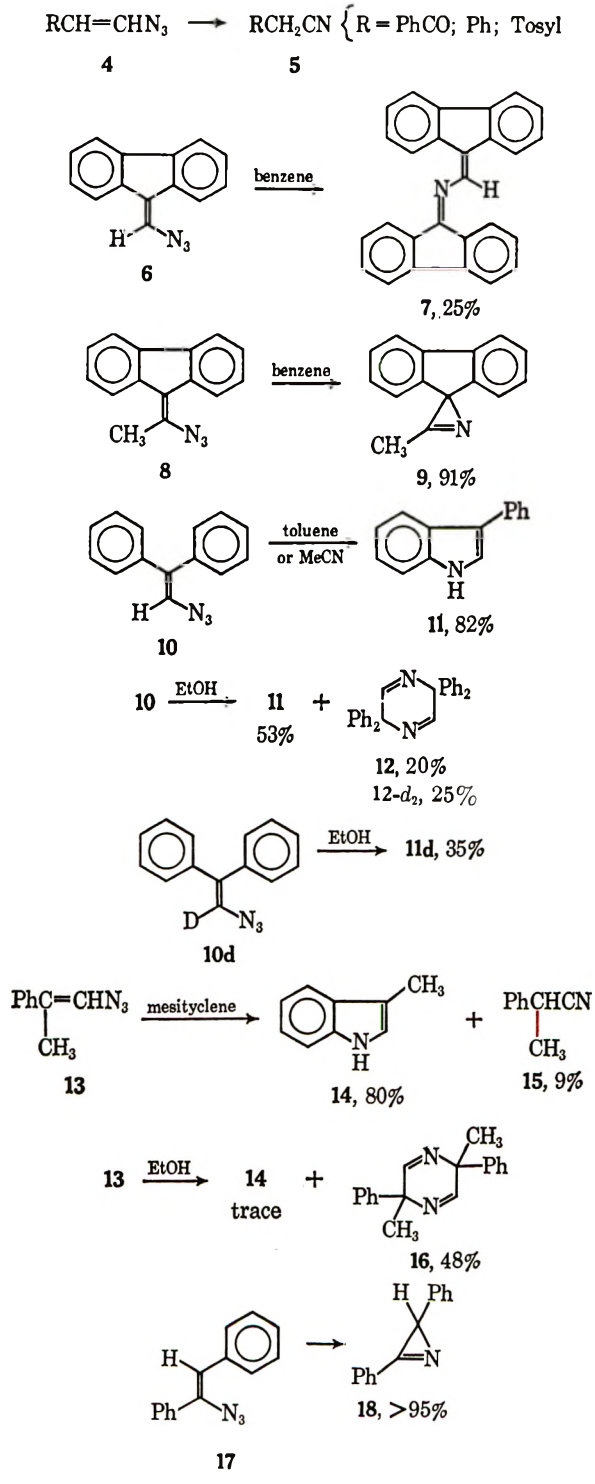
When the terminal azide, 2-azido-1,1-diphenylethylene (**10**), the diphenylmethane analog of fluorene derivative **6**, was decomposed in xylene or acetonitrile, approximately 80% of 3-phenylindole (**11**) was isolated from the reaction. However, when the decomposition was carried out in ethanol, only 53% of indole **11** was obtained, but now 20% of 2,2,5,5-tetraphenyldihydropyrazine (**12**) was also isolated. The structure of the latter material was established by a synthesis in which 2-chloro-2,2-diphenylacetaldehyde was heated in an ammoniacal ethanol solution. Our attempts to synthesize the corresponding methyl-substituted internal vinyl azide by methods analogous to those used in the preparation **10** and **13** failed.

On thermolysis, the behavior of 1-azido-2-phenylpropene (**13**) was found to be quite similar to that found for **10**. Decomposition of **13** in boiling mesitylene produced an 80% yield of 3-methylindole (**14**) accompanied by a small quantity of α-phenylpropionitrile (**15**). Changing the solvent from mesitylene to ethanol caused a pronounced effect: 48% 2,5-dimethyl-2,5-diphenyldihydropyrazine (**16**) was formed along with a trace of indole **14**; no nitrile **15** was formed.

The results reported in this paper demonstrate that the substituent on the carbon atom bearing the azido group determines whether or not azirine is formed in the thermally induced reactions. However, the nature of nonazirine-forming reactions is very much influenced also by the substituents on the β carbon of the terminal vinyl azide. For example, in the series 2-azido-1,1-diphenylethylene (**10**), 1-azido-2-phenylpropene (**13**), and β-styryl azide (**4**, R = Ph) thermolysis leads to 0, 9, and 74% H-migration product accompanied by 82, 80, and 0% insertion into an aromatic C–H bond, respectively. Moreover, the fact that α-azido-*trans*-stilbene (**17**) decomposed to 2,3-diphenyl-2H-azirine (**18**) in high yield[1b] with little if any accompanying indole formation shows clearly that indole does not result merely as a consequence of a *cis* relationship between the phenyl and azido groups. In addition, reactions in ethanol favored dimerization to dihydropyrazines at the expense of indole formation.

In considering a mechanistic rationale for vinyl azide chemistry one is strongly tempted to invoke a vinyl

CHART I
A SUMMARY OF PRODUCTS
OBTAINED FROM THERMOLYSIS OF VINYL AZIDES



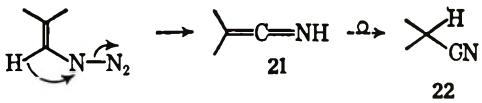
nitrene intermediate. Such a species in either its singlet **19** or triplet state **20** could lead to all the prod-

19 **20**

ucts found from photolytically or thermally induced fragmentation reactions of vinyl azides. Starting from a vinyl nitrene one can write reasonable mechanisms leading to azirine, iminoketene, indole, or dihydropyrazine. Unfortunately equivalent mechanistic pathways can be envisioned assuming that a thermally excited vinyl azide undergoes rearrangement and loss of molecular nitrogen concertedly. However, neither the vinyl nitrene nor azide mechanism implicates the substituent on the azide-bearing carbon atom and at least to this extent they are both unsatisfactory. Neither is any mechanism satisfactory which involves cleavage or the α-carbon–hydrogen bond in terminal vinyl azides. This was established by decomposing deuterated terminal vinyl azide **10d** in ethanol, and showing that all the deuterium remained bonded to the original nitrogen-bearing carbon atom. The observed increase in dihydropyrazine over indole when **10** and **13** were decomposed in ethanol rather than in a hydrocarbon solvent seems to imply the intermediacy of a highly polar species in dihydropyrazine formation. However, this explanation appeared less likely when it was found that decomposition of **10** in acetonitrile gave results identical with those found for decomposition in xylene. It may be that dihydropyrazines result from extremely mild proton-catalyzed decomposition of **10** and **13**. Unfortunately addition of even trace amounts of acetic or toluenesulfonic acid to the solutions of **10** in either benzene or acetonitrile gave intractable product mixtures. Similarly, decomposition of **10** in 2-propanol or *t*-butyl alcohol gave a tarry product from which it proved possible to isolate only 30–50% indole **11**.

An explanation for the production of nitriles from terminal vinyl azides **4** is found in a mechanism analogous to that for the Curtius rearrangement of acid azides to isocyanates (Scheme I) and is consistent with the pro-

SCHEME I

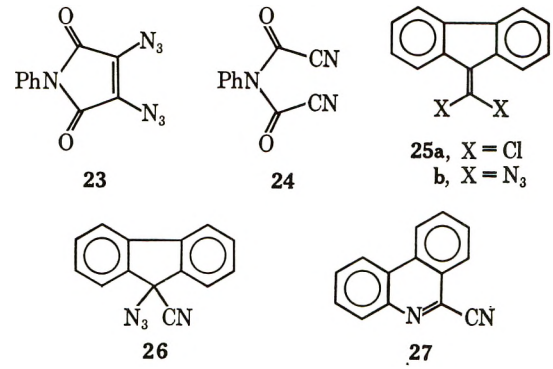


21 **22**

duction of N-substituted iminoketenes from the decomposition of internal vinyl azides. The iminoketene **21** first obtained is certainly more stable in its tautomeric nitrile form **22**. Unfortunately we are unable to explain why this Curtius-like rearrangement should range all the way from a principal to an insignificant reaction pathway in the thermolysis of terminal vinyl azides.

In the course of this study we prepared a vicinal and a geminal vinyl diazide. The thermally induced decomposition of these compounds shed no light on the mechanism of vinyl azide decompositions but did give interesting results. Vicinal vinyl diazide 2,3-diazido-(N-phenyl)maleimide (**23**), when heated in benzene, formed N,N-bis(cyanocarbonyl)aniline (**24**) in 83% yield. This result is in keeping with the findings of Hall and Paterson[3] on the thermolysis of 1,2-diazidobenzene and naphthalene derivatives, in which loss of the two molecules of nitrogen is accompanied by ring opening of the aromatic nucleus with production of dinitriles.

The labile[4] geminal diazide, 9-diazidomethylenefluorene (**25b**), is presumed to be an intermediate in the reaction of 9-dichloromethylenefluorene (**25a**)



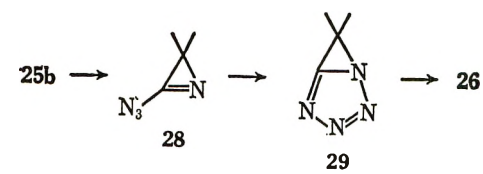
23 **24** **25a**, X = Cl; **b**, X = N_3

26 **27**

with azide ion. However, even at room temperature the only product isolated from this reaction was 9-azido-9-fluorenecarbonitrile (**26**). This compound exhibited strong infrared absorption characteristic of an azide group but no absorption for a nitrile group. Since the intensity of the band for various types of nitriles ranges from strong to undetectable,[5] additional proof of the structure of **26** was obtained by its thermolysis in chlorobenzene to 10-cyanophenanthridine (**27**) in 83% yield. This result is analogous to the conversion of 9-aryl-9-azidofluorenes into 10-arylphenanthridines.[6]

A reasonable mechanistic explanation for the formation of cyanoazide **26** from diazide **25b** is given in Scheme II. The proposed isomerization of **28** to **29** is a well-known type of rearrangement reaction. The resulting tetrazole **29** is certainly a highly strained molecule which finds relief in opening to **26**.

SCHEME II



28 **29**

Experimental Section[7]

9-(Azidomethylene)fluorene (6).—Sodium azide (5.2 g, 0.08 mol) was added to an ice-cold solution of 10 g (0.04 mol) of 9-bromomethylenefluorene[8] in 200 ml of dimethylformamide. The resulting mixture was stirred under a nitrogen atmosphere and cooled in an ice bath for 3 hr, after which it was placed in a refrigerator for 70 hr and swirled occasionally. The mixture was poured onto ice, diluted with ice–water and extracted with methylene chloride. The methylene chloride phase was washed six times with ice–water, dried (K_2CO_3), and evaporated at reduced pressure without external heating. The orange crystal-

(3) J. H. Hall and E. Patterson, *J. Amer. Chem. Soc.*, **89**, 5856 (1967).

(4) By working at less than 5° it was possible to isolate a substance believed to be **25b**, but this material decomposed to a tarry mass at room temperature.

(5) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).

(6) L. A. Pinck and H. E. Hilbert, *J. Amer. Chem. Soc.*, **59**, 8 (1937).

(7) All melting points are correct. Boiling points are uncorrected.

(8) D. F. DeTar, E. Broderick, G. Foster, and B. D. Hilton, *J. Amer. Chem. Soc.*, **72**, 2183 (1950).

line residue weighed 8.9 g and showed strong absorption in the infrared spectrum ($CHCl_3$) at 4.70 (azide) and 6.1 μ (C=C).[1b]

Conversion of 9-Azidomethylenefluorene (6) into 9-(N,N-Fluorenylidenaminomethylene)fluorene (7).—A deaerated solution of 2 g (9.1 mmol) of vinyl azide 6 in 50 ml of benzene was maintained at reflux in a nitrogen atmosphere for 3 hr. The gummy red solid obtained on evaporation of the benzene was recrystallized from a small quantity of benzene to give 0.4 g (25%) of **7**. Several additional recrystallizations from benzene gave shiny red needles of mp 324–326°. High resolution mass spectrometry confirmed the molecular formula of $C_{27}H_{17}N$, while the assigned structure was established definitively by comparison of melting point and infrared spectrum with that of independently synthesized material (see below).

9-(N,N-Fluorenylidenaminomethyl)fluorene (7).—To a deaerated solution of 193 mg (1 mmol) of 9-fluorenecarboxaldehyde[9] in 30 ml of pyridine was added 217 mg (1 mmol) of 9-aminofluorene hydrochloride. The resulting mixture was boiled for 3 hr in a nitrogen atmosphere after which the solution was cooled, swirled over anhydrous K_2CO_3, filtered, and evaporated to dryness. The semicrystalline orange residue was warmed with a small volume of benzene and cooled, and the insoluble portion was collected. This material weighed 200 mg (55%) and decomposed to a red oil at 225–230°.

To a solution of 178 mg (0.5 mmol) of the above condensation product in 15 ml of pyridine was added dropwise 0.5 mmol of bromine dissolved in pyridine (0.117 g/ml). The reaction turned bright red and a precipitate formed after a few minutes. After a half hour, the orange precipitate was collected, washed with benzene, and dried (Na_2SO_4) to give 90 mg (50%) of **7**, mp 322–325°. Several additional recrystallizations from benzene gave shiny red needles, mp 324–326°.

Anal. Calcd for $C_{27}H_{17}N$: C, 91.24; H, 4.82; N, 3.94. Found: C, 91.0; H, 4.8; N, 4.4.

9-(1-Bromoethylidene)fluorene.—Ethyl α-fluorenylidenepropionate [bp 188 (1.4 torr), mp 65–69°] was prepared in 70% yield by a Reformatsky condensation of fluorenone and ethyl α-bromopropionate in benzene solution following the procedure of Sieglitz and Jassoy[10] for the preparation of ethyl fluorenylideneacetate. In the present case it was found necessary to initiate the reaction by the addition of a small amount of magnesium and iodine.

The fluorenylidenepropionate was saponified by heating an aqueous ethanolic potassium hydroxide solution for 20 min in a nitrogen atmosphere. The acid was precipitated by the addition of hydrochloric acid, collected, and dried overnight in a vacuum oven at 60°. The crude acid was pulverized, suspended in carbon tetrachloride, and stirred 48 hr under nitrogen in the dark with 1 equiv of bromine. The residue remaining after evaporation of the solvent at reduced pressure, was boiled for 2 hr with a slight excess of 0.5 *N* sodium hydroxide. The bromide was extracted from the aqueous alkaline mixture with benzene. The crude bromoethylidenefluorene was sublimed (yield based on ester was 50%) and recrystallized from cyclohexane to give pale yellow crystals, mp 90–91°.

Anal. Calcd for $C_{15}H_{11}Br$: C, 66.42; H, 4.09; Br, 29.49. Found: C, 66.3; H, 4.0; Br, 29.8.

9-(1-Azidoethylidene)fluorene (8).—9-(1-Bromoethylidene)-fluorene was converted into the corresponding azide **8** with sodium azide in cold dimethylformamide as described above for the preparation of 9-(azidomethylene)fluorene (**6**). Crude **8** (pale yellow crystals) exhibited a strong split azide band in the infrared spectrum ($CHCl_3$) at 4.67 and 4.82 and C=C absorption at 6.15 μ.[1b]

Conversion of 9-(1-Azidoethylidene)fluorene (8) into 2,2-(2,2'-Biphenylene)-3-methyl-2H-azirine (9).—A benzene (20 ml) solution of 650 mg (2.8 mmol) of **8** was maintained at reflux in a nitrogen atmosphere for 2 hr after which the solvent was removed at reduced pressure and the residue transferred to a sublimer and heated at 100° (0.05 torr). The sublimate (590 mg 91%) had mp 86–88°. Recrystallization from methanol gave material of mp 97–99°. The infrared spectrum (CCl_4) exhibited the azirine, C=N, absorption at 5.6 μ. The nmr spectrum (CCl_4) showed a singlet at δ 2.51 and a multiplet centered at 7.1 in the ratio of 3:8.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.6; H, 5.2; N, 7.1.

2-Azido-1,1-diphenylethylene (10).—A mixture of 1.3 g (20 mmol) of sodium azide in 75 ml of methanol containing 2 g (10 mmol) of dissolved 1,1-diphenylethylene oxide[11] was stirred at reflux in a nitrogen atmosphere for 24 hr, after which the reaction was cooled and the solvent removed at reduced pressure. The residue was distributed between water and ether. The ether layer was dried (K_2CO_3) and evaporated at reduced pressure. The colorless, oily residue weighed 1.75 g and exhibited strong infrared absorption at 4.75 (azide) and 3.25 μ (hydroxyl).

Using the method of Hazen and Rosenburg[12] 2.0 g (8.4 mmol) of crude 1,1-diphenyl-2-azidoethanol was dehydrated in dimethylformamide–pyridine solution with methanesulfonyl chloride containing dissolved sulfur dioxide. The work-up consisted of dropwise addition of 25 ml of water to the ice bath cooled reaction mixture (temperature maintained below 30°) followed by addition of a large excess of water. The resulting aqueous mixture was twice extracted with methylene chloride. The methylene chloride solution was washed successively with cold dilute sulfuric acid, cold dilute carbonate solution, and water and then dried (Na_2SO_4) and evaporated to dryness at reduced pressure. The yellow, oily residue was taken up in petroleum ether (30–60°) and chromatographed on a 20-g silica gel column. The 1,1-diphenyl-2-azidoethylene (**10**) (950 mg 50%) was eluted with 1:1 petroleum ether–benzene and exhibited strong absorption in the infrared spectrum (neat) at 4.72 (azide) and 6.2 μ (C=C).[1b] Nmr (CCl_4) absorption was as follows: multiplets at δ 7.26 and 7.16 totaling ten protons and a singlet of one proton at 6.48.

Thermolysis of 2-Azido-1,1-diphenylethylene (10). A. In Xylene.—A solution of 1.2 g (4.5 mmol) of azide **10** in 25 ml of xylene was maintained at reflux in a nitrogen atmosphere for 22 hr. The residue obtained on evaporation of the xylene at reduced pressure was transferred to a sublimer and heated to 95° (0.001 torr) for several hours. The sublimate weighed 970 mg (82%) and had mp 76–79°. One recrystallization from benzene gave material of mp 88–89°. The picrate melted at 106–107°. Bettembourg and David[13] reported mp 86–88° for 3-phenylindole (**11**) and 107–109° for the picrate.

B. In Acetonitrile.—The only identifiable product was 3-phenylindole (**11**, 75%).

C. In Ethanol.—A solution of 260 mg (1.2 mmol) of azide **10** in 25 ml of ethanol was boiled in a nitrogen atmosphere for 16 hr during which time a slight precipitate formed. The solvent was removed at reduced pressure and the residue transferred to a sublimer and heated at 95° (0.001 torr) for several hours. The sublimate (53%) was identified as 3-phenylindole (**10**) by comparison of its infrared spectrum with that of authentic material. The residue (20%) was recrystallized several times from benzene–hexane to give material of mp 277–278° which was not depressed when admixed with authentic 2,2,5,5-tetraphenyldihydropyrazine (**12**).

2,2,5,5-Tetraphenyldihydropyrazine (12).—2-Chloro-2,2-diphenylacetaldehyde[14] (1 g, 5.3 mmol) in 4 ml of ether was added dropwise to a stirred, ice bath cooled solution of 1 g of ammonia in 15 ml of ethanol. After addition was complete, the reaction solution was stirred at room temperature for 2 hr and then boiled under nitrogen overnight. Crystals began to separate after several hours. The cooled reaction mixture was filtered and the crystals were collected (0.28 g, 33%). Recrystallization from benzene–hexane gave **12**, mp 277–278°.

Anal. Calcd for $C_{28}H_{22}N_2$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.1; H, 5.9; N, 7.2.

A high resolution mass spectrometric analysis was in agreement with the above assigned structure in that the parent peak had a mass in agreement with the formula $C_{28}H_{22}N_2$ and the major fragments had masses corresponding to the following formula: $C_{27}H_{21}N$, $C_{21}H_{16}N$, $C_{15}H_{11}N$, $C_{14}H_{11}N$, $C_{14}H_{10}N$.

2-Azido-1,1-diphenylethylene-2-d_1 (10-d).—A solution of 50 g (0.78 mol) of commercially available acetic acid-d_4 in 40 ml of methanol containing 1 ml of sulfuric acid was allowed to stand at room temperature overnight. A fractionation of this solution

(9) Prepared by the method of W. Wislicenus and M. Waldmuller [*Ber.*, **42**, 785 (1909)], except that sodium hydride in tetrahydrofuran was substituted for potassium dissolved in ethanol.

(10) A. Sieglitz and H. Jassoy, *Ber.*, **54**, 2133 (1921).

(11) S. J. Cristol, J. R. Douglass, and J. S. Meek, *J. Amer. Chem. Soc.*, **73**, 816 (1951). It was found that a temperature of 5–10° gave better results than 0° during bromohydrin formation.

(12) G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, **29**, 1931 (1964).

(13) M. C. Bettembourg and S. David, *Bull. Soc. Chim. Fr.*, 772 (1962).

(14) D. Y. Curtain, J. A. Kompmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 875 (1965).

through a 2-ft spinning-band column gave 61 g of material boiling at 53.5° which was shown by an nmr analysis to consist of a mixture of 64 mol % methyl acetate-d_3 and methanol.

The total methyl acetate-d_3–methanol mixture was added to 2 mol of phenyl magnesium bromide in ether and the resulting methyl-d_3-benzhydrol was isolated in the usual way. Recrystallization from 95% ethanol gave 85 g of the benzhydrol, mp 80–81° (lit.[15] mp 81°).

To a solution of 20 g (0.1 mol) of the benzhydrol-d_3 in 100 ml of warm (50–60°) 80% aqueous acetic acid was added dropwise 16 g (0.1 mol) of bromine in 10 ml of acetic acid. After an initial induction period warming was discontinued and bromine was rapidly consumed. When addition was complete, the reaction was diluted with benzene, washed well with water, dried (Na_2SO_4), and evaporated to dryness. The crystalline bromohydrin-d_2 was recrystallized from hexane (mp 73–75°) and converted into 1,1-diphenylene oxide-d_2 by the method of Cristol, Douglass, and Meek.[11] The 2-azido-1,1-diphenylethylene-2-d_1 (**10**-d) was prepared as described above for 2-azido-1,1-diphenylethene (**10**). The nmr spectrum of the deuterium compound exhibited phenyl proton absorption at δ 7.18 and 7.26 and at most 1% vinyl proton absorption. The infrared spectrum (neat) showed N_3 absorption at 4.7 μ.

Thermolysis of 2-Azido-1,1-diphenylethylene-2-d_1 (10-d) in Ethanol.—A solution of 1.8 g (0.008 mol) of the deuterated vinyl azide **10**-d in 50 ml of ethanol was maintained at reflux in a nitrogen atmosphere for 16 hr. 2,2,5,5-Tetraphenyldihydropyrazine-3,6-d_2 (**12**-d, 400 mg, 25%; mp 275–276°) was collected by filtration and its deuterium content was established by mass spectrometry (m/e 388).

The oily residue obtained on evaporation of the filtrate was transferred to a sublimer and heated at 90–100° (0.001 torr). The crystals collected on the cold finger weighed 610 mg (38%). Recrystallization from hexane gave 3-phenylindole-2-d_1 (**11**-d), mp 87.5–88° which was not depressed on admixture with authentic 3-phenylindole. The deuterated compound had an identical ultraviolet spectrum but different nmr and infrared spectra from that of fully protonated 3-phenylindole.

1-Azido-2-phenylpropene (13).—1-Methyl-1-phenylethylene oxide[11] was allowed to react with sodium azide as described above for the preparation of 2-azido-1,1-diphenylethylene (**10**). The almost colorless, oily, crude 2-azido-1-methyl-1-phenylethanol showed absorption in the infrared spectrum (neat) at 4.7 (azide) and 2.8 μ (hydroxyl).

The crude azidomethylphenylethanol (11 g, 0.062 mol) was dehydrated by the method of Hazen and Rosenburg[12] as described above for the preparation of the azidodiphenylethylene **10**. In this way 2.5 g (25%) of **13** was obtained having the following properties: infrared spectrum (neat) showed absorption at 4.72 (azide) and 6.12 μ (C=C);[1b] the nmr spectrum (CCl_4) showed phenyl absorption at δ 7.20 with a multiplet at 6.25 (vinyl hydrogen) and a slightly split methyl absorption at 1.95. On decoupling, the methyl doublet collapsed to a singlet while the multiplet at δ 6.25 became two singlets at 6.18 and 6.27 with a ratio of 1:7.

Thermolysis of 1-Azido-2-phenylpropene (13). A. In Mesitylene.—To 20 ml of boiling mesitylene, under nitrogen, was added 1.2 g (76 mmol) of **13**. After 14 hr, the solvent was evaporated at reduced pressure and the residue was transferred to a sublimer and heated for several hours at 80–100° (0.2 torr). The white, crystalline sublimate weighed 870 mg (89%) and was shown by glpc analysis (6 ft × 0.125 in. UCON POLAR 2000 on 80/100 acid-washed Chromosorb W), using authentic compounds as standards, to consist of a 1:9 mixture of 2-phenylproprionitrile (**15**) and 3-methylindole (**14**). Pure **14** was obtained by recrystallization of the sublimate from benzene–hexane.

B. In Ethanol.—A solution of 1.4 g (0.0088 mol) of azide **13** in 50 ml of deaerated ethanol was boiled in a nitrogen atmosphere for 20 hr. The solvent was removed at reduced pressure and the residue was heated at 50–60° (0.001 torr) in a sublimer. A small quantity of liquid collected on the cold finger; this contained some 3-methylindole (**14**) as shown by glpc analysis. Raising the bath temperature to 100–110° caused a solid to collect (550 mg, 48%). This was recrystallized from benzene–hexane and resublimed to give pure 2,5-dimethyl-2,5-diphenyldihydropyrazine (**16**). The mp 156° was not depressed by admixture of this product with an authentic sample.

(15) A. Klages, *Ber.*, **35**, 2646 (1902).

2,5-Dimethyl-2,5-diphenyldihydropyrazine (16).—2-Chloro-2-phenylpropionaldehyde (5.0 g, 0.03 mol), prepared from 2-phenylpropionaldehyde and sulfuryl chloride,[14] was dissolved in 60 ml of ethanol saturated with ammonia. After stirring for 0.5 hr at room temperature a white precipitate formed; the resulting mixture was then boiled overnight (16 hr). The residue obtained after evaporation of the ethanol was taken up in methylene chloride. This solution was washed with water, dried (K_2CO_3), and evaporated to dryness. This residue was transferred to a sublimer and pumped at 0.001 torr. A colorless oil, which was discarded, collected on the cold finger at a pot temperature of 70–95°. A white solid (2.5 g, 64%) sublimed at 100–120°; after four recrystallizations from benzene–hexane this gave **16** of mp 155–156° which exhibited an nmr spectrum ($CDCl_3$) with three singlets in the ratio 1:5:3 at δ 8.24, 7.42, and 1.63.

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68. Found: C, 82.5; H, 6.8; N, 10.9.

Conversion of 2,3-Diazido(N-phenyl)maleimide (23) into N,N-Bis(cyanocarbonyl)aniline (24).—2,3-Diazido(N-phenyl)maleimide[16] (**23**, 2.0 g, 0.078 mol) in 60 ml of benzene was maintained at reflux in a nitrogen atmosphere for 3 hr. The solvent was removed at reduced pressure, and the brownish residue was transferred to a sublimer and heated at 70° (0.01 torr). The sublimate weighed 1.3 g (83%) and had mp 95–97°. Two recrystallization from benzene followed by a second sublimation gave **24**, mp 95–96.5°, with moderate and strong absorptions in the infrared at 4.45 and 5.81 μ, respectively.

Anal. Calcd for $C_{10}H_5N_3O_2$: C, 60.30; H, 2.53; N, 21.10. Found: C, 60.4; H, 2.7; N, 21.0.

9-Azido-9-fluorenecarbonitrile (26).—A mixture of 5.0 g (20.5 mmol) of 9-dichloromethylenefluorene (**25a**)[17] and 4 g (61 mmol) of sodium azide in 250 ml of dimethylformamide was stirred in a nitrogen atmosphere at ambient temperature overnight. This reaction mixture was diluted with *ca.* 1 l. of water and extracted five times with benzene. The benzene extracts were washed well with water, dried (Na_2SO_4), and evaporated to dryness at reduced pressure. The residue was chromatographed on 60 g of Woelm neutral alumina. Azidocyanofluorene (**26**, 1.6 g, 34%), mp 77–78°, was eluted with 1:3 benzene–hexane. The analytical sample was recrystallized from hexane and sublimed at 70° (0.001 torr) and had mp 77.5–78.5°. A carbon tetrachloride solution infrared spectrum showed the N_3 absorption at 7.74 μ. The ultraviolet spectrum in ethanol exhibited three maxima (ϵ_{231} 34,900; ϵ_{238} 33,800; ϵ_{272} 14,800) and three minima (ϵ_{217} 25,500; ϵ_{235} 30,200; ϵ_{248} 6700).

Anal. Calcd for $C_{14}H_8N_4$: C, 72.40; H, 3.44; N, 24.13. Found: C, 72.5; H, 3.8; N, 23.7.

Conversion of 9-Azido-9-fluorenecarbonitrile (26) into 10-Cyanophenanthridine (27).—A solution of 458 mg (1.92 mmol) of **26** in 2 ml of chlorobenzene was maintained at a boil in a nitrogen atmosphere for 3 hr. The reddish colored reaction solution was evaporated to dryness at reduced pressure and the residue transferred to a small sublimer. Most of the material sublimed at 140° (0.005 torr). A resublimation at 80° (0.005 torr) gave 325 mg (83%) of material having mp 138–139°. This compound had an identical infrared spectrum with that of authentic[18] 10-cyanophenanthridine (**27**) and did not depress the melting point upon mixing.

Thermolysis of Methyl Azidofumarate to 2,3-Dicarbomethoxy-2H-azirine.—Methyl azidofumarate[19] was pyrolyzed at 230° in an apparatus previously described[20] with the modification that the azide was introduced at the top of the reaction tube by suction through a very fine capillary. The pressure in the pyrolysis tube was maintained at less than 1.5 torr and the products were trapped at ice–acetone temperatures. The crude pyrolysate was Claisen distilled at 0.7 torr; the fraction collected at 70–80° was redistilled to give azirine boiling over a few degrees in an over-all yield of 35%. The azirine exhibited infrared (neat) absorption at 5.60 (C=N) and 5.73 μ (C=O). The ultraviolet spectrum (cyclohexane) consisted mainly of end absorption with

(16) A. Mustafa, S. M. A. D. Zayed, and S. Khattob, *J. Amer. Chem. Soc.*, **78**, 145 (1956).

(17) R. Oda, Y. Ito, and M. Okano, *Tetrahedron Lett.*, 7 (1964).

(18) We thank Messrs. E. Hayashi and H. Ohki for a sample of 10-cyanophenanthridine [*Yakugaku Zasshi*, **81**, 1033 (1961)].

(19) V. G. Ostroverkhov and E. A. Shilov, *Ukr. Khim. Zh.*, **23**, 615 (1957).

(20) G. Smolinsky, *J. Org. Chem.*, **26**, 4108 (1966).

an inflection at 234 mμ (ε 420) tailing off to zero at about 300 mμ. The nmr (CCl_4) spectrum consisted of three sharp peaks at δ 2.85, 2.72, and 4.0 with area ratios of 1:3:3, respectively.

Anal. Calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.92. Found: C, 45.7; H, 4.3; N, 8.7.

Registry No.—**7,** 16504-38-4; 9-(1-bromoethylidene)-fluorene, 16504-39-5; **9,** 16504-40-8; **12,** 16504-41-9; **16,** 16504-42-0; **24,** 16504-43-1; **26,** 16520-65-3; 2,3-dicarbomethoxy-2H-azirine, 16504-44-2.

Reactions of Phosphorus Compounds. XV. A General Synthesis of 2H-1-Benzopyrans

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Substituted 2H-1-benzopyrans and 3H-naphtho[2,1-*b*]pyran (IX) have been prepared from vinyltriphenylphosphonium bromide (III), substituted salicylaldehydes, or 2-hydroxy-1-naphthaldehyde, respectively.

In a previous communication in this series, 2H-1-benzopyran[1] was prepared by utilizing the vinylphosphonium salt (III) and salicylaldehyde. In addition to 2H-1-benzopyran, the following series of compounds have been synthesized: pyrrolizines,[2] carbocyclics,[3] olefins,[4a] 1,2-dihydroquinolines,[4b] and 2,5-dihydrofurans[5] from the vinylphosphonium salt (III) and suitable addenda. We now wish to report a general preparation of substituted 2H-1-benzopyrans (VI) and 3H-naphtho[2,1-*b*]pyran (IX) utilizing the vinylphosphonium salt (III) and suitable phenolic aldehydes as shown in Scheme I.

These types of compounds are of interest because of the occurrence of the benzopyran ring system in the active constituents of several plants used as insecticides[6] and natural dyes.[7] Previous preparations have been accomplished in the following manners: (a) by the intramolecular cyclization of phenyl propargyl ether;[8,9] (b) by the slow distillation of a crude mixture of 4- and 6-bromochroman in the presence of alcoholic sodium ethoxide;[10] (c) by dimethyl sulfoxide dehydration of 4-chromanol or a two-step conversion from the 4-chromanol involving a Kraft pyrolysis of 4-chromanyl acetate.[11]

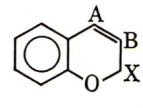
In situ preparation and reaction of the sodium salts of salicylaldehyde (Id), 3-methoxy salicylaldehyde (Ia), or 2-hydroxy-1-naphthaldehyde (VIII) with the vinylphosphonium salt (III) in an acetonitrile–ether solvent system afforded 2H-1-benzopyran (VId), 8-methoxy-2H-1-benzopyran (VIa), and 3H-naphtho[2,1-*b*]pyran (IX) in 71, 57, and 14% yields respectively. 5-Chlorosalicylaldehyde (Ic) was treated in the same way (except that the solvent system used was a N,N-dimethylformamide (DMF)–ether mixture) to give 6-chloro-2H-1-benzopyran (VIc) in 29% yield. Attempted preparation of 6-nitro-1,2-benzopyran (VIb) from 5-nitrosalicylaldehyde (Ib) and the vinylphosphonium salt (III) utilizing the above procedure was unsuccessful. However, preparation and isolation of the sodium salt of 5-nitrosalicylaldehyde followed by pyrolysis with the vinylphosphonium salt (III) *in vacuo* afforded the desired benzopyran (VIb) in 27% yield.

The 2H-1-benzopyrans were characterized by their physical constants, nmr spectra, and absorption in the infrared region of 1200–1260 cm^{-1} which is characteristic for the C–O stretch of aromatic ethers.[12,13]

The nuclear magnetic resonance spectra of the synthesized 2H-1-benzopyrans show patterns which are characteristic for this type of structure. The spectra can be divided into three major parts. (1) The aromatic protons appear as a multiplet. (2) The protons associated with the substituents of the aromatic ring, *i.e.*, the methyl protons of 8-methoxy-2H-1-benzopyran (VIa), exhibit a singlet centered at 3.72 ppm downfield from tetramethylsilane. (3) The protons of the pyran ring system exhibit an ABX_2 system.

The protons of the ABX_2 system exhibit the following splitting characteristics. The protons associated with the carbon α to the oxygen atom (CH_2) appear as a quadruplet (J_{BXCH_2} = 3 cps; J_{AXCH_2} = 2 cps) centered in the range of 4.37–4.96 ppm downfield from tetramethylsilane for 6-chloro-2H-1-benzopyran and 5-nitro-2H-1-benzopyran (VIb), respectively (with the others lying in between). The proton associated with the β-carbon atom appears as a pair of triplets (J_{AB} = 10 cps; J_{BX} = 3 cps) centered in the range of 5.30–5.83 ppm downfield from tetramethylsilane for 6-chloro-2H-1-benzopyran and 5-nitro-2H-1-benzopyran, respectively, at the extremes (Table I). The proton associated with the A-

TABLE I
CENTER OF NMR BANDS ASSOCIATED WITH THE PYRAN RING PROTONS OF VARIOUS 2H-1-BENZOPYRANS IN PARTS PER MILLION FROM TETRAMETHYLSILANE



Compound	X	B	A
2H-1-Benzopyran	4.53	5.38	6.20
8-Methoxy-2H-1-benzopyran	4.75	5.70	6.43
6-Nitro-2H-1-benzopyran	4.96	5.83	6.42
3H-Naphtho[2-1-*b*]pyran	4.65	5.60	6.92
6-Chloro-2H-1-benzopyran	4.37	5.30	6.88

(1) E. E. Schweizer, *J. Amer. Chem. Soc.*, **86**, 2744 (1964).
(2) E. E. Schweizer and K. Light, *J. Org. Chem.*, **31**, 870 (1966).
(3) E. E. Schweizer and G. O'Neill, *ibid.*, **30**, 2082 (1965).
(4) (a) E. E. Schweizer, L. Smucker, and R. Votral, *ibid.*, **31**, 467 (1966); (b) E. E. Schweizer and L. Smucker, *ibid.*, **31**, 3146 (1966).
(5) E. E. Schweizer and J. Liehr, *ibid.*, **33**, 583 (1968).
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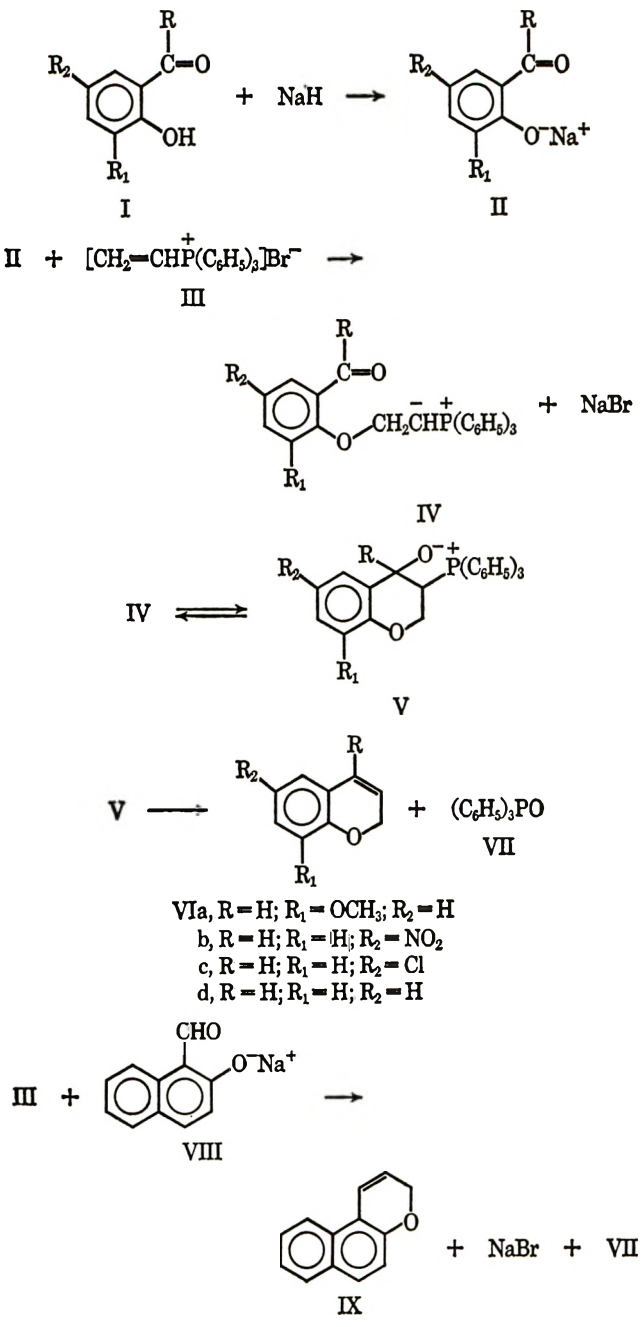
(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1958, pp 45–48.
(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., p 172.

SCHEME I



carbon atom also appears as a pair of triplets (J_{AB} = 10 cps; J_{AX} = 2 cps) centered in the range of 6.20–6.92 ppm downfield from tetramethylsilane for 2H-1-benzopyran and 3H-naphtho[2,1-*b*]pyran, respectively, as extremes. The above assigned splitting patterns for the vinyl group agree with previously reported results[4] for open-chain vinyl compounds.

The reaction of the sodium salt of *o*-hydroxybenzophenone with the vinyl salt (III) utilizing both solution and pyrolysis techniques did not give the anticipated product, 4-phenyl-2H-1-benzopyran, in sufficient yield for isolation and positive identification. However, its probable formation was demonstrated by infrared spectroscopy and the identification of trace amounts of triphenylphosphine oxide (VII) in the reaction residue. In addition to the above, triphenylphosphine and starting material were also isolated.

In the reaction of *o*-hydroxyacetophenone with the vinylphosphonium salt (III) utilizing both solution and pyrolysis techniques triphenylphosphine oxide was isolated, indicating that a Wittig reaction had taken place; however, none of the anticipated product, 4-methyl-2H-1-benzopyran, could be isolated and only a trace of product could be detected by vapor phase chromatography. In addition to the phosphine oxide, starting material and triphenylphosphine were also isolated.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord 137 and nmr spectra were obtained on a Varian A-60 analytical nmr spectrometer, using tetramethylsilane as standard. All melting points were uncorrected and obtained on a Fischer–Johns melting point apparatus. Analyses were by Micro-Analysis, Inc., Wilmington, Del.

The vinyltriphenylphosphonium bromide[14] and *o*-hydroxybenzophenone[15] were prepared according to reported procedures. The latter may also be bought from the Aldrich Co. The 2-hydroxy-1-naphthaldehyde was obtained from Columbia Organic Chemicals Co., Inc.; the 5-nitrosalicylaldehyde, 5-chlorosalicylaldehyde, and 3-methoxy-2-hydroxybenzaldehyde were obtained from Eastman Kodak Co. Sodium hydride was obtained as an approximately 53% dispersion in mineral oil from Metal Hydrides, Inc., Beverly, Mass. Anhydrous reagent grade solvents were used in all cases. All reactions were carried out under a nitrogen blanket.

General Procedure. The Preparation of 8-Methoxy-2H-1-benzopyran (VIa).—3-Methoxy-2-hydroxybenzaldehyde (10.0 g, 0.072 mol) was added to a stirred mixture of 2.9 g of sodium hydride dispersion in mineral oil (52% NaH, 1.5 g, 0.0625 mol) and 100 ml of ether. After the gas evolution abated, 22.8 g (0.062 mol) of salt III was introduced to the mixture and 100 ml of acetonitrile was added dropwise. The reaction mixture was

TABLE II

Product	Ir bands, cm^{-1}		Nmr data, δ
VIa	1262 (aromatic ether)		3.72 (s, 3, O-CH_3)
	1570 (s)	1070 (s)	4.75 (quad, 2, O-CH_2—)
	1470 (s)	1030 (s)	5.70 (m, 1, O-CH_2-CH=)
	1205 (s)	790 (s)	6.43 (m, 1, C_6H_3-CH=)
	1095 (s)	735 (s)	6.60–6.93 (m, 3, C_6H_3)
VIb	1258 (aromatic ether)		4.96 (quad, 2, O-CH_2—)
	1600 (s)	1025 (s)	5.83 (m, 1, O-CH_2CH=)
	1500 (s)	900 (s)	6.42 (m, 1, C_6H_3-CH=)
	1480 (s)	832 (s)	7.32–7.90 (m, 3, C_6H_3)
	1240 (s)	794 (s)	
	1090 (s)	744 (s)	
VIc	1235 (aromatic ether)		4.37 (quad, 2, O-CH_2)
	1480 (s)	1085 (s)	5.30 (m, 1, O-CH_2-CH=)
	1420 (s)	1030 (s)	6.88 (m, 1, C_6H_3-CH=)
		885 (s)	6.21–6.92 (m, 3, C_6H_3—)
	1200 (s)	820 (s)	
	1120 (m)	750 (s)	
VId	1230 (aromatic ether)		4.53 (quad, 2, O-CH_2—)
	1610 (s)	1195 (s)	5.38 (m, 1, O-CH_2-CH=)
	1570 (s)	1110 (s)	6.20 (m, 1, C_6H_4-CH=)
	1480 (s)	1040 (s)	6.60–7.13 (m, 4, C_6H_4)
	1380 (s)	930 (s)	
	1360 (s)	750 (s)	
IX[a]	1220 (aromatic ether)		4.65 (quad, 2, O-CH_2)
	1580 (s)	1010 (s)	5.60 (m, 1, O-CH_2-CH=)
	1510 (s)	810 (s)	6.92 (m, 1, $C_{10}H_6$-CH=)
	1460 (s)	800 (s)	7.10–7.89 (m, 6, $C_{10}H_6$—)
	1180 (s)	742 (s)	
	1085 (s)	718 (s)	

[a] The uv spectrum of IX showed bands at 218, 261 (sh), 290 (sh), 303, 316, and 349 mμ (lit.[9] uv bands at 242, 261 (sh), 290 (sh), 301, 314, and 347 mμ).

(14) E. E. Schweizer and R. Bach, *J. Org. Chem.*, **29**, 1746 (1964).

(15) N. M. Cullinane, N. M. Morgan, and C. A. Plummer, *Rec. Trav. Chim. Pays-Bas*, **56**, 629 (1937).

TABLE III

$$\text{Ia–d} + \text{III} \xrightarrow[\text{solvent}]{\text{NaH}} \text{VI} + (C_6H_5)_3PO$$

Compd (mol)	NaH, mol	Temp, °C	Solvent	Time	Product (yield, %)	Bp, (mm) or mp, °C	Refractive index	—Calcd, %— C	H	—Found, %— C	H
Ia (0.0721)	0.0625	Reflux	Acetonitrile	5 days	VIa (57.5)	91–92 (0.85)[a]	$n^{29}D$ 1.5860				
IIb (0.016)		155–160 (2.0 mm)	Fusion		VIb (27.2)	125–126		61.01	3.99	60.78	4.03
Ic (0.064)	0.064	100	DMF	3 days	VIc (29)[b]	79.5–80 (1.0)		64.88	4.23	64.81	4.07
IId (0.06)		Reflux	Acetonitrile	24 hr	VId (71)[c]	63–67 (3.0)[d]	$n^{20}D$ 1.5886				
VIII (0.065)	0.054	Reflux	Acetonitrile	5 days	IX (13.7)	34–35[e]					

[a] Lit.[8] bp 115–118° (1.0 mm) bath temp, $n^{16}D$ 1.5917. [b] In an unsuccessful attempt to obtain VIc, the only product was 1.1 g (9%) of a dimeric acetal, mp 176–178°. Analysis and ir and nmr spectra are in agreement with assigned structure for anhydro di(chlorosalicylaldehyde) (lit.[16] mp 172°). [c] The acetonitrile is distilled off. Remains are distilled to yield product. [d] Lit.[11] bp 49.5–50.0° (1.0 mm), $n^{20}D$ 1.5879. [e] Purification by sublimation at 60° (0.05 mm) (lit.[9] mp 40–41.5°).

heated to reflux for 5 days, cooled to room temperature, poured into 1 l. of a 10% sodium hydroxide solution, and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled affording 5.75 g (57.5%) of 8-methoxy-2H-1-benzopyran (VIa): bp 91–92° (0.85 mm); $n^{29}D$ 1.5860 (lit.[8] bp 115–118° (1.0 mm), bath temperature; $n^{16}D$ 1.5917). The ir and nmr data may be found in Table II; the reaction conditions employed and, in case the product is a new compound, the analyses may be found in Table III.

Fused Reaction. Preparation of 6-Nitro-2H-1-benzopyran (VIb).—5-Nitrosalicylaldehyde (5 g, 0.03 mol) was added slowly to a stirred mixture of 2.9 g of a sodium hydride dispersion in mineral oil (52% NaH, 1.5 g, 0.0625 ml) and 100 ml of ether. After the gas evolution abated, the reaction mixture was cooled to ice-bath temperature and filtered under a nitrogen cover. The precipitated sodium salt of nitrosalicylaldehyde was washed with cold ether and dried over night. Salt III (6.3 g, 0.017 mol) was intimately blended with 3.0 g (0.016 mol) of the sodium salt of IIb and heated *in vacuo* in a sublimer. At 155–160° (2.0 mm), a yellow solid was collected on the cold finger of the sublimer which upon recrystallization from methanol afforded 0.76 g (27.2%) of 6-nitro-2H-1-benzopyran, mp 125–126°. Analysis is found in Table III.

(16) W. P. Bradley and F. B. Dains, *Amer. Chem. J.*, **14**, 293 (1892).

The preparation of 4-methyl-2H-1-benzopyran and 4-phenyl-2H-1-benzopyran has been attempted by two workers more than ten times (in each case) using both the synthetic procedures described above.

In the case of the 4-methyl-2H-1-benzopyran, the vapor phase chromatogram showed a small peak of a compound boiling higher than DMF but lower than the starting material. The amount of material was too small to allow identification of this product. A trace amount of triphenylphosphine oxide was identified by melting point and ir spectrum. The presence of it indicates that the products are formed but only in very small yields.

In the case of 4-phenyl-2H-1-benzopyran, the vapor phase chromatogram also showed a peak which would be assumed to originate from the product, but the amount was too small to allow positive identification. A trace amount of isolated triphenylphosphine oxide hints toward a reaction in very low yield.

Registry No.—VIa, 16336-25-7; VIb, 16336-26-8; VIc, 16336-27-9; VId, 254-04-6; IX, 229-80-1.

Acknowledgment.—This investigation was supported by a Public Health Service Grant GM 12692-01 for which we are most grateful.

The Selective Reduction of the Carbobenzoxy Group in Carbobenzoxyamino Acid and Peptide *p*-Nitrophenyl Esters

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The N-carbobenzoxy group of *p*-nitrophenyl esters of N-carbobenzoxyamino acids and N-carbobenzoxy peptides can be removed by catalytic hydrogenation in the presence of 1 equiv of hydrochloric acid without noticeable reduction of the nitro group. This method can be used for preparing oligo peptides by Goodman's "backing-off" procedure and for preparing polyamino acids and sequential polypeptides when the *t*-butyl ester groups are present.

Removal of the N-carbobenzoxy group from N-carbobenzoxyamino acid and N-carbobenzoxy peptide *p*-nitrophenyl esters is usually achieved by treatment with hydrogen bromide in glacial acetic acid,[1] since catalytic hydrogenation is expected to reduce the nitro group under the usual conditions. In the case of trifunctional amino acids, where, in addition to the N-carbobenzoxy group, an acid-sensitive group such as the *t*-butyl group[2] is also present, the hydrogen bromide method cannot be used.

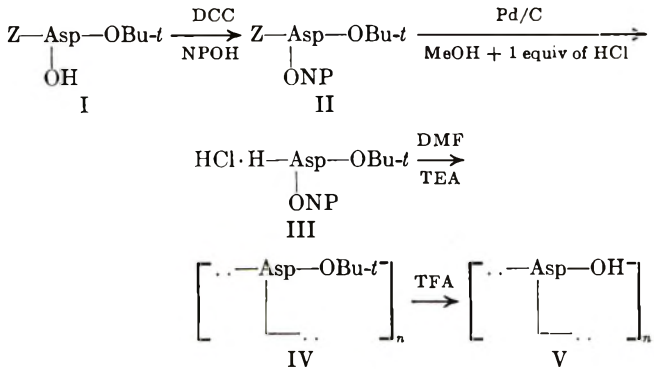
In this paper, a method is described for the selective removal of the N-carbobenzoxy group by catalytic hydrogenation from N-carbobenzoxyamino acid and N-carbobenzoxy peptide *p*-nitrophenyl esters, without noticeable reduction of the nitro group. This method can be used with the "backing-off" procedure of Goodman[3] as well as for preparing C-activated peptides or amino acids where *t*-butyl containing trifunctional amino acids are present. These C-activated peptides and amino acids can, in turn, be polymerized to sequential polypeptides and polyamino acids.

This selective catalytic hydrogenation procedure was studied on N-carbobenzoxyglycine *p*-nitrophenyl ester, N-carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester, N-carbobenzoxy-α-*t*-butyl-L-glutamic acid *p*-nitrophenyl ester, and N-carbobenzoxy-L-phenylalanylglycine *p*-nitrophenyl ester. The procedure was best illustrated by the preparation of α-*t*-butyl-L-aspartic acid *p*-nitrophenyl ester hydrochloride and the polym-

(1) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(2) G. W. Anderson and F. M. Callahan, *J. Amer. Chem. Soc.*, **82**, 3359 (1960).

(3) M. Goodman and K. C. Steuben, *ibid.*, **81**, 3980 (1959).



erization of this active ester to the corresponding polyamino acid derivative.

N-carbobenzoxy-L-aspartic acid *p*-nitrophenyl ester (II), prepared from the corresponding free acid I by the carbodiimide[4,5] method, was hydrogenated with prehydrogenated palladium catalyst in a methanolic suspension in the presence of 1 equiv of hydrogen chloride. The rate of removal of the N-carbobenzoxy group under these conditions is much faster than the rate of reduction of the nitro group. The reaction was usually complete within 5 min.[6] It was important to complete the reaction and to isolate the active ester hydrochloride within the shortest period of time to avoid side reactions. The hydrochloride salt III, which was obtained in 90% yield, analyzed correctly and showed strong peaks which are characteristic for *p*-nitrophenyl ester, *t*-butyl ester, and nitro groups in its infrared spectrum. Further evidence for structure III was provided by polymerization of this compound to poly-α-*t*-butyl-L-aspartate (IV). Polypeptide IV, which has a molecular weight of 17,000 as determined by the sedimentation equilibrium[7] method was converted into poly-β-L-aspartic acid (V) by the usual treatment with trifluoroacetic acid. After extensive dialysis and lyophilization, the poly-β-L-aspartic acid was obtained as a white fluffy material which had an infrared spectrum identical with a sample prepared by another method.[8,9] The molecular weight was 8000 as determined by the sedimentation equilibrium[7] method.

The selective removal of the N-carbobenzoxy group from N-carbobenzoxyglycine *p*-nitrophenyl ester,[10] N-carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester,[11] and N-carbobenzoxy-α-*t*-butyl-L-glutamic acid *p*-nitrophenyl ester was carried out as described above. Under normal catalytic hydrogenation conditions, when much more than half of the theoretical amount of hydrogen was absorbed (see Experimental Section), N-carbobenzoxyglycine *p*-nitrophenyl ester gave glycine *p*-aminophenyl ester dihydrochloride.

The dipeptide, N-carbobenzoxy-L-phenylalanylglycine *p*-nitrophenyl ester, prepared from N-carbobenzoxy-L-phenylalanine and glycine *p*-nitrophenyl ester hydrochloride or glycine *p*-nitrophenyl ester hydrobromide using the mixed anhydride coupling procedure, gave, after the above-described catalytic hydrogenation, the dipeptide active ester hydrochloride in 80% yield.

Experimental Section

All melting points are uncorrected. The microanalyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined in potassium bromide pellets using a Perkin-Elmer Model 137 spectrophotometer.

N-Carbobenzoxy-α-*t*-butyl-L-aspartic Acid *p*-Nitrophenyl Ester (II).—A suspension of 45 g (0.14 mol) of N-carbobenzoxy-α-*t*-butyl-L-aspartic acid,[12] 31.5 g (0.153 mol) of dicyclohexylcarbodiimide, and 19.4 g (0.139 mol) of *p*-nitrophenol in 250 ml of methylene chloride was stirred at 0° for 3 hr and overnight at room temperature. Ten drops of acetic acid were added and the mixture was stirred for an additional 30 min. The dicyclohexylurea was filtered and the filtrate was concentrated under reduced pressure. The product was an oil (61 g) which solidified after 2 hr under high vacuum. The solid was dissolved in hot ethyl acetate. The solution was cooled to room temperature and filtered to remove additional dicyclohexylurea. The filtrate was concentrated under vacuum and the solid residue recrystallized from 90 ml of hot ethanol to yield 42 g (68%): mp 79.5–80°; $[\alpha]^{23}D$ 30.9° (*c* 2, chloroform); ir peaks at 5.7 (active ester), 6.59 and 7.4 (nitro), and 5.9 μ (carbobenzoxy).

Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.45; H, 5.44; N, 6.31. Found: C, 59.42; H, 5.55; N, 6.54.

α-*t*-Butyl-L-aspartic Acid *p*-Nitrophenyl Ester Hydrochloride (III).—To a prehydrogenated suspension of 100 mg of 10% palladium on charcoal in 60 ml of absolute methanol, 2.3 g (5.18 mmol) of II and 1.46 ml of absolute methanol containing 190 mg (5.22 mmol) of hydrogen chloride were added. Hydrogenation was continued for 5 min, at which time the measured amount of hydrogen absorbed was only one half the theoretical amount (57 ml). The reaction mixture was filtered and the filtrate was concentrated to 2 ml under reduced pressure. Anhydrous ether was added to the turbidity point. After standing overnight at −7°, the crystalline product was filtered, washed with anhydrous ether, and dried under vacuum to yield 1.7 g (94.2%), mp 139° dec. Recrystallization from methanol–ether raised the melting point to 146° dec and yielded 1.6 g (90%), $[\alpha]^{23}D$ 14° (c 1.37, dimethylformamide). The infrared spectrum showed peaks at 5.7 (active ester), 6.55 and 7.4 μ (nitro); the carbobenzoxy peak was absent at 5.9 μ.

Anal. Calcd for $C_{14}H_{19}ClN_2O_6$: C, 48.48; H, 5.52; Cl, 10.24; N, 8.09. Found: C, 48.76; H, 5.46; Cl, 10.85; N, 8.51.

Poly-α-*t*-butyl-L-aspartate (IV).—A mixture of 1.3 g (3.67 mmol) of III, 3 ml of purified dimethylformamide,[13] and 0.51 ml (3.67 mmol) of purified triethylamine[13] was shaken for 2 days at room temperature. The reaction mixture was diluted with 500 ml of ether and filtered. The solid residue was washed with water to remove triethylamine hydrochloride, with methanol to remove the low molecular weight polymer (29.3%), and finally with ether. The product was dried for 16 hr at 60° (0.1 mm) to yield 116 mg (17%). The infrared spectrum showed peaks at 6.0 (amide I), 6.5 (amide II), and 11.7 μ (*t*-butyl). The molecular weight was 17,000 as determined by the sedimentation equilibrium method.[7] Measurements were made using concentrations in the range of 0.2–0.5% in dimethylacetamide at 26° and a Schieren angle of 75°.

Anal. Calcd for $(C_8H_{13}NO_3)_n$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.43; H, 7.67; N, 8.26.

(4) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

(5) H. C. Khoranna, *Chem. Ind.* (London) 1087 (1955).

(6) The reaction was complete when it was observed that one-half of the theoretical amount of hydrogen had been absorbed. During this time the same volume of carbon dioxide was liberated; however, it is partially soluble in the solvent system; therefore the measured amount of hydrogen absorbed is not a true indication of the completeness of the reaction.

(7) H. K. Schachman, "Ultracentrifuge in Biochemistry," Academic Press Inc., New York, N. Y., 1955.

(8) J. Kovacs, R. Ballina, and R. L. Rodin, *Chem. Ind.* (London), 1955 (1963).

(9) J. Kovacs, R. Ballina, R. L. Rodin, D. Balasubramanian, and J. Applequist, *J. Amer. Chem. Soc.*, **87**, 119 (1965).

(10) M. Bodanszky, *Nature*, **175**, 685 (1955); B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 373 (1957).

(11) M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 6072 (1959).

(12) This compound was prepared in this laboratory by U. R. Ghatak and G. N. Schmit through the esterification of N-carbobenzoxy-β-methyl-L-aspartic acid with isobutylene in dichloromethane solution in presence of a catalytic amount of sulfuric acid. Selective alkaline hydrolysis of the methyl ester group in aqueous dioxane solution gave N-carbobenzoxy-α-*t*-butyl-L-aspartic acid (I) as an oil. The dicyclohexylamine salt of I, mp 119–120° (from aqueous methanol), gave the correct elemental analysis.

(13) Dimethylformamide and triethylamine were treated with 2% N-carbobenzoxyglycine *p*-nitrophenyl ester overnight, filtered, and distilled to remove primary and secondary amines.

Poly-β-L-aspartic Acid (V).—A solution of 145 mg (0.55 mmol) of IV in 2.91 ml of 90% aqueous trifluoroacetic acid was allowed to stand at room temperature for 50 min. The reaction mixture was diluted with 52 ml of anhydrous ether. The precipitate was centrifuged and the supernatant liquid was decanted. The ether washing was repeated three times and the polymer was dried under vacuum to yield 69.3 mg (73%). The polypeptide was dissolved in 5 ml of water and dialyzed against 800 ml of water for 24 hr. The solution was lyophilized and polymer V (36.3 mg, 48%) was recovered. Lack of absorption at 11.7 μ in the infrared spectrum indicated complete removal of the *t*-butyl groups. The molecular weight was 8000 as determined by the sedimentation equilibrium method. The concentrations used were in the range of 0.2–0.5% in 0.1 *M* aqueous lithium chloride at 26° and a Schieren angle of 75°. When water was used as a solvent for polymer V, a molecular weight of 4500 was obtained. This low value was ascribed to a charge effect which was minimized by using 0.1 *M* aqueous lithium chloride as the solvent.

Anal. Calcd for $(C_4H_5NO_3 \cdot {}^1/_2H_2O)_n$: C, 38.71; H, 4.87; N, 11.30. Found: C, 38.26; H, 5.01; N, 11.20.

Glycine *p*-Nitrophenyl Ester Hydrochloride.—A suspension of 1.21 g (3.67 mmol) of N-carbobenzoxyglycine *p*-nitrophenyl ester[10] was hydrogenated within 2 min using the method described above to yield 0.67 g (78.7%), mp 183.5 dec. Recrystallization from methanol–ether did not change the melting point.

Anal. Calcd for $C_8H_9ClN_2O_4$: C, 41.31; H, 3.90; Cl, 15.24; N, 12.04. Found: C, 41.15; H, 3.87; Cl, 15.55; N, 11.80.

Glycine *p*-Aminophenyl Ester Dihydrochloride.—To a prehydrogenated suspension of 100 mg of 10% palladium on charcoal in 2 ml of glacial acetic acid and 80 ml of absolute methanol, 0.4 g (1.21 mmol) of N-carbobenzoxyglycine *p*-nitrophenyl ester, and 1.12 ml of absolute methanol containing 178 mg (4.87 mmol) of hydrogen chloride were added. Hydrogenation was continued for 5 min, during which time an apparent volume of 81.4 ml of hydrogen was absorbed. The reaction mixture was filtered and the filtrate was concentrated to 2 ml under reduced pressure. Anhydrous ether was added to the solution until the turbidity point was reached. The product, which crystallized on standing overnight at −10°, was filtered, washed with anhydrous ether, and dried under vacuum at 78° to yield 0.211 g (74%), mp 237° dec. The absorptions of the carbobenzoxy group at 5.9 and of the nitro group at 6.4 and 7.4 μ were absent in the infrared spectrum.

Anal. Calcd for $C_8H_{12}Cl_2N_2O_2$: C, 40.05; H, 5.38; Cl, 29.56; N, 11.68. Found: C, 39.86; H, 5.18; Cl, 29.60; N, 11.41.

L-Phenylalanine *p*-Nitrophenyl Ester Hydrochloride.—N-Carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester[11] (0.76 g, 1.81 mmol) was hydrogenated in 2 min as described above to yield 0.47 g (80%), mp 187° dec (recrystallization from methanol–ether did not change the melting point), $[\alpha]^{23}D$ 47.0° (*c* 0.995, methanol).

Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.69; Cl, 10.99; N, 8.68. Found: C, 55.50; H, 4.74; Cl, 11.00; N, 8.71.

α-*t*-Butyl-L-glutamic Acid *p*-Nitrophenyl Ester Hydrochloride.—A methanolic suspension of 1.68 g (3.67 mmol) of N-carbobenzoxy-α-*t*-butyl-L-glutamic acid *p*-nitrophenyl ester was hydrogenated, as above, until half of the theoretical amount of hydrogen had been absorbed to yield 1.04 g (77.7%), mp 128° dec. (recrystallization from methanol–ether did not change the melting point), $[\alpha]^{23}D$ 2.3° (*c* 1.89, methanol).

Anal. Calcd for $C_{15}H_{21}ClN_2O_6$: C, 49.93; H, 5.87; Cl, 9.83; N, 7.78. Found: C, 49.79; H, 5.54; Cl, 9.83; N, 7.91.

N-Carbobenzoxy-L-phenylalanylglycine *p*-Nitrophenyl Ester.—N-Carbobenzoxy-L-phenylalanine (0.597 g, 2 mmol) was dissolved in 20 ml of ethyl acetate and the solution was cooled to −20°. N-Methylmorpholine (0.22 ml, 2 mmol) and isobutylchloroformate (0.28 ml, 2.1 mmol) were added consecutively. The mixture was stirred at −20° for 15 min and 0.466 g (2 mmol) of glycine *p*-nitrophenyl ester hydrochloride and 0.28 ml (2 mmol) of triethylamine were also added consecutively and stirring was continued for 1 hr at −20°. The mixture was stored for 2 hr at −10°. The reaction mixture was concentrated under vacuum and then distributed between 80 ml of chloroform and 30 ml of water. The chloroform layer was washed with 30 ml of water, 20 ml of 0.25 *N* sodium bicarbonate, 30 ml of water, 25 ml of 0.5 *N* hydrochloric acid, and three times with 30 ml of water. The solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was crystallized from absolute ethanol to yield 0.701 g (73.5%): mp 182–183°; $[\alpha]^{23}D$ −19.8° (*c* 1, dimethylformamide); ir peaks at 5.7 (active ester), 6.0 (amide I), 6.45 (amide II), and 7.4 μ (nitro group).

Anal. Calcd for $C_{25}H_{23}N_3O_7$: C, 62.89; H, 4.86; N, 8.80. Found: C, 62.80; H, 4.95; N, 8.71.

N-Carbobenzoxy-L-phenylalanylglycine *p*-nitrophenyl ester was also prepared using glycine *p*-nitrophenyl ester hydrobromide to yield 2.84 g (77.76%): mp 182–183°, $[\alpha]^{23}D$ −19.2° (*c* 1.92, dimethylformamide).

L-Phenylalanylglycine *p*-Nitrophenyl Ester Hydrochloride.—A suspension of 0.3 g (0.63 mmol) of N-carbobenzoxy-L-phenylalanylglycine *p*-nitrophenyl ester was hydrogenated within 2 min using methanol as described above to yield 0.2 g (83.9%), mp 183.5–184.5° dec. (recrystallization from methanol–ether did not change the melting point), $[\alpha]^{23}D$ 19.6° (*c* 1, methanol).

Anal. Calcd for $C_{17}H_{18}ClN_3O_5$: C, 53.76; H, 4.78; Cl, 9.34; N, 11.06. Found: C, 53.66; H, 5.10; Cl, 9.23; N, 10.52.

Registry No.—II, 6997-15-5; III, 16336-34-8; glycine *p*-nitrophenyl ester hydrochloride, 16336-29-1; glycine *p*-aminophenyl ester dihydrochloride, 16336-30-4; L-phenylalanine *p*-nitrophenyl ester hydrochloride, 16336-31-5; α-*t*-butyl-L-glutamic acid *p*-nitrophenyl ester HCl, 16336-35-9; N-carbobenzoxy-L-phenylalanylglycine *p*-nitrophenyl ester, 16336-36-0; L-phenylalanylglycine *p*-nitrophenyl ester hydrochloride, 16336-32-6.

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Cycloserine Peptides[1]

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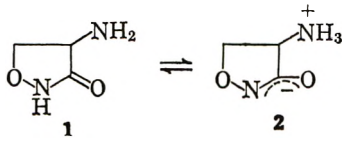
The synthesis of glycyl-DL-cycloserine, DD,LL-alanylcycloserine, and DL,LD-alanylcycloserine has been accomplished. A cycloserine derivative having the isoxazolidone ring blocked by a trityl group was prepared and shown to be a key intermediate in the synthesis of these compounds.

Our long-standing interest in the chemistry of cycloserine and its derivatives has led us to investigate the synthesis of cycloserine peptides. It has been established[3] that D-cycloserine (**1**) inhibits the incorporation of D-alanine into the cell wall peptide of certain bacteria by inhibition of L-alanine racemase and D-Ala-D-Ala synthetase enzymes. It was our intention to synthesize D-Ala-D-CS (CS = cycloserine) in order to determine its potential as an inhibitor of the synthetase enzyme and the results of these efforts are reported in this paper.

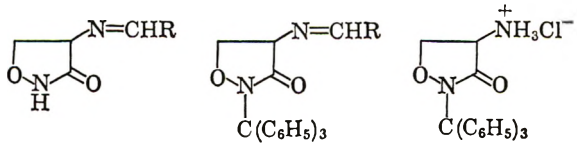
Several attempts to acylate cycloserine with appropriately derivatized amino acids gave complex mixtures which were not resolved. This result, apparently, is due to the fact that cycloserine exists to a large extent as the zwitterion,[4] **2**, making not only the



1 **2**

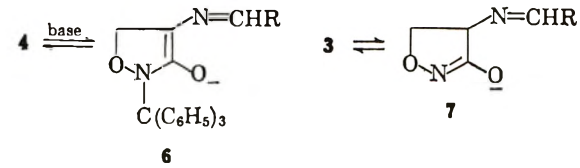
amino group, but also the centers of negative charge in the ambident cyclic hydroxamic acid anion available for acylation. Derivatization, then, at either of these two anionic sites should leave only the amino group available to an acylating agent. The sensitivity of the isoxazolidone ring to hydrogenolysis and to hydrolysis in acid media[5] precluded the use of many protecting groups commonly used in peptide synthesis. We found, however, that the ring was stable to anhydrous hydrogen bromide in acetic acid and to hot 50% aqueous acetic acid, reagents used to remove the trityl protecting group. The desired cycloserine derivative was, then, a ring-tritylated compound.

In some earlier work, we had prepared some 2-alkylated cycloserines; thus, a synthetic sequence, shown below, was already in hand for the preparation of a 2-trityl cycloserine. The Schiff base[6] **3** (R = 5-



3 **4** **5**

cyclosalicylidene) was tritylated rapidly in acetone with potassium carbonate as acid scavenger giving the trityl compound **4**. An infrared band at 1710 cm^{-1} in the spectrum of this product was consistent with the N-alkylated structure **4**, since O-alkylation would require the presence of an azomethine group (–N=C–) absorbing at lower frequency. Consistent with our earlier work[6] on the acetylation of **3**, was the finding that the 2-trityl compound **4** was completely racemized during the tritylation. Although thermal racemization of **3** was quite slow[6] and its racemization in the presence of bases was somewhat faster,[7] the 2-substituted Schiff bases racemized at rates comparable to their rates of formation. This is apparently due to rapid enolization of the carbonyl group giving the new enol anion **6** and destroying the steric integrity



6 **7**

of the asymmetric center at the 4 position.[8] Enolization of this type is kinetically unfavorable in **3** since the formation of enolate **7** is preferred; consequently, **3** is racemized much more slowy than **4**.

The racemic Schiff base **4** was then readily converted into the desired blocked cycloserine **5** by careful acid hydrolysis. The treatment of **5** with *ca.* 1 *N* HBr in glacial acetic acid gave, as shown by paper chromatography, cycloserine as the sole product.[9] With **5** in hand we had the blocked cycloserine necessary to the successful synthesis of the desired peptides.

We proceeded to couple **5**, using the mixed anhydride procedure,[10] with N-trityl-, N-*t*-butoxycarbonyl- and N-trifluoroacetylglycine. Each of the resulting blocked dipeptides was a crystalline, readily characterizable substance having acceptable elemental analyses[11] and spectra consistent with the proposed structures **8**. Both **8a** and **b** were smoothly converted into the

(1) This work was supported by a National Aeronautics and Space Administration Traineeship and is extracted from the thesis of R. A. P. which was submitted in partial fulfillment of the requirements for a Master of Science degree, University of Georgia, 1967.

(2) To whom inquiries should be addressed.

(3) (a) J. L. Strominger, R. H. Threnn, and S. S. Socti, *J. Amer. Chem. Soc.*, **81**, 3803 (1959); (b) E. Ito and J. L. Strominger, *J. Biol. Chem.*, **237**, 2696 (1962).

(4) J. B. Nielands, *Arch. Biochem. Biophys.*, **62**, 151 (1956).

(5) F. A. Kuehl, *et al.*, *J. Amer. Chem. Soc.*, **77**, 2344 (1955); P. H. Hidy, *et al.*, *ibid.*, 2345 (1955).

(6) C. H. Stammer and J. D. McKinney, *J. Org. Chem.*, **30**, 3436 (1965).

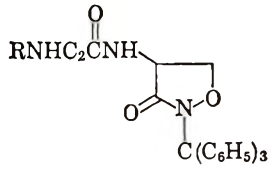
(7) Unpublished results.

(8) The asymmetric center in **4** is flanked by carbonyl and azomethine groups as is the asymmetric center of azlactones. M. Goodman and coworkers (Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 345) have shown that these compounds very rapidly racemize in the presence of bases.

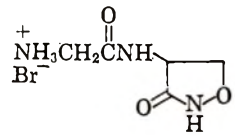
(9) If the HBr concentration was too high or the deblocking reaction was allowed to proceed too long, a second ninhydrin positive material was formed which had the same R_f as serine amide. Since it is difficult, mechanistically, to rationalize the formation of this product from cycloserine and HBr/HOAc, we are investigating this further.

(10) N. Izumiya and J. P. Greenstein, *Arch. Biochem. Biophys.*, **52**, 203 (1954).

(11) A great deal of difficulty was experienced in obtaining acceptable values on 2-trityl cycloserine derivatives. Since the completion of this work, we have found that purification of **5** through its free base reduces these problems.



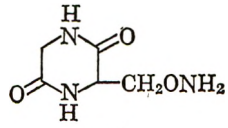
8a, R = *t*-BOC
b, R = $(C_6H_5)_3C$—
c, R = CF_3C(=O)—



9

crystalline dipeptide hydrobromide **9** with HBr–HOAc, as expected. Attempts to remove only the *t*-butoxycarbonyl (*t*-BOC) group from **8a** using hydrogen chloride in aprotic solvents failed to afford tractable products and the deblocking of **8c** in basic solution also failed. We had hoped to prepare the 2-trityl dipeptide by these means so that the peptide chain might be extended before detritylation. We did find that **9** itself could be benzoylated, albeit in low yield, using the standard Schotten–Baumann benzoylation conditions giving N-benzoylglycyl-DL-cycloserine. Possibly the peptide chain can be extended by direct acylation of **9** at high pH using the appropriate amino acid derivatives.

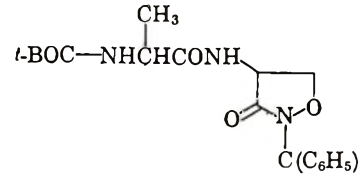
The dipeptide hydrobromide **9** rapidly cyclized at room temperature to the aminoxymethyl-2,5-piperazinedione (**10**) when neutralized with Amberlite IR-4B,



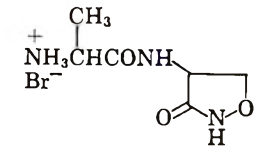
10

a weakly basic resin. This rearrangement was not altogether unexpected, since it is known that dipeptide esters[12] also slowly ring close to give piperazinediones.[13] The high rate at which **9** was converted[14] into **10** is another indication of the acylating power of the isoxazolidone ring. The piperazine derivative **10** was readily characterized by spectral and analytical data and the presence of the aminoxy function was shown by its conversion into a *p*-nitrobenzylidene derivative.

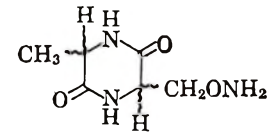
The required "protected" cycloserine (**5**) now in hand, we attacked the problem of alanylcycloserine synthesis. This was, of course, complicated by the fact that our blocked cycloserine was racemic and would afford diastereomeric mixtures on coupling with both active and racemic amino acid derivatives.[15] When **5** was coupled with *t*-BOC-DL-alanine, two racemic diastereomers were obtained, **11a** and **b**, each of which could be deblocked to give an alanylcycloserine salt, **12a** and **b**. Two 2,5-piperazinediones, **13a** and **b**, were formed when these dipeptide salts were neutralized. We tentatively assigned the *cis* configuration to **13a** and the *trans* configuration to **13b** based on an examination of Dreiding models and a comparison of melting points. We might expect the higher melting diastereomer (**13a**)



11a, mp 164°
b, mp 248°



12a, b



13a, mp >300°
b, mp 196°

to have the more symmetrical molecule. The large amount of double-bond character[16] in the amide C–N bond causes the 2,5-piperazinedione ring to exist in a quasi-boat conformation which places the 3 and 6 substituents in either quasi-axial or quasi-equatorial positions. In *cis* **13**, then, the 3,6 substituents should both reside in *quasi*-equatorial[17] conformations giving a more symmetrical structure than *trans* **13** which necessarily has one substituent quasi-equatorial and the other *quasi*-axial. Thus **13a**, the high melting isomer, should have the *cis* configuration.[18] Further work supported this assignment.

When *t*-BOC-D-alanine was coupled with 2-trityl-DL-cycloserine (**5**), a mixture of diastereomeric peptides was again obtained. These were not separable by fractional crystallization and the mixture was converted directly through deblocking and resin treatment into a mixture of piperazinediones. Recrystallization of this mixture afforded a product melting at about 300°, $[\alpha]D$ +21.3°. The high melting point of this material indicates a *cis* configuration and the positive optical rotation supported this conclusion, since the dimer of D-cycloserine, *cis*-3,6-bisaminoxymethyl-2,5-piperazinedione, also has a positive rotation.[19] If these structural assignments are correct, then the blocked dipeptide **11a** must be the DD,LL racemate and **11b** is the DL,LD racemate.

The recent work of Halpern and coworkers[20] provided confirmation for these assignments. We found that the methyl resonances of **11a** and **b** occurred at 74 and 70 cps, respectively, indicating that **11a** was the DD,LL isomer since its methyl resonance was the more deshielded. Thus, the three pieces of evidence used to deduce the configurations of the alanyl dipeptides, **12a** (DD,LL) and **b** (DL,LD), are consistent and constitute

(12) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961, p 796.

(13) The rapid formation of **10** from **9** at neutral pH also tends to support an earlier speculation[6] that an aminoxyalanylcycloserine derivative is intermediate in cycloserine dimer formation.

(14) The eluate from the resin column was ninhydrin negative almost immediately after collection.

(15) For biological testing purposes, however, we felt it advantageous to make all the possible isomers.

(16) R. C. Elderfield, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N.Y., 1957, p 440.

(17) The models show large "flagpole–flagpole" interactions when the substituents are quasi-axial.

(18) A recent report by K. D. Kopple and D. H. Marr, *J. Amer. Chem. Soc.*, **89**, 6193 (1967), indicates that in 3-benzyl-2,5-piperazinediones the piperazine ring is flat. This may be due to interactions peculiar only to this system and does not invalidate our arguments invoking the symmetry of the *cis* and *trans* isomers, **13a** and **b**.

(19) H. Brockmann and H. Musso [*Chem. Ber.*, **89**, 241 (1965)] reported a positive rotation for *cis*-DD-3,6-dimethyl-2,5-piperazinedione (from D-alanine) and a melting point (288–290°) greater than that of the *trans* compound (277–278°).

(20) B. Halpern, L. F. Chew, and B. Weinstein, *J. Amer. Chem. Soc.*, **89**, 5051 (1967); B. Halpern, D. E. Nitecki, and B. Weinstein, *Tetrahedron Lett.*, 3075 (1967). In some ten dipeptides, these workers found the DD,LL isomers to have the alanine methyl resonance some 5–10 cps downfield of the DL,LD compound.

a strong case for our assignments. We were unable to characterize **12a** and **b**, other than through their conversions into piperazinediones **13a** and **b** since the dipeptides were amorphous highly hydroscopic solids.

Experimental Section

N-(5-Chlorosalicylidene)-D-cycloserine,[6] N-triphenylmethylglycine,[21] N-*t*-butoxycarbonylglycine,[22] N-*t*-butoxycarbonyl-DL-alanine,[22] N-*t*-butoxycarbonyl-D-alanine,[21] and N-trifluoroacetylglycine[23] were prepared according to known methods. All melting points were taken on a Nalge hot stage and are corrected. Infrared spectra were determined either on a Perkin-Elmer Model 137 or Model 237B spectrometer; ultraviolet spectra were determined on a Perkin-Elmer Model 202 ultraviolet-visible spectrometer; and nmr spectra were determined on a Varian Associates Model A-60 nmr spectrometer. All microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

N-(5-Chlorosalicylidene)-2-triphenylmethyl-DL-cycloserine (4).—To a solution of 4.82 g (20 mmol) of N-(5-chlorosalicylidene)-D-cycloserine in 100 ml of purified acetone[24] in a 250-ml, round-bottomed flask stirred magnetically and protected with a Drierite tube was added 3.04 g (22 mmol) of anhydrous powdered potassium carbonate. The suspension was stirred at room temperature for 5 min, 6.14 g (22 mmol) of triphenylmethyl chloride was added, and stirring was continued at room temperature for 2.5 hr. The resulting suspension was centrifuged and the supernatant liquid was concentrated to an oil *in vacuo*. The residual oil was dissolved in *ca.* 50 ml of anhydrous ether from which crystals immediately began to form. Filtration gave 7.43 g of yellow prisms, mp 155–167°. The filtrate afforded a second crop weighing 0.75 g (87% total yield). An analytical sample was prepared by recrystallization from acetone–methanol: mp 166–167°; uv ($CHCl_3$), 246 mμ (ε 15,090), 256 (13,140), and 339 (4702); ir (Nujol), 1710 (C=O), 1625 (C=N), 825 (C–Cl), 750–650 cm^{-1} (aromatic); nmr ($CDCl_3$), δ 4.4 (m, 3, cycloserine ring), 6.9 (d, 3), 7.3 (m, 15, $(C_6H_5)_3C$–), and 8.22 ppm (s, 1, –CH=). *Anal.* Calcd for $C_{29}H_{23}N_2O_3Cl$: C, 72.21; H, 4.77; N, 5.81; Cl, 7.31. Found: C, 71.89; H, 4.72; N, 6.10; Cl, 7.52.

2-Triphenylmethyl-DL-cycloserine Hydrochloride (5).—To a solution of 4.71 g (9.78 mmol) of N-(5-chlorosalicylidene)-2-triphenylmethyl-DL-cycloserine in 200 ml of dry DME[25] stirred magnetically was added dropwise 0.89 ml (11 mmol) of concentrated hydrochloric acid. The solution was stirred at ambient temperature for 30 min while the color changed from deep to light yellow and was evaporated to dryness *in vacuo* giving a yellow amorphous solid which was subsequently stirred magnetically in 100 ml of dry ether for 3 hr. Filtration gave 3.48 g (94% yield) of white amorphous solid.

An analytical sample was necessarily prepared by adding 0.38 g (1.0 mmol) of the product to 20 ml of 1% aqueous sodium bicarbonate and extracting the mixture with three 20-ml portions of methylene chloride. The combined organic layers were washed with 10 ml of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of dry ether. The solution was cooled in an ice bath and anhydrous hydrogen chloride was passed over the surface of the cold solution causing a white precipitate to form immediately. The suspension was stirred for 5 min and filtered giving 0.22 g (58% yield) of white amorphous solid. A sample was recrystallized from methanol–ether for analysis: mp 149–152°, uv (CH_3OH), 210 mμ (ε 27,280), 237 (9120), and 265 (3294); ir (Nujol), 1700 (C=O), and 800–650 cm^{-1} (aromatic); nmr (acetone-d_6–D_2O), δ 5.5 (m, 3, cycloserine ring) and 7.3 ppm (m, 15, $(C_6H_5)_3C$–). *Anal.* Calcd for $C_{22}H_{21}N_2O_2Cl$: C, 69.37; H, 5.56; N, 7.36; Cl, 9.31. Found: C, 69.09; H, 5.84; N, 7.21; Cl, 9.07.

An acceptable analysis could not be obtained by several recrystallizations from methanol–ether of the crude hydrolysis product.

N-*t*-Butoxycarbonylglycyl-2-triphenylmethyl-DL-cycloserine (8a).—To a solution of 1.05 g (6.0 mmol) of *t*-butoxycarbonylglycine in 150 ml of dry ethyl acetate in a 250-ml, round-bottomed flask protected with a "Drierite" tube, stirred magnetically and held at −10°, was added 0.93 ml (6.6 mmol) of triethylamine and 0.87 ml (6.6 mmol) of isobutyl chloroformate. A white precipitate formed immediately and the suspension was stirred at −10° for 30 min. To this suspension was added 2.28 g (6.0 mmol) of 2-triphenylmethyl-DL-cycloserine hydrochloride and 0.87 ml (6.2 mmol) of triethylamine, the ice bath was removed, and the suspension was stirred at room temperature for 18 hr. The precipitated triethylamine hydrochloride (1.74 g) was removed by filtration. The filtrate was concentrated to an oil *in vacuo* which was dissolved in *ca.* 25 ml of dry ether. The white crystals which formed were collected by filtration (2.90 g, 96% yield), mp 204–206°. An analytical sample was prepared by recrystallization from DME–petroleum ether (bp 30–60°): mp 201–203°; ir (Nujol), 1715 (C=O, ring), 1695 (C=O, urethan), 1670 (C=O, amide I), 1550 (amide II), and 775–675 cm^{-1} (aromatic); nmr (acetone-d_6), δ 1.4 (s, 9, $(CH_3)_3C$–), 3.7–4.5 (m, 5, cycloserine ring and $-CH_2-$) and 7.3 ppm (m, 15, $(C_6H_5)_3C$–). *Anal.* Calcd for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.11; H, 6.40; N, 8.43.

N-Triphenylmethylglycyl-2-triphenylmethyl-DL-cycloserine (8b).—A solution of 2-triphenylmethyl-DL-cycloserine free base in dry[26] ethyl acetate was prepared by adding 0.38 g (1.0 mmol) of 2-triphenylmethyl-DL-cycloserine hydrochloride to 20 ml of 1% aqueous sodium bicarbonate and extracting the mixture with four 20-ml portions of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 20 ml of dry ethyl acetate and the solution was filtered before use. Simultaneously with the above procedure, 0.32 g (1.0 mmol) of N-triphenylmethylglycine was dissolved in 25 ml of dry ethyl acetate in a 50-ml round-bottomed flask protected from moisture with a Drierite tube and stirred magnetically. This solution was cooled to −10° and 0.154 ml (1.1 mmol) of triethylamine and 0.145 ml (1.1 mmol) of isobutyl chloroformate was added. A precipitate formed immediately and the mixture was stirred for 20 min at −10°. The precipitated triethylamine hydrochloride was removed by filtration and washed with 15 ml of dry ethyl acetate. To the combined filtrate and washing in a 100-ml, round-bottomed flask protected with a Drierite tube and magnetically stirred was added the above solution of 2-triphenylmethyl-DL-cycloserine and the resulting solution was stirred for 20 hr at ambient temperature during which time the product crystallized. Filtration afforded 0.43 g (67% yield) of white crystals, mp 250–253°. A second crop weighed 0.05 g (75% yield). An analytical sample was prepared by recrystallization from chloroform–propanol: mp 255–256°; ir (Nujol), 1720 (C=O, ring), 1660 (C=O, amide I), 1520 (amide II), and 800–675 cm^{-1} (aromatic); nmr ($CDCl_3$), δ 3.0 (s, 2, $-CH_2-$), 4.6 (m, 3, cycloserine ring), and 7.3 ppm (m, 30, $(C_6H_5)_3C$–). *Anal.* Calcd for $C_{43}H_{37}N_3O_3$: C, 80.22; H, 5.79; N, 6.53. Found: C, 78.30; H, 5.73; N, 6.80.

N-Trifluoroacetylglycyl-2-triphenylmethyl-DL-cycloserine (8c).—A solution of 2-triphenylmethyl-DL-cycloserine in dry methylene chloride was prepared by adding 0.38 g (1.0 mmol) of 2-triphenylmethyl-DL-cycloserine hydrochloride to 20 ml of 1% aqueous sodium bicarbonate and extracting the mixture with four 20-ml portions of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 20 ml of dry methylene chloride. To this solution in a 50-ml, round-bottomed flask protected with a Drierite tube and stirred magnetically was added 0.17 g (1.0 mmol) of trifluoroacetylglycine and 0.19 g (0.92 mmol) of N,N′-dicyclohexylcarbodiimide. All the solid dissolved immediately and after 2 min a precipitate formed. Stirring was continued at room temperature for 4 hr and the solid, weighing 0.13 g was removed by filtration. The filtrate was evaporated *in vacuo* and 15 ml of ether was added to the residue. An insoluble solid (0.05 g) was removed by filtration and 10 ml of petroleum ether (bp 30–60°) was added to the filtrate causing the formation of 0.38 g (83%) of white crystals, mp 126–131°. An analytical sample

(21) L. Zervas and D. M. Theodoropoulas, *J. Amer. Chem. Soc.*, **78**, 1359 (1956).

(22) R. Schwyzer, P. Sieber, and H. Koppeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

(23) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).

(24) The acetone was purified by refluxing reagent grade acetone over potassium permanganate for 24 hr, distilling it from the potassium permanganate, and drying it over anhydrous potassium carbonate.

(25) DME = 1,2-dimethoxyethane. The DME was dried by refluxing it over and distilling it from sodium.

(26) The ethyl acetate was dried over molecular sieves (Linde Type 4A).

was prepared by recrystallization from benzene–petroleum ether: mp 153–156°; ir (Nujol), 1725 (C=O, ring) 1685 (C=O, acetyl), 1655 (C=O, amide I) 1555 (amide II), 1180 (C–F), and 750–675 cm^{-1} (aromatic); nmr (acetone-d_6), δ 3.0 (s, 2, $-CH_2-$), 4.2 (m, 3, cycloserine ring), and 7.3 ppm (m, 18, $(C_6H_5)_3C-$ and benzene). *Anal.* Calcd for $C_{26}H_{22}N_3O_4F_3 \cdot {}^1/_2C_6H_6$: C, 64.92; H, 4.70; N, 7.83. Found: C, 64.70; H, 5.20; N, 7.93.

The elemental analysis of this compound was a function of the temperature and duration of drying *in vacuo*. Variable amounts of benzene (see nmr data) were apparently present in the analytical samples. The analysis reported here is the most acceptable one obtained.

N-Glycyl-DL-cycloserine Hydrobromide (9). A.—To a stirred suspension of 4.00 g (6.22 mmol) of N-triphenylmethylglycyl-2-triphenylmethyl-DL-cycloserine in 20 ml of glacial acetic acid was added 20 ml of 1 *N* hydrogen bromide[27] in glacial acetic acid. All the solid dissolved within 3 min followed by the immediate precipitation of a granular solid. The suspension was stirred at room temperature for 5 min more and was poured slowly into 300 ml of dry ether which was magnetically stirred. The white suspension was stirred for 30 min at room temperature and filtered, affording 1.50 g (100% yield) of a white, amorphous, hygroscopic solid. Further purification was obtained by dissolving the solid in 30 ml of dry ethanol and slowly adding 75 ml of dry ether, causing the precipitation of 1.25 g of amorphous solid; the ir spectrum (Nujol) showed bands at 1725 (C=O, ring), 1690 (C=O, amide I), and 1555 cm^{-1} (amide II).

B.—To a stirred suspension of 2.00 g (4.0 mmol) of N-*t*-butoxycarbonylglycyl-2-triphenylmethyl-DL-cycloserine in 20 ml of glacial acetic acid in a 50-ml erlenmeyer flask was added 13 ml of 1 *N* hydrogen bromide in glacial acetic acid. All the solid did not dissolve before a granular solid precipitated. The suspension was stirred at room temperature for 5 min and was poured slowly into 300 ml of dry ether magnetically stirred. The white suspension was stirred for 1 hr at room temperature and filtered, affording 1.04 g (108% yield) of slightly pink, amorphous, hygroscopic solid. The infrared spectrum of a sample obtained by dissolving the crude product in ethanol followed by addition of ether was identical with that of the sample from procedure A.

N-Benzoylglycyl-DL-cycloserine.—To 3.4 ml (3.3 mmol) of 0.965 *N* aqueous sodium hydroxide in a round-bottomed flask was added 240 mg (1 mmol) of N-glycyl-DL-cycloserine hydrobromide. To this solution was added 0.13 ml (1.1 mmol) of benzoyl chloride. The flask was stoppered and shaken vigorously for 5 min, during which time heat was evolved. The solution was diluted with 7 ml of water, extracted with two 15-ml portions of ethyl acetate, and diluted with 10 ml of ethanol. After 1 hr, the solvent was removed *in vacuo*, the residue as dissolved in 10 ml of water, acidified to pH 4.5 with acetic acid, and extracted with two 10-ml portions of ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated *in vacuo* giving 0.11 g (42% yield) of a white solid, mp 173–177°. An analytical sample was prepared by several recrystallizations from ethanol: mp 196–198°; ir (Nujol), 1695 (C=O, ring), 1650 (C=O, amide I, peptide), 1635 (C=O, amide I, aromatic), and 1530 cm^{-1} (amide II). *Anal.* Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.34; H, 5.26; N, 15.58.

DL-3-Aminoxymethyl-2,5-piperazinedione (10).—A solution of 0.32 g (1.3 mmol) of N-glycyl-DL-cycloserine hydrobromide in 75 ml of water was passed through a neutral column of 15 ml (37.5 mequiv) of Amberlite IR-4B. The column was washed with 75 ml of water and the combined effluents were lyophilized, giving 0.14 g (90% yield) of white powder. An analytical sample was prepared by recrystallization from water–ethanol: mp 300°; ir (Nujol), 1670 (C=O), 1335 (C–O), and 1010 cm^{-1} (N–O). *Anal.* Calcd for $C_5H_9N_3O_3$: C, 37.74; H, 5.70; N, 26.40. Found: C, 37.53; H, 5.94; N, 26.10.

DL-3-[N-(4-Nitrobenzylidene)aminoxymethyl]-2,5-piperazinedione.—A suspension of 97.7 mg (0.614 mmol) of 3-DL-aminoxymethyl-2,5-piperazinedione and 93.0 mg (0.615 mmol) of 4-nitrobenzaldehyde in 5 ml of dry methanol was stirred magnetically for 1 hr at room temperature. The solvent was evaporated *in vacuo*, the residue was dissolved in 6 ml of hot DMF, the solution was centrifuged, and 4 ml of water was added to the supernatant liquid. The white crystals which formed were recrystallized several times from DMF–water: mp 243–244°; ir (Nujol), 1675 (C=O), 1520 (C=N), 1350 (C–O), and 1020 cm^{-1} (N–O).

N-*t*-Butoxycarbonyl-DL-alanyl-2-triphenylmethyl-DL-cycloserine (11a,b).—To a solution of 2.84 g (15 mmol) of *t*-butoxycarbonyl-DL-alanine in 250 ml of dry ethyl acetate in a 500-ml, round-bottomed flask protected from moisture with a Drierite tube, stirred magnetically and held at −10°, was added 2.35 ml (16.5 mmol) of triethylamine and 2.20 ml (16.5 mmol) of isobutyl chloroformate. A white precipitate formed immediately and the suspension was stirred at −10° for 25 min. To this suspension was added 2.35 ml (16.5 mmol) of triethylamine and 5.71 g (15 mmol) of 2-triphenylmethyl-DL-cycloserine hydrochloride, the ice bath was removed, and the suspension was stirred at room temperature for 18.5 hr. The precipitated solid (6.46 g) was removed by filtration and the filtrate was concentrated to an oil *in vacuo*. The residue was dissolved in 25 ml of ether from which 4.60 g (60% of theory) of white crystals formed, mp 164–166°. An analytical sample was prepared by repeated recrystallization from diethylene glycol–dimethyl ether–petroleum ether: mp 191–193°; ir (Nujol), 1755 (C=O, ring), 1680 (C=O, urethan), 1665 (C=O, amide I), 1525 (amide II), and 775–700 cm^{-1} (aromatic); nmr ($CDCl_3$), δ 1.2 (d, 3, $-CH_3$), 1.4 (s, 9, $-CH_3$), 3.0 (m, 1, $-CH=$), 4.5 (m, 3, cycloserine ring), 5.3 (d, 1, urethan NH), 6.85 (broad singlet, 1, amide NH), 7.3 ppm (m, 15, $(C_6H_5)_3C-$). This racemate has been assigned the structure of DD,LL-N-*t*-butoxycarbonylalanyl-2-triphenylmethylcycloserine (**11a**). *Anal.* Calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 68.86; H, 6.77; N, 8.07.

The solid filtered from the reaction mixture was washed with four 50-ml portions of water to remove the triethylamine hydrochloride and dried giving 2.78 g (36% of theory) of a white solid, mp 240–242°. An analytical sample was prepared by repeated recrystallization from DMF–ethanol–water (10:10:2): mp 247–248°; ir (Nujol), 1710 (C=O, ring), 1685 (C=O, urethan), 1665 (C=O, amide I), 1535 (amide II), and 705 cm^{-1} (aromatic); nmr (dimethylsulfoxide-d_6), δ 1.2 (d, 3 $-CH_3$), 1.4 (s, 9, $(CH_3)_3C-$), 4.2 (m, 3, cycloserine ring), 7.3 ppm (s, 15 H, $(C_6H_5)_3C-$). This racemate has been assigned the structure of DL,LD-N-*t*-butoxycarbonylalanyl-2-triphenylmethylcycloserine (**11b**). *Anal.* Calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 69.13; H, 6.58; N, 8.51.

***rac-cis*-3-Aminoxymethyl-6-methyl-2,5-piperazinedione (13a).**—To a suspension of 2.06 g (4.0 mmol) of DD,LL-*t*-butoxycarbonylalanyl-2-triphenylmethylcycloserine (**11a**) in 20 ml of glacial acetic acid stirred magnetically was added 15 ml of 1 *N* hydrogen bromide in glacial acetic acid. The suspension was stirred at room temperature for 5 min and poured slowly into 300 ml of dry ether magnetically stirred. The white suspension was stirred for 1 hr at room temperature and filtered, affording 0.58 g (57% yield) of slightly pink, amorphous, hygroscopic solid. The solid was dissolved in 100 ml of water and passed through a column of 16 ml (40 mequiv) of Amberlite IR-4B. The column was washed with 100 ml of water and the combined effluents were lyophilized giving 0.32 g (81% yield) of a white amorphous solid. An analytical sample was prepared by recrystallization from methanol: mp >300°; ir (Nujol), 1690 (C=O), 1340 (C–O), 1010 cm^{-1} (N–O). *Anal.* Calcd for $C_6H_{11}N_3O_3$: C, 41.62; H, 6.40; N, 24.26. Found: C, 41.90; H, 6.69; N, 24.13.

***rac-cis*-3-[N-(4-Nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione.**—A suspension of 17.3 mg (0.10 mmol) of *rac-cis*-3-aminoxymethyl-6-methyl-2,5-piperazinedione (**13a**) and 15.2 mg (0.10 mmol) of 4-nitrobenzaldehyde in 0.2 ml of water and 5 ml of methanol was stirred magnetically for 1 hr at room temperature. The solvent was evaporated *in vacuo*, the residue was dissolved in 3 ml of hot DMF and centrifuged, and 10 ml of water was added to the supernatant liquid. The white crystals which formed were recrystallized from DMF–water and washed with ethanol: mp 220–222°; ir (Nujol), 1685 (C=O), 1515 (C=N), 1340 (C–O), and 1005 cm^{-1} (N–O). *Anal.* Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 50.45; H, 5.15; N, 18.35.

***rac-trans*-3-Aminoxymethyl-6-methyl-2,5-piperazinedione (13b).**—To a suspension of 1.65 g (3.2 mmol) of DL,LD-N-*t*-butoxycarbonylalanyl-2-triphenylmethylcycloserine (**11b**) in 15 ml of glacial acetic acid stirred magnetically was added 12 ml of 1 *N*

(27) The 1 *N* hydrogen bromide in acetic acid was prepared by diluting 60 ml of 30–32% hydrogen bromide in acetic acid (obtained from Eastern Organic Chemicals, Co.) to 210 ml with glacial acetic acid.

hydrogen bromide in glacial acetic acid. The suspension was stirred at room temperature for 4 min and poured slowly into 225 ml of dry ether which was stirred magnetically. The white suspension was stirred for 1.5 hr at room temperature and filtered, affording 0.55 g (68% yield) of white, amorphous, hygroscopic solid. The solid was dissolved in 100 ml of water and passed through a column of 12 ml (30 mequiv) of Amberlite IR-4B. The column was washed with 100 ml of water and the combined effluents were lyophilized, giving 0.40 g (106% yield) of a white amorphous solid which exhibited a negative halogen test with silver nitrate. An analytical sample was prepared by recrystallization from methanol: mp 195–196°; ir (Nujol), 1690 (C=O), 1330 (C–O), and 1080 cm^{-1} (N–O); nmr (dimethylsulfoxide-d_6), δ 1.3 (d, 3, $-CH_3$), 3.7 (broad multiplet), and 8.1 ppm (broad doublet, –NH). *Anal.* Calcd for $C_6H_{11}N_3O_3$: C, 41.62; H, 6.40; N, 24.26. Found: C, 41.86; H, 6.63; N, 23.98.

rac-trans-**3-[N-(4-Nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione.**—A suspension of 17.5 mg (0.10 mmol) of *rac-trans*-3-aminoxymethyl-6-methyl-2,5-piperazinedione and 15.2 mg (0.10 mmol) of 4-nitrobenzaldehyde in 0.2 ml of water and 5 ml of methanol was stirred magnetically for 1.5 hr at room temperature. The solvent was evaporated *in vacuo*, the residue was dissolved in 2 ml of hot DMF and centrifuged, and water was added to the supernatant liquid until it was slightly turbid. The crystals which formed were recrystallized from DMF–water: mp 244–245°; ir (Nujol), 1680 (C=O), 1665, (C=O, hydrogen bonded), 1335 (C–O), and 970 cm^{-1} (N–O). *Anal.* Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 50.70; H, 4.80; N, 18.24.

N-*t*-Butoxycarbonyl-D-alanyl-2-triphenylmethyl-DL-cycloserine.—To a solution of 2.84 g (15 mmol) of *t*-butoxycarbonyl-D-alanine in 250 ml of dry ethyl acetate in a 500-ml, round-bottomed flask protected from moisture with a Drierite tube, stirred magnetically and held at −10°, was added 2.35 ml (16.5 mmol) of triethylamine and 2.20 ml (16.5 mmol) of isobutyl chloroformate. A white precipitate formed immediately and the suspension was stirred at −5° for 25 min. To this suspension was added 2.35 ml (16.5 mmol) of triethylamine and 5.71 g (15 mmol) of 2-triphenylmethyl-DL-cycloserine hydrochloride, the ice bath was removed, and the suspension was stirred at room temperature for 16.5 hr. The solid, weighing 4.24 g, was removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was dissolved in 25 ml of ether. No crystals formed and the solution was filtered and concentrated to an oil under a stream of anhydrous nitrogen, and the residue was covered with 60 ml of petroleum ether (bp 30–60°). Upon cooling and scratching, the oil solidified giving 7.13 g (92% yield) of a white amorphous solid, $[\alpha]^{27}D$ +9.4° (*c* 2.04, $CHCl_3$). Crystallization attempts from standard solvent systems were unsuccessful.

Optically Active Mixture of DD-*cis*- and LD-*trans*-3-Aminoxymethyl-6-methyl-2,5-piperazinediones.—To a solution of 5.15 g (10 mmol) of crude N-*t*-butoxycarbonyl-D-alanyl-2-triphenylmethyl-DL-cycloserine in 50 ml of glacial acetic acid stirred magnetically was added 35 ml of 1 *N* hydrogen bromide in glacial acetic acid. The solution was stirred for 5 min at room temperature, during which time a precipitate formed. This suspension was poured into 750 ml of dry ether magnetically stirred and the white suspension was stirred for 1 hr at room temperature and filtered affording 1.75 g (69%) of amorphous, hygroscopic solid. The solid (1.5 g) was dissolved in 200 ml of water and passed through a column of 45 ml (112 mequiv) of Amberlite IR-4B. The column was washed with 100 ml of water, and the combined effluents were lyophilized, giving 0.90 g (80% yield) of a slightly yellow amorphous solid. A sample of 0.80 g was dissolved in 30 ml of hot methanol from which 0.44 g (55% recovery) of white crystals formed: mp >300°; $[\alpha]^{28}D$ +19.6° (*c* 1.42, water). A second crop gave 0.08 g of white crystals, $[\alpha]^{28}D$ +19.5° (*c* 1.53, water). The 0.44-g sample was recrystallized from 2.5 ml of water giving 0.30 g of white crystals which were recrystallized from 3 ml of water giving 0.12 g of white crystals, mp >300°, $[\alpha]^{29}D$ +21.3° (*c* 1.7, water); ir (Nujol), 1670 (C=O), 1340 (C–O), and 1000 cm^{-1} (N–O).

Registry No.—**4**, 16561-89-0; **5**, 16561-90-3; **8a**, 16561-91-4; **8b**, 16561-92-5; **8c**, 16561-93-6; **9**, 16561-94-7; **10**, 16561-95-8; **11a**, 16561-96-9; **11b**, 16561-97-0; **13a**, 16561-98-1; **13b**, 16561-99-2; N-benzoylglycyl-DL-cycloserine, 16562-00-8; DL-3-[N-(4-nitrobenzylidene)-aminoxymethyl]-2,5-piperazinedione, 16562-01-9; *rac-cis*-3-[N-(4-nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione, 16562-02-0; *rac-trans*-3-[N-(4-nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione, 16562-05-3; DD-*cis*-3-aminoxymethyl-6-methyl-2,5-piperazinedione, 16562-03-1; LD-*trans*-3-aminoxymethyl-6-methyl-2,5-piperazinedione, 16562-04-2.

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The Synthesis and Characterization of Ring-B Cholestane 3-Oxetanones[1a]

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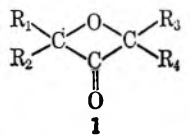
Received December 27, 1967

The synthesis of 5,7β-epoxy-6-oxo-5β-cholestanes has been investigated. These compounds, which are examples of highly substituted 3-oxetanone ring systems, were prepared from C-3-substituted 7α-bromo-5β-hydroxy-6-oxocholestanes. When treated with methanolic potassium hydroxide in dimethyl sulfoxide, the bromo ketones bearing 3β substituents (hydroxy, acetoxy, or benzoyloxy) were converted in good yields (>70%) into 3β-hydroxy-5,7β-epoxy-5β-cholestan-6-one (**7a**). The C-3 epimers of the bromo ketones, as well as the 3-desoxybromo ketone (**11b**), were transformed in very poor yields into the corresponding oxetanones under these conditions. The use of aqueous potassium bicarbonate as the base instead of methanolic potassium hydroxide resulted in retention of acyloxy groups but gave lower yields of oxetanones. Speculation is raised concerning the mechanism of the transformation, especially regarding the nature of the conformational change in the A/B steroid ring system that occurs during the reaction. The α-bromo ketones and oxetanones were examined by nmr spectroscopy in order to characterize accurately the structure of starting materials and products. Although entrance into the 3α-substituted oxetanone series was hindred by the poor yields of these compounds that were obtained from the 3α-substituted α-bromo ketones, a simple method of converting the 3β-hydroxyoxetanone (**7a**) into its 3α epimer (**10a**), and also to the 3-desoxyoxetanone **12**, has been developed.

Compounds known as 3-oxetanones (**1**) are of interest because they possess an ether linkage and a carbonyl group in a strained four-membered ring. It has been



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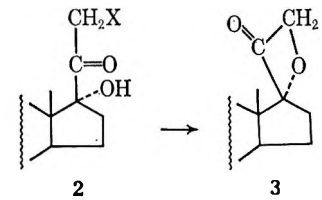
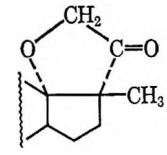
noted[2] that 3-oxetanones undergo normal carbonyl reactions in spite of their strained ring structure; however, literature examples of studies dealing with the preparation and reactions of these compounds are limited in number and scope and generalizations concerning the reactivity of 3-oxetanones cannot be made at this time.

The parent member of this class, 3-oxetanone (**1**, $R_1 = R_2 = R_3 = R_4 = H$), was first characterized as its 2,4-dinitrophenylhydrazone[3a] and has been recently isolated in the pure state.[3b] The syntheses of some alkyl derivatives of 3-oxetanone have been given[4a-e] while earlier inadvertent preparations of substituted 3-oxetanones[4f,5a] have been more recently verified.[4b,5b,c] Few reports on the chemistry of 3-oxetanones are available.[4c,6]

The sole examples of which we are aware where the 3-oxetanone ring system has been prepared as part of more complex structures are in steroids and in each instance the compound was reported to be a 17α,21-oxido-20-one (partial structure **3**). A claim that an oxetanone of this type resulted from the acid-catalyzed hydrolysis of the corresponding ethylene ketal[7a] of partial structure **3** was shown to be erroneous by two groups[7b,c] who demonstrated that the true 17α,21-oxido-20-one underwent rearrangement when treated with acid to give a five-membered oxetanone ring (partial structure **4**). Thus, while the ketal (of partial



2 **3**



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structure **3**) was represented correctly as a derivative of a 3-oxetanone,[7a] the lability toward acid of the 3-oxetanone itself (resulting from hydrolysis) was demonstrated. All known examples[7] of 17α,21-oxido-20-ones were synthesized by internal displacement reactions (**2** → **3**) involving a 17α-hydroxyl and a common leaving group (mesylate, tosylate, iodide) at C-21, employing basic catalysts (potassium fluoride, silver dihydrogen phosphate, potassium hydroxide) in solvents such as dimethyl sulfoxide, ethanol, or dimethylformamide. The yields of oxetanones under these conditions were low (or not given) and, with the exception of the rearrangement **3** → **4**, little information on the reactivity of the oxetanones was given.

An earlier interest[8] in α-bromo keto steroids has led us to examine the reactions of α-bromo-α′-hydroxy keto steroids with dimethyl sulfoxide (DMSO). Examples of the reactions of DMSO with steroidal α-bromo ke-

(1) (a) This investigation was supported by Public Health Service Research Grant AM-11190-01 from the National Institute of Arthritis and Metabolic Diseases and, in its preliminary stages, by a grant from Research Corporation. Presented at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 2, 1968. (b) To whom inquiries should be directed.

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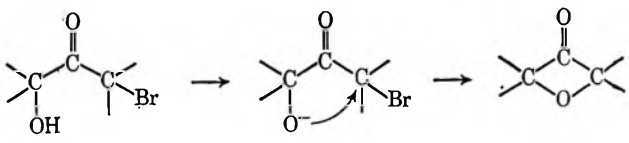
(8) A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962).

tones bearing a β hydrogen atom are known[9] to yield complex mixtures of products which include α-diketones (as diosphenols), α,β-unsaturated ketones, α-hydroxy ketones, and saturated ketones (by reductive elimination of bromide). The product composition obtained from a particular bromo ketone is dependent upon the reaction conditions employed[9b] as well as upon the stereochemistry of, and degree of substitution in, the reactant. To our knowledge the effect of neighboring groups upon the course of reaction of α-bromo ketones with DMSO has not been examined and we therefore engaged in a study of the reactivity of DMSO toward ring-B α-bromo-α'-hydroxy keto steroids. We have found that compounds of this type bearing 3β substituents are transformed readily into oxetanones.

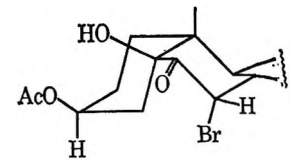
The starting material for the synthesis of the bromo ketones was 3β-acetoxy-5-hydroxy-5β-cholestan-6-one (**5b**).[8] Bromination of this hydroxy ketone with pyridinium bromide perbromide (PBP)[10] in hot glacial acetic acid gave the 7α-bromo derivative **6b** in 80% yield. The configuration at C-7 was determined spectroscopically (*vide infra*). The bromo ketone **6b** was easily debrominated by zinc in hot acetic acid to give **5b**. In addition, 3β,5-dihydroxy-7α-bromo-5β-cholestan-6-one (**6a**) and its diacetate **6c** were prepared by PBP bromination of the hydroxy ketones **5a**[8] and **5c**,[11] respectively. The interrelationships of the three α-bromo ketones were established as follows: monoacetylation of the diolone bromide **6a** with hot acetic anhydride gave the 3-acetate (**6b**), while diacetylation[11] of **6a** gave **6c** and acetylation[11] of **6b** gave **6c**. The configuration at C-7 was therefore shown to be identical in **6a**, **b**, and **c**.

Treatment of bromo ketone **6b** with DMSO containing suspended sodium bicarbonate[9b] at 100° led to the formation of 3β-acetoxy-5,7β-epoxy-5β-cholestan-6-one (**7b**) in 72% yield. The product was identified readily by the characteristic infrared absorption of an oxetanone carbonyl group[7b] at 1815 cm^{-1} (in addition to the acetate carbonyl at 1746 cm^{-1}) and the substituted trimethylene oxide ring vibration[12] at 903 cm^{-1}. When **6b** was heated in DMSO in the absence of sodium bicarbonate no reaction occurred. Also, treatment of the diacetate **6c** gave no oxetanone under these conditions. These results seemed to indicate that a free hydroxyl group at C-5 must be present in order to give oxetanone and that the reaction presumably proceeds *via* hydrogen abstraction from the hydroxyl group by base, followed by an intramolecular displacement of bromine by the resulting oxy anion (Scheme I).

SCHEME I

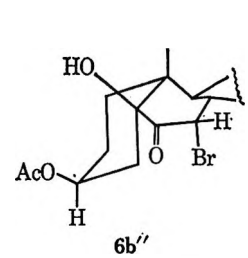


In order for a displacement of this type to occur, the bromine atom at C-7 must be *trans* to the nucleophilic oxy anion, as is the case in bromo ketone **6b**. Inspection of **6b** in perspective form **6b′** indicates clearly that a conformational change in the A/B ring system must

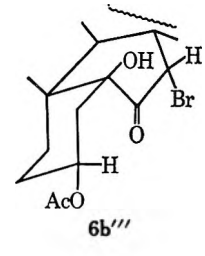


6b′

necessarily take place prior to, or during, oxetanone formation in order to position the oxyanion at C-5 properly for the displacement. Such a change might be a minor one involving the B ring only in which this ring adopts a boat form (**6b″**) or, at an extreme, may involve a more



6b″



6b‴

drastic alteration of both rings A and B, giving a conformation represented by perspective formula **6b‴**. Consideration of **6b‴** as a possible conformer leading to oxetanone formation stems from the relief of the 1,3-diaxial hydroxy–acetoxy interaction[13] found in **6b′** (and **6b″**) and the minimal distance between the C-5 oxygen atom and C-7.

Several additional 5β-hydroxy-6-oxo-7α-bromocholestanes with 3β and 3α acyloxy substituents (**6b**, **9a–c**), along with the 3-desoxy compound (**11b**), were synthesized. This was accomplished with two purposes in mind. (1) Examination of the nmr spectra of the bromo ketones would yield information regarding the environment of the C-3 hydrogen in these compounds. Since the configurations at C-3 in the substituted 5β-ol-6-ones (**5** and **8**) are known[8,14] the position and $W_{1/2}$ of the C-3 hydrogen signal would indicate whether a conformation such as **6b′** (hydrogen equatorial) or **6b‴** (hydrogen axial) is the major contributor to the ground-state structure of the bromo ketones. (2) If a conformation similar to **6b‴** is necessary for oxetanone formation, then 3α-substituted bromo ketones might be expected to undergo ring closure to the oxide less readily than the 3β isomers since the alkyl oxygen of the acyloxy substituent at C-3 (with hydrogen and acyloxy exchanged in formula **6b‴**) would be close to the C-6 carbonyl oxygen, thus introducing an instability factor not present in the 3β-substituted compounds. Also, the absence of a 1,3-diaxial acyloxy–hydroxy interaction in the 3α-acyloxy bromo ketones (**9**) would not provide a driving force for a conformation change as may occur in the 3β-substituted compounds. If group size at C-3 is important in determining the relative pop-

(9) (a) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967). (b) H. R. Nace and R. N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964); R. N. Iacona, A. T. Rowland, and H. R. Nace, *ibid.*, **29**, 3495 (1964); and references cited in these articles.

(10) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 65.

(11) A. T. Rowland, *J. Org. Chem.*, **29**, 222 (1964).

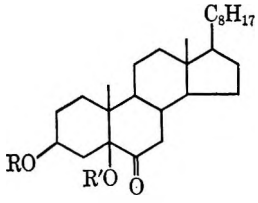
(12) G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.*, **75**, 1175 (1953).

(13) While it is clear that this diaxial orientation is stabilized by hydrogen bonding in 3β-acetoxy-5-hydroxy-5β-cholestane [A. Nickon, *ibid.*, **79**, 243 (1957)], we have shown that in 3β-acetoxy-5β-hydroxy-6-oxocholestanes the hydroxy group is hydrogen bonded to the C-6 carbonyl oxygen and not to the alkyl oxygen of the C-3 ester [A. T. Rowland, *Steroids*, **7**, 527 (1966)]. Stabilization by hydrogen bonding of the diaxial interaction in **6b′** or **6b″** should therefore be negligible.

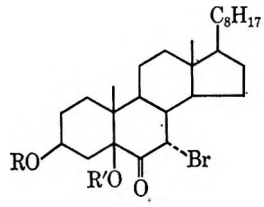
(14) B. W. Sands and A. T. Rowland, *ibid.*, **4**, 175 (1964).

ulation of conformers such as **6b′** and **6b‴**, it would be anticipated that an increase in the size of the 3β substituent would enhance oxetanone formation by increasing the amount of conformer type **6b‴** whereas an increase in the bulk of the 3α substituent would inhibit oxetanone formation by increasing interaction with the C-6 carbonyl oxygen in conformation type **6b‴**.

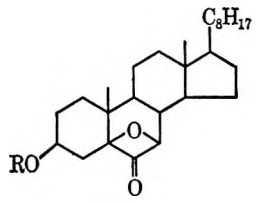
PBP bromination of the hydroxy ketones **5d**, **8b**, and **8c** gave bromo ketones **6d**, **9b**, and **9c**, respectively. Bromination of 5-hydroxy-5β-cholestan-6-one (**11a**)[14] gave the α-bromo ketone (**11b**) as an oil. Inspection of the uv and ir spectra of the various fractions obtained from column chromatography of the oil indicated that the bulk of the reaction product was the 7α-bromo ketone **11b**. The bromination of the 3α,5β-diol-6-one (**8a**) gave gelatinous products or crystalline material with a wide melting point range. When the bromination of **8a** was conducted in pure tetrahydrofuran at 60°, pyridinium bromide was deposited from the reaction mixture. The steroid product had a uv maximum (311 mμ) consonant with the expected 7α-bromo derivative (**9a**) but column chromatography revealed the presence of numerous compounds, one of which was 3β,5-epoxy-5β-cholestan-6-one (**13**, 16% yield).[13] The fractions obtained from the column whose uv spectra were in agreement with the anticipated bromo ketone **9a** were combined and crystallized, but no pure product could be obtained.[15]



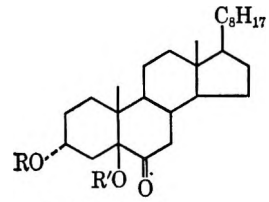
5a, R = R′ = H
b, R = Ac; R′ = H
c, R = R′ = Ac
d, R = Bz; R′ = H



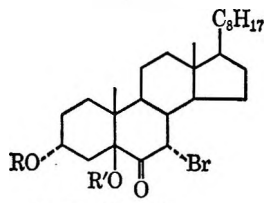
6a, R = R′ = H
b, R = Ac, R′ = H
c, R = R′ = Ac
d, R = Bz, R′ = H



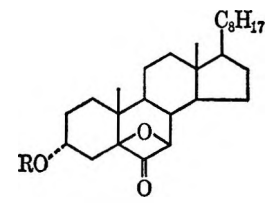
7a, R = H
b, R = Ac
c, R = Bz
d, R = Ts



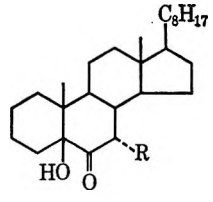
8a, R = R′ = H
b, R = Ac, R′ = H
c, R = Bz, R′ = H



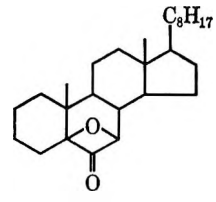
9a, R = R′ = H
b, R = Ac, R′ = H
c, R = Bz, R′ = H



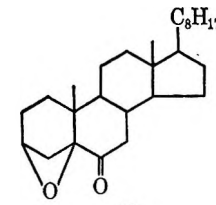
10a, R = H
b, R = Ac
c, R = Bz
d, R = Formyl



11a, R = H
b, R = Br



12



13

The spectral data (accompanied by molecular rotations) of the α-bromo ketones and the parent ketones reported here are summarized in Table I. The changes noted in λ_{max} and ϵ_{max} of the parent ketones upon bromination and the related minor alterations in the position of the carbonyl stretching frequencies are in full accord with a C-7 axial configuration of bromine in each of the bromo ketones.[16,17]

TABLE I[a]

INFRARED, MOLECULAR ROTATION, AND ULTRAVIOLET DATA OF THE α-HYDROXY KETONES AND THEIR 7α-BROMO DERIVATIVES

5β-Cholestane	$\nu_{max}^{C=O}$, cm^{-1}	$[\phi]_D$, deg	λ_{max}, mμ (ε)
-5β-ol-6-one (**11a**)	1706[b]	−69[b]	283 (54)
-7α-bromo-5β-ol-6-one (**11b**)	1704	±0	311.5 (114)
-3β,5β-diol-6-one (**5a**)	1711[c]	−21[c]	284.5 (51)
-7α-bromo-3β,5β-diol-6-one (**6a**)	1706	+55	318 (110)
-3β,5β-diol-6-one 3-acetate (**5b**)	1712[c]	−101[c]	282.5 (56)
-7α-bromo-3β,5β-diol-6-one 3-acetate (**6b**)	1712	+49	316.5 (110)
-3β,5β-diol-6-one 3-benzoate (**5d**)	1712[c]	+120[c]	*d*
-7α-bromo-3β,5β-diol-6-one 3-benzoate (**6d**)	1712	+235	314.5 (123)
-3β,5β-diol-6-one diacetate (**5c**)	1730[e]	−116[e]	291 (53)
-7α-bromo-3β,5β-diol-6-one diacetate (**6c**)	1724	+128	317 (90)
-3α,5β-diol-6-one (**8a**)	1708[b]	−59[b]	282.5 (58)
-7α-bromo-3α,5β-diol-6-one (**9a**)	...	...	*f*
-3α,5β-diol-6-one 3-acetate (**8b**)	1712[b]	−23[b]	282 (43)
-7α-bromo-3α,5β-diol-6-one 3-acetate (**9b**)	1712	+129	312 (105)
-3α,5β-diol-6-one 3-benzoate (**8c**)	1712	−100	*d*
-7α-bromo-3α,5β-diol-6-one 3-benzoate (**9c**)	1706	+12	314 (95)

[a] Conditions at which measurements were taken are given in ref 28. [b] Reference 14. [c] Reference 8. [d] λ_{max} obscured by aromatic absorptions. [e] Reference 11. [f] Could not be prepared in pure state.

(15) The production of the 3β,5β-epoxy-6-one (**13**) from this reaction is interesting and an attempt was made to determine the mode of its formation. The PBP might be expected to break down into pyridinium bromide and bromine in tetrahydrofuran. The oxide formation almost certainly involves an attack by the C-5 hydroxyl on an electron deficient C-3; this deficiency may be brought about by the action of an acid such as the pyridinium ion or by hydrogen bromide which is generated from the pyridinium bromide or from the bromination reaction itself. When the diolone **8a** was heated under reflux with hydrobromic acid in tetrahydrofuran solution, only starting material was recovered. Treatment of **8a** with suspended pyridinium bromide in boiling tetrahydrofuran gave a mixture of at least four compounds (tlc) but none of the oxide (**13**). The agent responsible for the production of **13** is therefore still unknown.

(16) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 35.

(17) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 170.

TABLE II[a]

NMR DATA OF THE BROMO KETONES AND THE EPIMERIC 3-ACETOXY-5β-OL-6-ONES[b]

5β-Cholestane	C-7 hydrogen (J)[c]	C-3 hydrogen ($W_{1/2}$)[d]	Hydroxyl hydrogen	Acetate methyl	C-4α hydrogen (J)	C-19	C-18
-3β,5β-diol-6-one 3-acetate (**5b**)	...	294 (8)	225.5	117.5	...	42	40
-3α,5β-diol-6-one 3-acetate (**8b**)	...	295 (18)	229.5	116.3	...	41.5	40
-7α-bromo-5β-ol-6-one (**11b**)	257.6 (4.2)	...	207.5	...	163[e]	43	41.7
-7α-bromo-3β,5β-diol-6-one (**6a**)	260.5 (3.0)	233 (8)	*f*	...	176.5 (15)[g]	46	42
-7α-bromo-3β,5β-diol-6-one 3-acetate (**6b**)	261 (2.5)	295 (8)	213.5	118.5	177 (15.5, 3)[h]	46	42
-7α-bromo-3β,5β-diol-6-one 3-benzoate (**6d**)	260.3 (2.5)	315 (8)	218.5	...	187.5 (16, 4)[h]	49.5	42
-7α-bromo-3β,5β-diol-6-one diacetate (**6c**)	257	306.5 (7)	...	115, 123	192 (26.5, 17)[h]	49.5	42
-7α-bromo-3α,5β-diol-6-one 3-acetate (**9b**)	260 (3.0)	296 (22)	220.5	117	167 (12.5, 12)[i]	44	42
-7α-bromo-3α,5β-diol-6-one 3-benzoate (**9c**)	261.5 (3.0)	314.5 (22)	223.5	...	176.5 (12, 12)[i]	46	42

[a] Conditions at which measurements were taken are given in ref 28. [b] All chemical shifts are given in cycles per second (cps) downfield relative to tetramethylsilane used as an internal standard. [c] All C-7 hydrogens appeared as doublets except where no J value is given, in which case a single peak was observed. [d] Shifts and half-band widths are approximations owing to broad signal. [e] Broad, low hump. [f] One hydroxyl hydrogen masked by C-3 and C-7 hydrogens each, as shown by integration of spectrum. [g] Doublet. [h] Doublet of doublets. [i] Doublet of doublets with center peaks superimposed.

The nmr spectra of the bromo ketones were obtained (Table II). Included with the bromo ketones are 3β-acetoxy-5-hydroxy-5β-cholestan-6-one (**5b**) and its C-3 epimer **8b**. The importance of the C-3 hydrogens to any conclusion regarding the conformations of the halo ketones may be seen by comparing conformation **6b′**, in which the hydrogen is equatorial, to extreme conformation **6b‴**, where the hydrogen is axial to the A ring. Axial hydrogens generally are less deshielded than equatorial hydrogens in isomeric alcohols[18a] and C-3 axial protons exhibit resonances whose half-band widths ($W_{1/2}$) are over twice as large as the $W_{1/2}$ for the corresponding equatorial hydrogens in epimeric compounds.[18b] Table II shows that the axial C-3 proton in the 3α-acetoxy compound **8b** occurs at 295 Hz which is almost identical with the position (294 Hz) found for the C-3 equatorial hydrogen in the 3β-acetoxy steroid (**5b**). The coincidental signals are not unexpected since the 5β (axial) hydroxy group deshields the 3β (axial) hydrogen in **8b**.[19] The half-band width for the C-3 hydrogens in these isomers indicate that the A ring probably exists in a normal chair conformation.

Inspection of the nmr data for the bromo ketones shows the C-3 hydrogens in the 3β-substituted compounds (**6a–d**) as broad signals with $W_{1/2} \simeq 8$ Hz. The positions of the individual peaks are a reflection of the nature of the substituents (OAc, OBz, OH) at carbons 3 and 5 and are in no way anomalous.[18a] The 3α-acyloxy bromo ketones **9b** and **9c** exhibit C-3 axial hydrogen absorptions at expected positions and have predictable half-band widths ($W_{1/2} \simeq 22$ Hz); the C-3 hydrogens in 5-hydroxy-7α-bromo-5β-cholestan-6-one (**11b**) are not deshielded enough to be shifted from within the methylene envelope of the steroid and cannot be detected. The equatorial C-7 hydrogens all (except in **6c**) appear as doublets with J from 2.5 to 4.2 Hz, indicative of coupling with the C-8 axial proton. Of interest is the deshielding effect of the axial bromine atom at C-7 upon the 4α (axial) hydrogen in these compounds. In the 3β-substituted compounds **6b–d** this axial hydrogen appears as a doublet of doublets due to geminal coupling with the C-4 equatorial proton, with further splitting due to additional coupling with the equatorial proton at C-3.[20] In the 7α-bromo-3β,5β-diol-6-one (**6a**) the C-4 axial proton appears as a doublet with unresolved splitting of the legs. The reason for the large coupling constants in the diacetoxy bromo ketone **6c** is not clear although it may be due to distortion caused by mutual repulsion of the acetoxy groups. The C-4 axial protons of the 3α-acyloxy bromo ketones **9b** and **c** give rise to three peaks (doublet of doublets with center peaks superimposed) with $J = 12$ Hz, indicative of geminal splitting of the proton and further coupling with the C-3 axial hydrogen atom.[20] In the case of the bromo ketone **11b**, the axial C-4 hydrogen signal appears as a broad low hump centered at about 163 Hz. This appearance is not surprising since the lack of a substituent at C-3 would give rise to further couplings with the C-4 axial hydrogen, resulting in a smeared absorption. The deshielding of hydrogen by the halogen in α-halo ketones had been reported previously,[21a] notably in the case of 3β-acetoxy-7α-bromo-5α-cholestan-6-one, where the 5α hydrogen appears as a pair of doublets ($J = 12$ and 3.7 Hz) centered at δ 3.28.[21b]

The nmr data found for α-bromo ketones **6a–d** and **9b** and **c** and the hydroxy ketones **5b** and **8b** indicate that these compounds exist mainly in ground-state conformations represented by **6b′** and to no significant extent as **6b″** or **6b‴**.

The reactions of some of the α-bromo ketones with sodium bicarbonate–DMSO were investigated. When heated at 100–120° for 19.5 hr, the bromo ketone **9b** gave 3α-acetoxy-5,7β-epoxy-5β-cholestan-6-one (**10b**) in 24% yield. Variations in time, temperature, and the quantity of sodium bicarbonate did not increase the yield of **10b**. Under similar conditions **11b** gave 5,7β-epoxy-5β-cholestan-6-one (**12**) in 21% yield. Saponification of the 3β- and 3α-acetoxy oxetanones (**7b** and **10b**) gave the free hydroxy oxetanones **7a** and **10a**, respectively. Benzoylation of each of the hydroxy oxetanones gave the corresponding benzoates (**7c** and **10c**).

In order to obtain a quantitative measure of the reaction in terms of rate and product composition data, a system was sought which would give oxetanone formation and yet would not cause saponification of ester

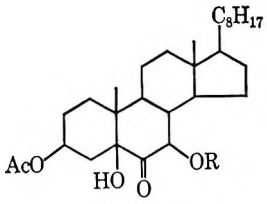
(18) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 77; (b) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

(19) Examples of deshielding of axial protons by axial hydroxy groups are recorded; see ref 18a, p 186.

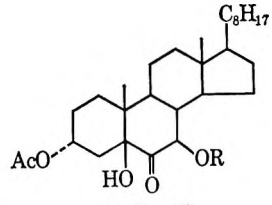
(20) The C-4 axial (α) proton forms the M portion of an AMX system in which X is the C-3 hydrogen and A is the C-4 equatorial (β) hydrogen (which is lost in the methylene envelope).

(21) (a) See ref 18a, p 75; (b) private communication from Professor Alex Nickon, Johns Hopkins University, Dec 1967.

groups at C-3. Treatment at room temperature of a solution of the 3β-substituted bromo ketones (**6a, b**) in DMSO with a standard methanolic potassium hydroxide solution gave *rapid* formation of the hydroxy oxetanone **7a**.[22] The reaction was, however, accompanied by acetate saponification in the case of **6b**; acetylation of the crude reaction products gave the 3β-acetoxy oxetanone (**7b**) as the major product (>70%). In contrast, the 3α-acetoxy oxetanone **10b** was obtained in extremely poor yield (~6%) [along with a low yield of the debrominated hydroxy ketone (**8b**) and a larger amount of an oil whose ir spectrum indicated that it consisted largely of the diacetoxy hydroxy ketone **15b**] when the 7α-bromo ketone **9b** was subjected to the same reaction procedures and the 7α-bromo-5β-ol-6-one **11b** gave a 34% yield of the oxetanone **12**.



14a, R = H
b, R = Ac

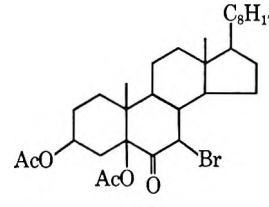


15a, R = H
b, R = Ac

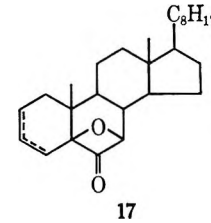
A third system that was employed involved the addition of a calculated amount of a standard aqueous solution of potassium bicarbonate to a DMSO solution of the bromo ketone at ~75°. This gave oxetanones without removal of acyl groups. Yields were reasonably good (50–69%) from the 3β-substituted bromo ketones (**6a, b, d**), low (22%) from the 3-desoxy compound (**11b**), and minute (4–7%) from the 3α-acyloxy bromo ketones (**9b, c**). Attempts at ascertaining relevant rate data in this potassium bicarbonate–DMSO medium were not successful since the potassium bicarbonate started to precipitate immediately after the addition of its aqueous solution to the bromo ketone–DMSO mixture.

The other products produced from the bromo ketone–potassium bicarbonate–DMSO reactions have been investigated in order to determine reaction paths followed as alternatives to oxetanone formation. In addition to the oxetanone (**7b**) obtained from the 3β-acetoxy bromo ketone **6b**, a 6% yield of a compound identified as 3β-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**14a**) was isolated. This material is representative of hydroxy ketones sometimes obtained from treatment of α-halo ketones with base.[8,9b] The 3β-benzoyloxy bromo ketone **6d** gave the oxetanone **7c** (69%) and small amounts of unidentified impure crystalline products. The dihydroxy bromo ketone **6a** gave (after acetylation) a small amount (~5%) of the bromo ketone **6b**, corresponding to acetylated unreacted starting material, and a low yield of another compound best represented as 3β,7β-diacetoxy-5-hydroxy-5β-cholestan-6-one (**14b**). Complete characterization of this compound was impossible owing to an insufficient quantity of material, but the ir and analytical data appear to fit the proposed structure.

The reaction of the diacetoxy bromo ketone **6c** with the DMSO–aqueous potassium bicarbonate is of special interest since it had been noted before that this compound did not give oxetanone when treated with sodium bicarbonate in DMSO. In this case, ir analysis of the crude product again demonstrated the lack of oxetanone formation, while chromatography permitted isolation of starting material (21%), the debrominated diacetoxy ketone **5c** (5%),[23] and a bromo ketone which was apparently the C-7 epimer (**16**) of the starting material (**6c**). The ir and uv evidence fit the proposed structure well, as did the elemental analysis for bromine, but the carbon–hydrogen analysis did not correspond to the theoretical values.[24]



16



17

The by-products isolated from the 7α-bromo-5β-ol-6-one (**11b**) were complex mixtures which could not be separated and identified. The 3α-acetoxy-7α-bromo ketone **9b** gave ~6% of the debrominated hydroxy ketone **8b** and ~12% of 3α-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**15a**). The latter compound was identified on the basis of ir, uv, and analytical data. The only identifiable product (other than the 3α-benzoyloxy oxetanone **10c**) obtained from the 3α-benzoyloxy-7α-bromo ketone (**9c**) was the debrominated hydroxy ketone **8c** (13%).

The inability to obtain rate data for the conversions of the bromo ketones into oxetanones makes speculation concerning the mechanism of the reactions difficult. The yields of oxetanones from 3β-substituted bromo ketones compared with the 3-desoxy and 3α-substituted bromo ketones, however, may be a reflection of the Curtin–Hammett principle. If in **6b**, for example, conformer **6b′** is in rapid equilibrium with **6b″** and **6b‴**, the rate of formation of oxetanone will not depend upon the ground-state population of **6b‴** (which must be extremely small, according to the nmr data previously given) but only upon the differences in the energies of the transition states leading to products from **6b‴** and other conformations. Presumably a 3β substituent serves to raise the energy of pathways competing with oxetanone formation while a 3α substituent would exert an opposite effect, perhaps because of the acyl–C_6 oxygen interaction in a conformer such as **6b‴**.

(22) When a solution of **6a** in DMSO was titrated with a standard methanolic potassium hydroxide–DMSO solution in the presence of thymol blue indicator, no indicator color change was noted until slightly more than 1 equiv of base had been added, indicating the rapidity with which the bromo ketone reacts. (A blank run gave color immediately upon addition of 1 drop of base.)

(23) E. W. Warnhoff and D. R. Marshall [*J. Org. Chem.*, **32**, 2000 (1967)] have shown conclusively that α-bromo ketones may undergo reductive debromination with α-disubstituted pyridines when structural features of the bromo ketone prevent or retard displacement or dehydrohalogenation reactions. It appears that a similar path is followed by some of the bromo ketones reported here. While the isolation of debrominated ketones may be ascribed to their presence as impurities from the bromination reactions (*e.g.*, **5b** → **6b**), no unreacted hydroxy ketones could be found in the bromo ketones, each of which was examined by ir, nmr, uv, tlc, and column chromatography. We therefore consider those cases in which the parent hydroxy ketones have been isolated from reactions of the α-bromo ketones with potassium bicarbonate–DMSO as true reaction products.

(24) This may have been due to decomposition during drying of the sample for analysis. See Experimental Section.

TABLE III[a]

INFRARED AND ULTRAVIOLET DATA OF THE OXETANONES

Oxetanone	$\bar{\nu}_{max}$, cm^{-1} OH	C-6 carbonyl	Ester carbonyl	Oxetanone ring[b]	λ_{max}, mμ (ϵ)
-5,7β-epoxy-6-one (12)	...	1808	...	907, 896	286 (27)
-5,7β-epoxy-3β-ol-6-one (7a)	3636,[c] 3460[d]	1808	...	900	285 (42)
-5,7β-epoxy-3β-ol-6-one acetate (7b)	...	1815	1746	903	284.5 (26)
-5,7β-epoxy-3β-ol-6-one benzoate (7c)	...	1812	1727	905	*e*
-5,7β-epoxy-3β-ol-6-one tosylate (7d)	...	1806	...	903	*e*
-5,7β-epoxy-3α-ol-6-one (10a)	3546	1802	...	904, 894	280 (42)
-5,7β-epoxy-3α-ol-6-one acetate (10b)	...	1813	1739	908, 897	285.5 (31)
-5,7β-epoxy-3α-ol-6-one benzoate (10c)	...	1815	1718	912, 903	*e*

[a] Conditions at which measurements were taken are given in ref 28. [b] All absorptions were of medium to strong intensity. [c] Weak absorption. [d] Broad absorption. [e] λ_{max} obscured by aromatic absorptions.

TABLE IV[a]

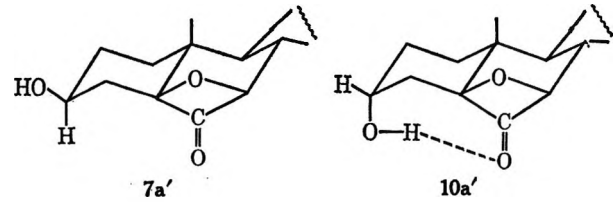
NMR DATA OF THE OXETANONES[b]

Oxetanone	C-7 hydrogen (J)[c]	C-3 hydrogen ($W_{1/2}$)[d]	Hydroxyl hydrogen	Acetate methyl	C-19	C-18
-5,7β-epoxy-6-one (12)	277 (1.6)	...	...	...	61.5	44.5
-5,7β-epoxy-3β-ol-6-one (7a)	281.3 (1.5)	227 (20)	187.5	...	63	44.5
-5,7β-epoxy-3β-ol-6-one acetate (7b)	281 (1.0)	285 (20)	...	117	62.5	43.5
-5,7β-epoxy-3β-ol-6-one benzoate (7c)	283.5	305 (23)	...	...	66	44
-5,7β-epoxy-3β-ol-6-one tosylate (7d)	280	268 (23)	...	147[e]	60	42.1
-5,7β-epoxy-3α-ol-6-one (10a)	282.7 (1.4)	237.5 (8)	162.5	...	61.5	44.5
-5,7β-epoxy-3α-ol-6-one acetate (10b)	277.6 (1.5)	295 (7)	...	124	62.3	44
-5,7β-epoxy-3α-ol-6-one benzoate (10c)	279.8 (1.5)	316.5 (8)	...	...	64	44

[a] Conditions at which measurements were taken are given in ref 28. [b] All chemical shifts are given in cycles per second (cps) downfield relative to tetramethylsilane which was the internal standard. [c] All C-7 hydrogens appeared as doublets except where no J value is given, in which case a single peak was observed. [d] Shifts and half-band widths are approximations owing to broad signal. [e] Aromatic methyl.

Although the yields of the 3α-substituted and 3-desoxy oxetanones from the corresponding bromo ketones are low,[25] an efficient preparation of these compounds was found in the epimerization technique of Chang and Blickenstaff.[26a] This method involves the displacement, with inversion, of a tosyloxy group from a cyclohexane ring by dimethylformamide yielding a formate ester which may be converted into the free alcohol by saponification. The procedure has recently been used with success on 5,6α-epoxy-5α-cholestan-3β-ol tosylate;[26b] the oxide ring remained intact during the displacement reaction. When 3β-tosyloxy-5,7β-epoxy-5β-cholestan-6-one (**7d**) was heated under reflux in dimethylformamide containing suspended lithium carbonate,[26b] a mixture of the 3α-formate ester **10d** and an unsaturated oxetanone (**17**) was obtained. The mixture was saponified and then acetylated, giving the 3α-acetoxy oxetanone **10b** (64%) and **17** (16%) which were easily separated on alumina. The unsaturated oxetanone **17** may have been the 2- or 3-ene or a mixture of both. Catalytic hydrogenation of **17** gave the desired saturated oxetanone **12** (78%).

The pertinent spectral data of the oxetanones are given in Tables III and IV. All of the oxetanones have ir carbonyl absorptions in the expected range (1802–1815 cm^{-1})[3b,4,7b,c] and in addition show strong ring-absorption at *ca.* 900 cm^{-1}.[12] The latter peak appears as a single broad band in the 3β-substituted oxetanones while the absorption is split into two bands in the 3α epimers and in **12** (Table III). The uv spectra are similar to those of other four-membered ring ketones[27] and are in agreement with the only known recorded value for a 3-oxetanone.[3a] Inspection of the nmr data (Table IV) and hydroxyl absorption in the ir (Table III) permits a detailed analysis of the conformation of the A/B ring system in the oxetanones. In most of the compounds, the C-7 hydrogen appears at *ca.* 280 Hz as a doublet due to coupling with the C-8 proton. The position of the C-3 hydrogen varies as expected according to the type of substituent at C-3;[18a] of significance is the half-band width of the signals of these hydrogens. For the 3β-substituted oxetanones **7a–d**, the half-band width ($W_{1/2} \sim 20$ Hz) clearly indicates an axial orientation of hydrogen whereas the half-band width ($W_{1/2} \sim 8$ Hz) for the epimeric oxetanones (**10a–c**) shows the C-3 hydrogens in these compounds to be equatorial on the A ring. Since no configurational change at C-3 is possible during oxetanone formation from the bromo ketones, the reversal in environment of the C-3 hydrogen (*cf.* Table II) with respect to the ring in the oxetanones as compared with the bromohydroxy ketones must be accounted for by a conformational change; the structure of typical oxetanones may therefore be represented by **7a′** and **10a′**. Confirmation



7a′ **10a′**

(25) The reason for this is still not clear. Any mechanism in operation in bromo ketones does not involve a simple heterolysis of the C-7 to Br bond as the first step in oxetanone formation since bromo ketone **6b** is unreactive to hot DMSO in the absence of base, as noted earlier. Also, **6b** underwent no change when heated at 120° with silver nitrate in DMSO containing a small amount of pyridine or when treated similarly without the addition of silver nitrate.

(26) (a) F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.*, **80**, 2906 (1958); (b) G. A. Selter and K. D. McMichael, *J. Org. Chem.*, **32**, 2546 (1967).

(27) Reference 16, p 29.

comes from the ir spectra (Table III) which show a sharp peak for the intramolecularly bonded C-3 hydroxyl (3546 cm^{-1}) in **10a** while the corresponding hydroxyl absorption in **7a** indicates significant intermolecular association.

The ORD curves of the oxetanones all exhibited simple negative Cotton effects with slight inflections on the peaks at lower wavelengths (*ca.* 250 mμ). The molecular amplitudes varied from 5300 to 12,800° but, with the exception of the benzoates **7c** and **10c**, little differences in the amplitudes of the epimeric pairs were noted (see Experimental Section).

In summary, ring-B oxetanones may be easily prepared from the 3β-substituted 5β-hydroxy-6-oxo-7α-bromocholestanes. The 3β oxetanones are readily convertible into their C-3 epimers and to the 3-desoxy compound by the inversion–elimination reaction with dimethylformamide. While the mechanism of oxetanone formation from these α-bromo-α'-hydroxy ketones has not been completely identified, the importance of the substituent at C-3 and the action of a weak base have been shown. Further studies on the mechanism of this conversion and on the chemistry of oxetanones will be reported in the future.

Experimental Section[28,29]

3β-Acetoxy-5-hydroxy-5β-cholestan-6-one (5b).—A modification of a given preparation[8] was employed. A suspension of 75 g (140 mmol) of 3β-acetoxy-5-bromo-5α-cholestan-6-one in 650 ml of 1.33 *N* methanolic potassium hydroxide solution[30] was magnetically stirred at room temperature for *ca.* 18 hr. The orange solution (containing precipitated inorganic salts) that resulted was diluted with 1.5 l. of ether and washed twice with saturated salt solutions. The ether layer was dried, filtered, and evaporated, leaving a light brown oil which was covered with 375 ml of acetic anhydride and heated on the hot plate at 110–120° for 4 hr. After remaining at room temperature overnight, crushed ice and 40 ml of 2 *N* hydrochloric acid were added. After standing overnight, the precipitate was collected, washed with water, and recrystallized from methanol, yielding 48 g (72%) of **5b**, mp 138–142°. A further recrystallization from acetone–methanol gave large white plates with mp 142–143° (lit.[8] mp 142.5–144.5°).

3α-Benzoyloxy-5-hydroxy-5β-cholestan-6-one (8c).—A solution of 254 mg (0.607 mmol) of the dihydroxy ketone **8a** in 4 ml of pyridine containing 0.75 ml of benzoyl chloride was allowed to remain at room temperature for 23 hr. The standard work-up for benzoylations[8] gave material that crystallized from acetone–methanol, yielding 245 mg (77%) of **8c** as needles: mp 176–178°; $[\alpha]D$ −19° (c 1.014); ir, 3484 (w), 1727 (s), 1712 (s, sh) cm^{-1}; ir ($CHCl_3$), 3497 (w), 1709 (s) cm^{-1}. Recrystallization from ether did not alter the melting point.

Anal. Calcd for $C_{34}H_{50}O_4$ (522.74): C, 78.12; H, 9.64. Found: C, 78.12; H, 9.71.

Preparation of Bromo Ketones. General Procedure.—A solution of the appropriate ketone in glacial acetic acid was heated to 70–80°, when slightly greater than 1 equiv of pyridinium bromide perbromide was added to the magnetically stirred solution. After 5–15 min the product was precipitated with water, collected, and recrystallized, except for **11b** and **9c**, which were purified by chromatography on alumina. (No homogeneous bromo ketone was obtained from hydroxy ketone **8a**; ketone **5a** was dissolved in tetrahydrofuran prior to addition to the acetic acid.) The following bromo ketones were obtained; % yield, melting points, solvent used for recrystallization, specific rotations, and analytical data were determined. Additional physical data are given in Tables I and II.

3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a) was prepared in 63% yield: mp 148.5–150° from aqueous acetone; $[\alpha]D$ +11°.

Anal. Calcd for $C_{27}H_{45}BrO_3$ (497.55): C, 65.17; H, 9.11; Br, 16.06. Found: C, 65.35; H, 9.14; Br, 15.87.

3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b) was prepared in 80% yield: mp 137–139° from methanol; $[\alpha]D$ +9°.

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.59): C, 64.54; H, 8.77; Br, 14.81. Found: C, 64.31; H, 8.66; Br, 14.99.

3β,5-Diacetoxy-7α-bromo-5β-cholestan-6-one (6c) was prepared in 84% yield: mp 151–153° from aqueous acetone; $[\alpha]D$ +22°.

Anal. Calcd for $C_{31}H_{49}BrO_5$ (581.62): C, 64.01; H, 8.40; Br, 13.74. Found: C, 64.18; H, 8.51; Br, 13.58.

3β-Benzoyloxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6d) was prepared in 82% yield: mp 185.5–187° from acetone; $[\alpha]D$ +39°.

Anal. Calcd for $C_{34}H_{49}BrO_4$ (601.65): C, 67.87; H, 8.21; Br, 13.28. Found: C, 67.70; H, 8.17; Br, 13.41.

5-Hydroxy-7α-bromo-5β-cholestan-6-one (11b) was prepared in 83% yield as an oil, $[\alpha]D$ ±0°.

Anal. Calcd for $C_{27}H_{45}BrO_2$ (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.55; H, 9.45; Br, 16.55.

3α-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9b) was prepared in 88% yield: mp 144–146° from acetone–methanol; $[\alpha]D$ +24°.

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.59): C, 64.54; H, 8.77; Br, 14.81. Found: C, 64.69; H, 8.75; Br, 14.92.

3α-Benzoyloxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9c) was prepared in 58% yield: mp 130–131° from chloroform–ethanol; $[\alpha]D$ +2°.

Anal. Calcd for $C_{34}H_{49}BrO_4$ (601.65): C, 67.87; H, 8.21; Br, 13.28. Found: C, 68.07; H, 8.37; Br, 13.50.

A 16% yield of 3β,5-epoxy-5β-cholestan-6-one (**13**)[13] was the only identifiable product isolated from the bromination of **9a** conducted in tetrahydrofuran.

Debromination of 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b).—A mixture of 200 mg (0.371 mmol) of **6b** and 1.0 g of zinc dust in 7 ml of glacial acetic acid was heated under reflux for 2 hr. The zinc was removed by filtration and the filtrate was diluted with water. The resulting precipitate (162 mg, mp 140–142°) was collected and recrystallized from methanol to give 134 mg (78%) of **5b** as white plates with mp 142.5–144.5°. No depression in melting point was noted upon admixture with authentic **5b**.[8]

Interrelationships of the 3β-Substituted α-Bromo Ketones. A. Conversion of 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a) into Its 3-Acetate (6b).—A mixture of 52 mg (0.11 mmol) of **6a** and 1 ml of acetic anhydride was heated on the steam bath for 1.33 hr. The hot solution was treated with crushed ice and the precipitated material was recrystallized from methanol, yielding 22 mg (39%) of **6b**, mp 136–138°. Recrystallization from 95% ethanol sharpened the melting point to 137.5–138.5°. The mixture melting point with **6b** prepared from **5b** gave no depression.

B. Conversion of 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b) into Its Diacetate (6c).—A solution of 150 mg (0.278 mmol) of **6b** and 40 mg of *p*-toluenesulfonic acid monohydrate in 2 ml of glacial acetic acid and 2 ml of acetic anhydride was allowed to remain at room temperature for 20.5 hr. The

(28) Melting points were taken in open capillaries on a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in *ca.* 1% chloroform solutions and are accurate to ±2°. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrometer in 5–10% carbon tetrachloride solutions using a sodium chloride prism and 0.1-mm cells; s, m, and w indicate relative intensities of absorption bands, and sh denotes a shoulder. Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505 spectrophotometer in absolute ethanol solutions. Nmr spectra were determined in carbon tetrachloride solutions (TMS internal standard) on a Varian Model A-60A spectrometer by Sadtler Research Laboratories, Inc., Philadelphia, Pa. ORD measurements were made at 27° on dioxane solutions (c ~0.1) using a Cary Model 60 spectropolarimeter. Microanalyses were obtained by Micro-Analysis, Inc., Wilmington, Del. Preliminary examinations of crude reaction products and of column chromatographic fractions were carried out on a Beckman Microspec infrared spectrometer and by tlc on Gelman Type SG sheets using mixtures (generally 1:1) of benzene and cyclohexane as the irrigant, followed by spraying with a 100% (w/v) *p*-toluenesulfonic acid–ethanol solution.[29] "Drying" of solutions was accomplished with anhydrous sodium sulfate. Merck acid-washed alumina was employed for all column separations. Petroleum ether refers to 30–60° solvent. Dimethyl sulfoxide was Baker "analyzed" reagent and was used as purchased since preliminary experiments indicated that redistilled material had no effect upon the reactions.

(29) V. Vlasinich and J. B. Jones, *Steroids*, **3**, 707 (1964).

(30) The use of methanolic potassium hydroxide is favored over the ethanolic potassium hydroxide which was previously used[8] since the latter solution turns yellow soon after its preparation, whereas the methanolic solution remains colorless indefinitely.

reaction flask was then cooled in an ice bath and treated with water. The precipitate was recrystallized from aqueous acetone to give 142 mg (87%) of **6c** as white needles with mp 151.5–153.5°. A further recrystallization from the same solvents gave 125 mg of needles with mp 153–154.5°; no depression occurred upon admixture with **6c** prepared from **5c**.

C. Conversion of 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a) into Its Diacetate (6c).—A solution of 250 mg (0.502 mmol) of **6a** and 51 mg of *p*-toluenesulfonic acid monohydrate in 2.8 ml of glacial acetic acid and 2.8 ml of acetic anhydride was allowed to remain at room temperature for 69 hr. Work-up as in B gave a precipitate which was recrystallized from acetone–methanol, yielding 246 mg (84%) of **6c** as white needles with mp 152.5–154.5°, alone or upon admixture with **6c** prepared from **5c**.

Reaction of 3α,5-Dihydroxy-5β-cholestan-6-one (8a) with Hydrobromic Acid.—A solution of 263 mg (0.629 mmol) of **8a** in 15 ml of tetrahydrofuran (redistilled from lithium aluminum hydride) containing 0.50 ml of 48% hydrobromic acid was heated under reflux for 1.5 hr. The cooled solution was diluted with water and the precipitated product was collected, washed with water, and dissolved in chloroform. The dried solution was evaporated, giving material shown to be **8a** by tlc, ir spectroscopy, and recrystallization from acetone–water (203 mg with mp 121–123.5°).

Reaction of 3α,5-Dihydroxy-5β-cholestan-6-one (8a) with Pyridinium Bromide.—A solution of 315 mg (0.753 mmol) of **8a** in 15 ml of tetrahydrofuran containing 296 mg (1.85 mmol) of suspended pyridinium bromide was heated under reflux for 3.3 hr. The mixture was diluted with water and extracted twice with chloroform. The extracts were washed with water and dried. The resulting oil had an ir spectrum essentially identical with that of **8a** but tlc of the crystallized product (mp 88–115°) had four spots: R_f 0.52 (weak), 0.43 (weak), 0.28 (intense), and 0.13 (intense). On the same sheet, 3β,5-epoxy-5β-cholestan-6-one (**13**) had R_f 0.75 whereas **8a** had R_f 0.06. Since the absence of oxide **13** was shown by the ir and tlc examinations, no attempt was made to isolate and characterize the components of the mixture.

3β-Acetoxy-5,7β-epoxy-5β-cholestan-6-one (7b).—To a solution of 32.0 g (59.3 mmol) of **6b** in 1 l. of dimethyl sulfoxide was added 32.0 g of anhydrous sodium bicarbonate, The mixture was stirred mechanically at 100 ± 3° for 6 hr (tlc indicated complete disappearance of starting material within 2 hr). After cooling to room temperture the mixture was diluted with water and extracted with three 700-ml portions of ether. The combined extracts were washed with two 800-ml portions of water and then dried. The orange oil isolated upon evaporation of the ether was crystallized from aqueous ethanol and then recrystallized twice (aqueous ethanol, then methanol) to give 8.55 g of **7b** as off-white needles, mp 100–102°. The solids obtained from the three mother liquors were combined and chromatographed on 350 g of alumina. Elution with benzene gave an additional 13.0 g of **7b**. Recrystallization from aqueous ethanol gave 10.61 g as white plates with mp 100.5–102°. A further crop (0.462 g, mp 92–96°) was obtained from the mother liquor to give a total yield of 19.62 g (72%) of recrystallized **7b**.

Recrystallization of a sample from methanol gave mp 101–102°; $[\alpha]_D$ −49° (*c* 1.315); ORD, $[\phi]_{310}$ −4500° (trough), $[\phi]_{290}$ 0°, $[\phi]_{270}$ +3300° (peak).

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.93; H, 10.11. Found: C, 75.92; H, 9.99.

3α-Acetoxy-5,7β-epoxy-5β-cholestan-6-one (10b).—A solution of 5.077 g (9.41 mmol) of bromo ketone **9b** in 170 ml of DMSO containing 5.08 g of suspended sodium bicarbonate was stirred mechanically at 120 ± 5° under a nitrogen atmosphere. After 1 hr the mixture had turned a dark brown with much frothing; the temperature was lowered to 100° and the nitrogen stream was removed. After stirring a further 19.5 hr, the mixture was worked up as given in the previous procedure. Chromatography on 100 g of alumina and elution with benzene gave 1.17 g of a white solid. Recrystallization from acetone–methanol afforded 1.056 g (24.5%) of the 3α-acetoxy oxetanone (**10b**) as small white needles: mp 145–147°; $[\alpha]_D$ −28° (*c* 0.96); ORD, $[\phi]_{310}$ −4100° (trough), $[\phi]_{291}$ 0°, $[\phi]_{267}$ +3750° (peak).

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.93; H, 10.11. Found: C, 75.96; H, 9.97.

5,7β-Epoxy-5β-cholestan-6-one (12).—A solution of 570 mg (1.18 mmol) of bromo ketone **11b** in 25 ml of DMSO containing 2.0 g of sodium bicarbonate was mechanically stirred at 105 ± 3° for 6.5 hr. After remaining at room temperature overnight, the usual work-up was employed. The oil (455 mg) obtained was chromatographed on 10 g of alumina. The semicrystalline material (106 mg) eluted with 14% benzene–petroleum ether (bp 30–60°) mixtures was crystallized from acetone-methanol, giving 39 mg of the oxetanone **12**, mp 92–94°. Concentration of the mother liquor gave two additional crops of **12**: 51 mg, mp 93–94°, and 9 mg, mp 90.5–93° (total yield, 21%). Recrystallization gave the oxetanone as white needles: mp 93–94°; $[\alpha]_D$ −61° (*c* 1.077); ORD, $[\phi]_{310}$ −3650° (trough), $[\phi]_{288}$ 0°, $[\phi]_{270}$ +1650° (peak).

Anal. Calcd for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.84; H, 10.89.

Further elution of the column with benzene–petroleum ether mixtures gave mainly starting material (ir spectroscopy).

3β-Hydroxy-5,7β-epoxy-5β-cholestan-6-one (7a).—A solution of 334 mg (0.729 mmol) of the 3β-acetoxy oxetanone **7b** in 15 ml of 0.13 *N* methanolic potassium hydroxide containing 1 ml of water was boiled on the steam bath for 40 min. The clear, colorless solution was cooled and diluted with 1 ml of 2 *N* hydrochloric acid and water. The precipitate that formed was collected and recrystallized from aqueous ethanol to give 266 mg (88%) of **7a** as small white needles with mp 119–120°. Another recrystallization gave mp 119.5–120.5°; $[\alpha]_D$ −58° (c 1.112); ORD, $[\phi]_{310}$ −4500° (trough), $[\phi]_{288}$ 0°, $[\phi]_{270}$ +2500° (peak).

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.64. Found: C, 77.81; H, 10.63.

3α-Hydroxy-5,7β-epoxy-5β-cholestan-6-one (10a).—A suspension of 424 mg (0.925 mmol) of the 3α-acetoxy oxetanone **10b** in 3 ml of 1.33 *N* methanolic potassium hydroxide and 7 ml of methanol was boiled gently on the steam bath. The steroid dissolved completely within 5 min and the volume of the solution was reduced to about 5 ml over a total reaction time of 30 min. The solution was cooled, acidified with 2 ml of 2 *N* hydrochloric acid, and diluted with water. The amorphous product was extracted twice with chloroform and the combined extracts were washed once with water, dried, and evaporated yielding 383 mg (99%) of **10a** as a colorless oil that could not be crystallized but which was shown to be homogeneous by column chromatography; the 3α-hydroxy oxetanone (**10a**) had $[\alpha]_D$ −63° (c 1.09); ORD, $[\phi]_{307}$ −4150° (trough), $[\phi]_{285}$ 0°, $[\phi]_{265}$ +2700° (peak).

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.64. Found: C, 77.54; H, 10.55.

3β-Benzoyloxy-5,7β-epoxy-5β-cholestan-6-one (7c).—A solution of 400 mg (0.960 mmol) of the 3β-hydroxy oxetanone (**7a**) and 1 ml of benzoyl chloride in 6 ml of pyridine was allowed to remain at room temperature for 22 hr. The usual work-up of benzoylations[8] yielded a yellow oil that crystallized from acetone–methanol, giving 333 mg of **7c** as needles with mp 146.5–148°. Recrystallization of the solid obtained from the mother liquor from acetone–methanol gave an additional 79 mg of **7c** as needles, mp 146–147.5° (total yield, 82%). A sample recrystallized from the same solvents gave long white needles: mp 147–148°; $[\alpha]_D$ −33° (*c* 1.013); ORD, $[\phi]_{310}$ −4100° (trough), $[\phi]_{292}$ 0°, $[\phi]_{266}$ +4300° (peak).

Anal. Calcd for $C_{34}H_{48}O_4$ (520.72): C, 78.42; H, 9.29. Found: C, 78.26; H, 9.32.

3α-Benzoyloxy-5,7β-epoxy-5β-cholestan-6-one (10c).—A solution of 64 mg (0.15 mmol) of the 3α-hydroxy oxetanone (**10a**) and 0.25 ml of benzoyl chloride in 2 ml of pyridine was allowed to remain at room temperature for 21 hr. The usual work-up,[8] followed by crystallization of the product from acetone–methanol, yielded 60.5 mg (76%) of **10C**: mp 147.5–148.5°; $[\alpha]_D$ −73° (*c* 0.908); ORD, $[\phi]_{310}$ −6800° (trough), $[\phi]_{288}$ 0°, $[\phi]_{265}$ +6000° (peak). Recrystallization from acetone–methanol raised the melting point to 148–149.5°.

Anal. Calcd for $C_{34}H_{48}O_4$ (520.72): C, 78.42; H, 9.29. Found: C, 78.61; H, 9.35.

Reactions of Bromo Ketones with Methanolic Potassium Hydroxide in Dimethyl Sulfoxide (DMSO).—The work-up used in each case was as follows: after the indicated heating period the reaction vessel was cooled under the tap and its contents were then poured onto crushed ice contained in a separatory funnel. Sodium chloride and water were added and the mixture was extracted twice with ether. The combined extracts were washed once with water, dried, and evaporated.

A. 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a).—A suspension of 1.029 g (2.067 mmol) of **6a** in 30 ml of DMSO was stirred magnetically at room temperature as 2.65 ml of 1.126 *N* methanolic potassium hydroxide solution was added in one por-

tion. The steroid dissolved rapidly and the resulting yellow solution was worked up after 9 min. The oil thus obtained was acetylated with 5 ml of acetic anhydride in 5 ml of pyridine for 18.5 hr at room temperature. Crushed ice and 5 ml of concentrated hydrochloric acid were added and the precipitated product was collected, washed with water, and taken up in chloroform. The dried solution was evaporated and the residue was chromatographed on 30 g of alumina. Elution with 80% benzene–petroleum ether gave 822 mg of crystalline material which was recrystallized from aqueous ethanol, yielding 682 mg (72%) of the 3β-acetoxy oxetanone **7b** as white needles with mp 100–101.5°. Dilution of the mother liquor with water gave a further 67 mg of less pure **7b**, mp 92–97°. Three fractions totaling 49 mg of oil were eluted from the column with 20% ether–benzene mixtures. Infrared analysis indicated that these oils were complex mixtures of oxetanone, unsaturated ketones, and other compounds; the oils were not investigated further.

B. 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b).—A suspension of 1.023 g (1.899 mmol) of **6b** in 30 ml of DMSO was stirred magnetically at room temperature as 2.50 ml of 1.126 *N* methanolic potassium hydroxide was added in one portion. After 5 min the deep yellow solution was worked up; tlc indicated that the reaction oil consisted largely of the 3β-hydroxy oxetanone **7a**. Acetylation of this product was accomplished as in part A. Chromatography on 30 g of alumina and elution with 80% benzene–petroleum ether yielded 727 mg of oil which, when crystallized from aqueous ethanol, gave 640 mg (73.5%) of the 3β-acetoxy oxetanone (**7b**) as needles, mp 100.5–102°. Dilution of the mother liquor with water produced an additional 34 mg of **7b**, mp 95–99°. Further elution of the column with 20% ether–benzene mixtures gave several fractions of oils (45 mg total) whose ir spectra indicated mixtures similar to those obtained in part A.

When carried out on a larger scale, 68.1 g (126 mmol) of the bromo ketone (**6b**) gave 43.5 g (75%) of the oxetanone **7b**, mp 100.5–102°.

C. 3α-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9b).—A suspension of 410 mg (0.760 mmol) of **9b** in 13 ml of DMSO was magnetically stirred at room temperature as 1.00 ml of 1.126 *N* methanolic potassium hydroxide was added. After 15 min the bright yellow solution was subjected to the usual work-up. Tlc of the reaction oil showed several compounds and the ir spectrum exhibited intense hydroxyl absorption, a weak oxetanone carbonyl band, and no acetate absorptions. The oil was dissolved in 3 ml of pyridine and treated with 3 ml of acetic anhydride at room temperature for 18 hr. Crushed ice and 3 ml of concentrated hydrochloric acid were added. The amorphous material that separated was extracted into ether (two portions) and the combined ether extracts were washed twice with water, dried, filtered, and evaporated. The residue was chromatographed on 10 g of alumina. Elution with benzene gave 73 mg in two initial fractions. Crystallization from acetone–methanol produced 23 mg (6.6%) of impure 3α-acetoxy oxetanone **10b**, mp 139–143° (softened at 135°). Recrystallization from methanol gave 17 mg of **10b** as white needles, mp 143–145°.

The next three benzene fractions contained 31 mg of oil which crystallized from methanol, yielding 11 mg (3.1%) of 3α-acetoxy-5-hydroxy-5β-cholestan-6-one (**8b**) as needles with mp 120–122.5°. This material did not depress the melting point of authentic **8b** upon admixture.

The bulk of the material (139 mg) was eluted from the column with 15–40% ether–benzene mixtures. The ir spectrum of this oil was consistent with the diacetoxy hydroxy ketone **15b**, but no crystallization could be induced. Rechromatography and tlc of the fractions indicated that this oil was a mixture of at least three components, none of which could be isolated and identified.

D. 5-Hydroxy-7α-bromo-5β-cholestan-6-one (11b) (379 mg, 0.787 mmol) was covered with 45 ml of a 0.0178 *N* solution of methanolic potassium hydroxide in DMSO. The mixture was stirred magnetically overnight, during which time the oily bromo ketone dissolved very slowly. Work-up yielded 308 mg of a yellow oil which was chromatographed on 8 g of alumina. The solid (142 mg) eluted with 20% benzene–petroleum ether was recrystallized from acetone–methanol, giving 107.7 mg (34%) of 5.7β-epoxy-5β-cholestan-6-one (**12**), mp 91–93°. Recrystallization of a sample from acetone–methanol gave **12** as white needles with mp 93–94°.

The bulk of the remaining material (oil) eluted from the column was starting material, according to ir evidence and Beilstein tests.

Reactions of Bromo Ketones with Aqueous Potassium Bicarbonate Solution in DMSO. General Procedure.—A suspension of the bromo ketone in DMSO was heated in an oil bath (80–85°) until solution was complete. To the hot (*ca.* 1.1×10^{-2} *M*) solution was added a calculated volume of 0.403 *M* aqueous potassium bicarbonate solution to give a 3:1 molar ratio of base to steroid. The reaction flask was shaken periodically and the cloudy solution that resulted from the bicarbonate addition gradually cleared, accompanied by the deposition of small amounts of inorganic salts. After the indicated reaction time the product was isolated in the same manner employed in the bromo ketone–methanolic potassium hydroxide–DMSO reations.

A. Bromo Ketone 6b.—A solution of 614 mg (1.14 mmol) of **6b** in 104 ml of DMSO was heated until the internal temperature reached 75°, at which time 8.50 ml of the bicarbonate solution was added. After a reaction time of 25 min (tlc indicated reaction almost complete within 5 min) the product was isolated and chromatographed on 20 g of alumina. Elution with 80% benzene–petroleum ether gave 384 mg of the 3β-acetoxy oxetanone (**7b**) which crystallized from aqueous ethanol as 341 mg (65%) of white needles with mp 101–102°. An additional 20 mg of impure **7b**, mp 89–97°, was obtained by dilution of the mother liquor with water.

Elution with 25% ether–benzene gave 35 mg of an oil shown by tlc to consist of at least two compounds. This oil was not investigated further.

The 50% ether–benzene fractions yielded 39 mg of a solid that was recrystallized from petroleum ether giving 32.6 mg (6%) of a compound formulated as 3β-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**14a**): mp 150–152°; ir, 3509 (m, sharp with broad base), 1736 (s, acetate C=O), 1704 (s, C_6=O) cm^{-1}. Recrystallization from petroleum ether led to the recovery of 23 mg of **14a**: mp 150–152°; uv_{max} 278.5 mμ (ε 83).

Anal. Calcd for $C_{29}H_{48}O_5$ (476.67): C, 73.07; H, 10.15. Found: C, 73.06, 73.25; H, 10.07, 9.92.

B. Bromo Ketone 6a.—A solution of 608 mg (1.22 mmol) of **6a** in 112 ml of DMSO was heated at 73–76° (internal temperature) with 9.0 ml of the bicarbonate solution for 47 min. The product was isolated in the usual manner and then acetylated with 4 ml of acetic anhydride in 4 ml of pyridine for 16.7 hr at room temperature. The addition of crushed ice and 4 ml of concentrated hydrochloric acid gave amorphous material which was extracted with two portions of ether. The combined extracts were washed twice with water, dried, filtered, and evaporated. The resulting oil was chromatographed on 25 g of alumina. Elution with 50% benzene–petroleum ether gave 329 mg of crystalline material. Recrystallization from aqueous ethanol yielded 280 mg (50%) of the 3β-acetoxy oxetanone (**7b**) as needles, mp 101–102°.

Crystalline material (49 mg) eluted with 75% benzene–petroleum ether and with benzene was recrystallized from methanol to give 36.3 mg (5.5%) of the bromo ketone **6b**, mp 137–138.5°. No depression in melting point was observed upon admixture with authentic **6b**.

Eluted with 20% ether–benzene was 99 mg of a semicrystalline product. Recrystallization from methanol gave 48.8 mg (7.6%) of a white powder, mp 159–163° (37 mg was precipitated with water from the mother liquor, mp 125–145° with much previous softening). Recrystallization from methanol containing a little water afforded 27.7 mg of small white needles: mp 162–164°; ir, 3497 (w, *t*-hydroxyl), 1739 (s, with sh at higher and lower frequency) cm^{-1}; λ_{max} ~248 mμ (with inflection at longer wavelengths) (ε 178).

Anal. Calcd for $C_{31}H_{50}O_6 \cdot {}^1/_2H_2O$ (527.72): C, 70.55; H, 9.72. Found: C, 70.18, 70.48; H, 9.53, 9.53.

This compound is presumed to be 3β,7β-diacetoxy-5-hydroxy-5β-cholestan-6-one (**14b**) on the basis of the ir absorptions.

C. Bromo Ketone 6d.—A suspension of 605 mg (1.01 mmol) of **6d** in 92 ml of DMSO was heated to an internal temperature of 77–78°; the steroid had not dissolved at this point. An additional 20 ml of DMSO was added and heating was continued for a further 0.5 hr at 78°. At this point some steroid remained undissolved; 7.50 ml of the bicarbonate solution was added to the mixture. After 1.5 hr of treatment with the base, the reaction mixture was worked up and the semicrystalline residue was chromatographed on 30 g of alumina. The first fraction eluted with 80% benzene–petroleum ether gave 384 mg of a white solid. Recrystallization from acetone–methanol yielded 362 mg (69%) of the 3β-benzoyloxy oxetanone **7c** as beautiful white needles,

mp 147–148.5°. A second 80% benzene–petroleum ether fraction contained 21 mg of an oil which, when crystallized twice from methanol, gave an additional (impure) 7.5 mg of **7c** as needles with mp 142–147° (soften 135°). Further fractions of the benzene–petroleum ether mixture gave 25 mg of an oil that crystallized from aqueous acetone, giving 18 mg of material with mp 138–160°. Recrystallization from methanol produced 8 mg (mp 140–148°) of an unidentified mixture.

Elution with 25% ether–benzene gave 49 mg of an oil that crystallized from petroleum ether, giving 24 mg of tiny white needles which had a double melting point (79.5–81° and 163–165°). Recrystallization from the same solvent returned 3 mg, mp 88° and 164–166°. Lack of material precluded further investigation.

D. Bromo Ketone 6c.—A solution of 404 mg (0.694 mmol) of **6c** in 64 ml of DMSO was heated to 76°, when 5.10 ml of the bicarbonate solution was added. After 1.35 hr the product (no oxetanone was observed *via* ir spectroscopy) was isolated from the colorless reaction mixture and chromatographed on 20 g of alumina. Elution with 50–70% benzene–petroleum ether mixtures yielded 197 mg of oil that crystallized from aqueous acetone: 85 mg (21%) of starting material (**6c**) precipitated as white needles, mp 151.5–153.5° (*ca.* 210° dec) Elution with benzene produced an oil (108 mg) that crystallized from methanol, mp 175–177.5° (dec pt 185°). Recrystallization from methanol afforded 56 mg (14%) of **16** (positive Beilstein test) with mp 176.5–178.5° (dec pt 182°); uv_{max} 286 mμ (ε 49); ir, 1739 (s, with strong sh at 1754 and 1761) cm^{-1}. When a sample for analysis was recrystallized from methanol and dried at 80° (1 mm) for 3.2 hr, the melting point dropped to 152–154° (dec pt 175°).

Anal. Calcd for $C_{31}H_{49}BrO_5$ (581.62): C, 64.01; H, 8.40; Br, 13.74. Found: C, 65.60; H, 8.83; Br, 13.42.

Finally, elution of the column with 30% ether–benzene gave 56 mg of 3β,5-diacetoxy-5β-cholestan-6-one (**5c**) that crystallized from methanol (with seeding) as 17 mg (5%) of little prisms, mp 189–193°, some previous softening (lit.[11] mp 192–193.5°).

E. Bromo Ketone 11b.—A solution of 179 mg (0.371 mmol) of **11b** in 10 ml of anhydrous ether was added, in portions, to 34 ml of DMSO which had been preheated to 72°. After 10 min 2.80 ml of the potassium bicarbonate solution was added and the reaction was allowed to proceed at 75–77° for 2 hr. The work-up gave product containing little oxetanone (ir). Chromatography on 4 g of alumina gave 43 mg of oil from 20% benzene–petroleum ether fractions. Crystallization from acetone–methanol afforded 33 mg (22%) of 5,7β-epoxy-5β-cholestan-6-one (**12**) as white needles with mp 93–94°.

The remaining oils (61 mg) eluted with increasingly polar solvent mixtures were examined by uv spectroscopy. The maxima varied from *ca.* 274 to 314 mμ and most showed shoulders indicative of complex mixtures. None of the oils was investigated further.

F. Bromo Ketone 9b.—A solution of 319 mg (0.592 mmol) of **9b** in 55 ml of DMSO was heated to 81°; 4.40 ml of the bicarbonate solution was then added. The reaction product was chromatographed on 8 g of alumina. Eluted with 50% benzene–petroleum ether was 17 mg of an oil that crystallized from methanol, yielding 11.6 mg (4.3%) of the 3α-acetoxy oxetanone (**10b**), mp 146–147.5°. The 70% benzene–petroleum ether and benzene fractions yielded 58 mg of semicrystalline material. Crystallization from methanol gave 17.5 mg (6.4%) of 3α-acetoxy-5-hydroxy-5β-cholestan-6-one (**8b**) as white needles, mp 120–122.5°. No depression in melting point occurred upon admixture with authentic **8b** and the ir spectra were identical.

Elution with 15–25% ether–benzene mixtures gave 86 mg of semicrystalline material. Crystallization from ethanol gave 33 mg (11.7%) of a compound formulated as 3α-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**15a**) (negative Beilstein test): mp 141–142.5°; ir, 3521 (m), 1744 (s), 1709 (s) cm^{-1}; λ_{max} 286 mμ (ε 393).

Anal. Calcd for $C_{29}H_{48}O_5$ (476.67): C, 73.07; H, 10.15. Found: C, 72.93, 72.78; H, 10.19, 10.20.

G. Bromo Ketone 9c.—To a solution of 217 mg (0.361 mmol) of **9c** in 34 ml of DMSO at 76° was added 2.70 ml of the potassium bicarbonate solution. After 1.67 hr the product was isolated and chromatographed on 5 g of alumina. The 60% benzene–petroleum ether eluates gave 16 mg of crystalline material that was recrystallized from methanol, giving 14 mg (7.5%) of the 3α-benzoyloxy oxetanone (**10c**) as white plates, mp 148–149°.

The 30% ether–benzene fractions gave 28 mg of an oil which crystallized from methanol as white needles (25 mg, 13%) of 3α-benzoyloxy-5-hydroxy-5β-cholestan-6-one (**8c**), mp 173–175°.

No other fractions contained significant amounts of material.

3β-Tosyloxy-5,7β-epoxy-5β-cholestan-6-one (7d).—The 3β-acetoxy oxetanone **7b** (10.018 g, 21.90 mmol) was saponified with methanolic potassium hydroxide. The resulting 3β-hydroxy oxetanone (**7a**) was dissolved without prior recrystallization in 60 ml of pyridine and treated with 10.732 g (56.40 mmol) of recrystallized *p*-toluenesulfonyl chloride for 43.3 hr at room temperature. Crushed ice and 60 ml of concentrated hydrochloric acid were added to the vigorously swirled solution. After 2 hr, the precipitated product was collected, washed well with water, and dissolved in chloroform. The dried solution was evaporated and the residue was recrystallized from petroleum ether containing a small amount of chloroform, yielding 10.499 g of tosylate **7d** as a mat of white needles, mp 142.5–143.5° with dec at 185°. Concentration of the mother liquor yielded a further 1.715 g of product with mp 142–143.5° (total yield, 96.5%). Recrystallization of a 170-mg sample from chloroform–petroleum ether gave 148 mg of needles with mp 142–143.5° (dec 183°); $[\alpha]D$ −16° (c 0.857); ir, 1806 (s, oxetanone C=O), 1600 (w, aromatic ring), 1188 and 1176 (s, tosylate), 903 (s, oxetanone ring) cm^{-1}.

Anal. Calcd for $C_{34}H_{50}O_6S$ (570.81): C, 71.54; H, 8.83; S, 5.62. Found: C, 71.33; H, 8.66; S, 5.81.

Reaction of Tosylate 7d with Lithium Carbonate–Dimethylformamide.—To a solution of 7.073 g (12.39 mmol) of tosylate **7d** in 350 ml of dimethylformamide (Baker "analyzed") was added 7.180 g of lithium carbonate.[26b] The mixture was heated under reflux for 2.25 hr, during which time moderate bumping occurred. The mixture was cooled to 35° under the tap, diluted with ether, and filtered with suction to remove suspended salts. The filtrate was washed three times with water, dried, and evaporated to yield an orange oil whose ir spectrum [3534 (w, OH), 1808 and 1799 (s, oxetanone C=O), 1727 (s, H—C=O), 1189, 1186, and 1160 (m, O—CH=O), 903 (m, oxetanone ring) cm^{-1}] was consistent[26b] with a mixture consisting mainly of a formyloxy oxetanone (**10d**). A solution of the oil in 300 ml of 0.112 *N* methanolic potassium hydroxide was boiled for 20 min. The solution was cooled, acidified with 20 ml of 2 *N* hydrochloric acid, diluted with water, and extracted twice with chloroform. The combined extracts were washed once with water, dried, and evaporated. The resulting oil [ir 3534 (m, OH), 1802 (s, oxetanone C=O), 903 (m, oxetanone ring) cm^{-1}] was dissolved in 50 ml of pyridine and 50 ml of acetic anhydride and allowed to remain at room temperature for 41.5 hr. Crushed ice and 50 ml of conc hydrochloric acid were added and the crystalline precipitate that formed was collected, washed with water, and taken up in chloroform.

The dried solution was evaporated and the residue {ir, 1812 (s, oxetanone C=O), 1739 (s, acetate C=O), 1650 (very w, C=C), 1241 [s, O—C(CH$_3$)=O], 907 and 897 (m, oxetanone ring) cm^{-1}} was chromatographed on 175 g of alumina. Elution with 20% benzene in petroleum ether gave 900 mg of a colorless oil that crystallized from methanol as a mat of white needles (330 mg) with mp 91–93° (previous softening). The mother liquor was evaporated to dryness and the residue was recrystallized from aqueous ethanol, yielding an additional 477 mg of needles, mp 88–90° (previous softening). The ir spectrum of this material was identical with that of the first crop of crystals. The total yield was 16.3%. The first crop was recrystallized from aqueous ethanol to give 277 mg of needles with mp 91.5–94.5°, softened at 85°; $[\alpha]D$ −91° (c 1.48); ir, 3049 (w, H—C=C—H), 1808 (s, oxetanone C=O), 1661 (very w, C=C), 907 and 895 (m, oxetanone ring) cm^{-1}; λ_{max} 286 mμ (ε 56). The spectral results, taken with the melting point behavior, indicated that this material was probably a mixture of 5.7β-epoxy-6-oxo-5β-cholest-2- and -3-enes (**17**) as the half-hydrate.

Anal. Calcd for $C_{27}H_{42}O_2 \cdot {}^1/_2H_2O$ (407.62): C, 79.55; H, 10.63. Found: C, 79.87, 80.17; H, 10.38, 10.60.

Elution of the column with 40 to 55% benzene–petroleum ether mixtures and with pure benzene gave 3.705 g of crystalline residue which, when recrystallized from acetone–methanol, gave 3.257 g of the 3α-acetoxy oxetanone **10b**, mp 145.5–147°. A further 214 mg of the oxetanone (mp 144–146°) was obtained from the mother liquor. Elution of the column with ether gave an additional 159 mg of **10b**, which had mp 145.5–147° after recrystallization from methanol. The total yield of crystalline oxetanone **10b** was 64%.

Hydrogenation of the Unsaturated Oxetanone (17).—A solution of 477 mg (1.20 mmol) of **17** in 35 ml of ethyl acetate was hydrogenated in the presence of a Pd–C catalyst until uptake of the gas ceased. The catalyst was removed by suction filtration through magnesium sulfate and the filtrate was evaporated to dryness. Crystallization of the residue from acetone–methanol gave 309 mg of 5,7β-epoxy-5β-cholestan-6-one (**12**) as long white needles, mp 91–93.5°. The mixture melting point with starting material was 76–90°. A second recrystallization from the same solvents yielded 248 mg with mp 92.5–94°. The ir spectrum of this product was identical with that of **12** prepared from the bromo ketone **11b** and no depression in melting point was noted upon admixture of the two samples.

Dilution of the first mother liquor with water gave an additional 65 mg of **12**, mp 92–93°, softened at 87°, which brought the total yield to 78%.

Registry No.—**5a**, 16526-63-9; **5b**, 14956-13-9; **5c**, 6579-84-6; **6a**, 16526-66-2; **6b**, 16526-67-3; **6c**, 16525-96-5; **6d**, 16525-97-6; **7a**, 16525-98-7; **7b**, 16525-99-8; **7c**, 16526-00-4; **7d**, 16526-01-5; **8a**, 6580-08-1; **8b**, 6580-09-2; **8c**, 16564-29-7; **9b**, 16526-04-8; **9c**, 16526-05-9; **10a**, 16526-06-0; **10b**, 16526-07-1; **10c**, 16526-08-2; **11a**, 16526-09-3; **11b**, 16526-10-6; **12**, 16526-11-7; **14a**, 16526-12-8; **14b**, 16526-13-9; **15a**, 16526-14-0; **16**, 16526-15-1; **17** (2-ene), 16526-16-2; **17** (3-ene), 16526-17-3.

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A New Type of Steroid Dimer

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The cyclic ethylene hemithioketals of saturated steroidal ketones react with *p*-toluenesulfonic acid and acetic anhydride to form enol ether dimers. The reaction proceeds through the monomer enol ether formed by preferential acylative cleavage of the carbon–sulfur bond. It is shown that 3,3-dialkyl ketals and Δ^2- and Δ^3-enol ethers form similar dimers in yields of 40–90%. Hydrolysis of the enol ether dimers gives dimer β,γ-monoketones of the type obtained from cholestanone and dihydrotestosterone acetate by aldol condensation in highly acidic media.

It might be expected that polymers of steroidal ketones (or ketone derivatives) would readily be formed in reaction media of high acidity or basicity. There seems, however, to be only two instances of an aldol type of product having been isolated in sufficient quantity and purity to have merited reporting in the literature. Corey and Young[1] found that cholestanone is converted by hydrogen bromide in acetic acid into 2α-(2′-cholesten-3′-yl)-3-cholestanone (IIIa). What is presumed to be the same dimer, in less pure form, has recently been isolated from the products of oxidation of cholestanol with chromium trioxide–acetic acid.[2]

This report describes a new type of steroid dimer: enol ethers related to the Corey–Young type of 2,3′-β,γ-unsaturated ketone. Each of the cyclic ethylene hemithioketals of 5α-cholestanone[3] reacted readily at 25° with *p*-toluenesulfonic acid in acetic anhydride (but *not* in benzene), yielding 85% of a crystalline product whose infrared spectrum displayed typical bands of an acetylthio group (5.88 and 8.79 μ) and an ultraviolet absorption maximum at 230 mμ. Mild acid hydrolysis converted this presumed diene into a ketone identical with the dimer of Corey and Young, which for comparison was resynthesized in 10% yield by heating cholestanone in a 5% solution of anhydrous *p*-toluenesulfonic acid in benzene. Clearly, the hemithioketals Ia and Ia′ had been acetylatively cleaved at the carbon–sulfur bond and dimerized to the acetylthioethyl enol ether of structure IIa, which was then hydrolyzed to dimer ketone IIIa.

For further study, the isomeric 3-ethylene hemithioketals (Ib and Ib′) of 5α-dihydrotestosterone acetate[4] were prepared. Each of these reacted with toluenesulfonic acid in acetic anhydride to yield 60% of an acetylthioethyl enol ether (IIb) which could not be crystallized nor adequately purified by chromatography. Acid hydrolysis afforded 40–50% (over-all from hemithioketals) of dimer keto diacetate IIIb. By-products of this reaction sequence were dihydrotestosterone acetate and probably Wagner–Meerwein rearrangement products of the D ring.[5]

The dimer IIIb was also formed in low yield on heating dihydrotestosterone acetate in toluenesulfonic acid–benzene solution, but was extremely difficult to purify. Its N-acetyloxime was shown to be identical with the same derivative of the dimer ketone from IIb.

The Corey and Young structure for dimers of type III was supported by the nmr spectrum of IIIb, in which a one-proton quartet centered at δ 2.90 ppm is

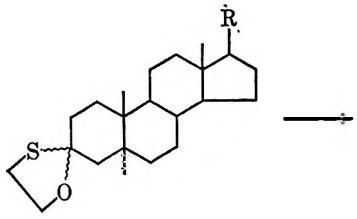
(1) E. J. Corey and R. L. Young, *J. Amer. Chem. Soc.*, **77**, 1672 (1955).

(2) C. W. Shoppee, R. E. Lack, S. C. Sharma, and L. R. Smith *J. Chem. Soc.*, 1155 (1967).

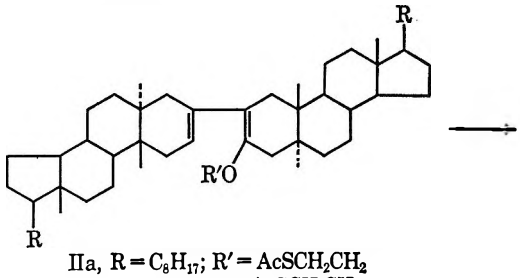
(3) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965), describe the stereoisomeric hemithioketals **Ia** and **Ia′**. (c) Also, for isomer **Ia**, see C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.*, **75**, 3704 (1953); (d) L. F. Fieser, *ibid.*, **76**, 1945 (1954); (e) C. Djerassi, M. Shamma, and T. Y. Kan, *ibid.*, **80**, 4723 (1958).

(4) For mixture of hemithioketals **Ib** and **Ib**, see (a) J. Romo, G. Rosenkranz, and C. Djerassi, *ibid.*, **73**, 4961 (1951); (b) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961). See Experimental Section for the individual isomers. The trivial name, 5α-dihydrotestosterone, is used throughout this report in referring to 5α-androstan-17β-ol-3-one.

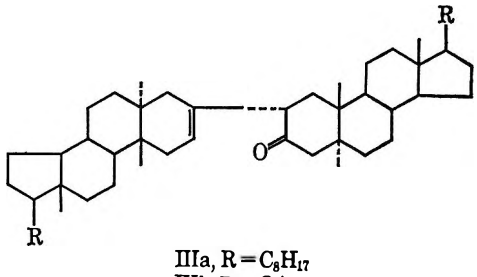
(5) (a) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); (b) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).



Ia, R = C_8H_{17}; α-O-β-S
Ia′, R = C_8H_{17}; β-O-α-S
Ib, R = OAc; α-O-β-S
Ib′, R = OAc; β-O-α-S

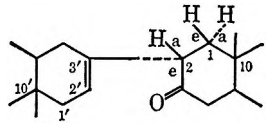


IIa, R = C_8H_{17}; R′ = $AcSCH_2CH_2$
IIb, R = OAc; R′ = $AcSCH_2CH_2$



IIIa, R = C_8H_{17}
IIIb, R = OAc

observed. This can be assigned to a 2 axial H coupled to the 1 equatorial H (J_1 = 6 cps) and also to the 1 axial H (J_2 = 12 cps), with α (equatorial) attachment of carbon 2 to carbon 3′.



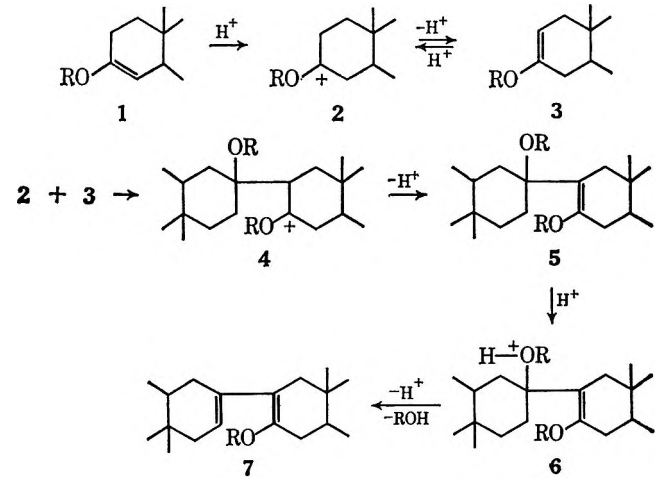
The α attachment at carbon 2 is also supported by the chemical shift (δ 1.07) of the 10-CH_3 of IIIa and b, which is precisely the value observed by Miller for the (2α,2′α-methylene)-bridged dimer of dihydrotestosterone acetate.[6] The previously discussed[1,2] preferences for a $\Delta^{2'}$-5α structure, rather than $\Delta^{3'}$-5α, seem most reasonable even though not yet unequivocally proved.

Dimers of type II must have been formed through the intermediacy of monomeric enol ethers. This dimerization is somewhat surprising in view of the preparation of monocyclic enol ethers from dialkyl ketals with small amounts of *p*-toluenesulfonic acid[7] and of cholestanone ethyl enol ether from the ketone and ethyl orthoformate–sulfuric acid.[3b] However, the validity of the assumption was demonstrated by treating the Δ^2- and Δ^3-methyl, or -ethyl, enol ethers of cholestanone and dihydrotestosterone acetate with 3–7% solutions of anhydrous *p*-toluenesulfonic acid in either acetic anhydride or benzene. The crystalline dimer methyl (IIa′, IIb′) and ethyl (IIb″) enol ethers (and an oily IIa″) analogous to IIa and IIb were formed in 40–60% yields. The formation of the same dimer enol ether from Δ^3-5α monomer as from Δ^2-5α monomer requires a double-bond shift to the thermodynamically favored Δ^2-enol ether prior to dimerization. Evidence for such a transformation in steroids has been elusive, having been only indirectly observed in the bromination of Δ^3-enol ethers.[8]

Acid hydrolysis of dimer enol ethers IIa′, a″, b′, and b″ afforded the same dimer ketones as derived from the cyclic ethylene hemithioketals.

The generality of the dimerization was apparent when it was observed that the dimethyl and diethyl ketals of 5α-dihydrotestosterone acetate and the dimethyl ketal of cholestanone were also converted by 3–4% anhydrous toluenesulfonic acid in acetic anhydride or benzene into 20–70% of dimer enol ethers IIa′, b′, and b″. In benzene, either heating or prolonged reaction times are necessary to yield significant amounts of dimer, although the reaction proceeds readily in acetic anhydride. Again, it is apparent that monomer Δ^2-enol ether is the intermediate for dimerization.

Mechanistically, these dimerizations obviously require only a high proton concentration, except that in the case of ethylene hemithioketals acetic anhydride is needed to provide acylium cation which effects preferential scisson of the carbon–sulfur bond, prior to dimerization. This is analogous to the acylative cleavage of cyclic ethylene dithioketals.[9] The enol ether **3** can dimerize to **4** by attack on its protonated form **2**. Subsequent loss, addition, and loss of a proton, followed by loss of alcohol then leads to the dimeric enol ether **7**, which is stable to anhydrous acid in the benzene or acetic anhydride medium. Other types of carbonium ion intermediates and other reaction paths may be postulated, but the proposed sequence invokes a minimum number of proton transfers and avoids multiply charged ions.



Experimental Section

Melting points are corrected (Fisher-Johns apparatus), with stage preheated to 10° below reported values. Ultraviolet spectra were taken in 95% ethanol with a Cary Model 11 spectrophotometer and infrared spectra were obtained with a Beckman

(6) T. C. Miller, *J. Org. Chem.*, **30**, 2922 (1965).
(7) U. Schmidt and P. Grafen, *Ann.*, **656**, 97 (1962).
(8) R. Gardi, P. P. Castelli, and A. Ercoli, *Tetrahedron Lett.*, 497 (1962).
(9) G. Karmas, *ibid.*, 1093 (1964).

IR-5 spectrophotometer, neat for oils, pressed KBr wafers for solids. Optical rotations were taken in chloroform (trace of pyridine) on a Rudolph Model 70 polarimeter. Nmr spectra were obtained on a Varian A-60 spectrophotometer in deuteriochloroform solution (*ca.* 1% pyridine). Chemical shifts are recorded as δ values (tetramethylsilane as internal standard), center of signal, and d = doublet, t = triplet, q = quartet, m = multiplet, with singlets not specified by abbreviation. Organic solutions were routinely dried with potassium carbonate prior to evaporation under vacuum. Elemental analyses were performed by Midwest Microlab, Inc., of Indianapolis, Ind.

5α-Dihydrotestosterone Acetate 3,3-Dimethyl Ketal.[10]—A solution of 1.5 g of dihydrotestosterone acetate and 50 mg of toluenesulfonic acid[11] in 20 ml of anhydrous methanol was boiled for 5 min, then made alkaline with solid sodium methylate, diluted with 500 ml of water, and twice extracted with ether. After being washed twice with water and dried, the ether solution was evaporated, and the residue was recrystallized from methanol (pyr) to give 1.35 g of the ketal: mp 144–146° (lit.[10] mp 143–147°); λ_{max} 5.74, 8.00, 9.07, 9.48, 9.68 μ.

5α-Dihydrotestosterone Acetate 3,3-Diethyl Ketal.[12]—A solution of 6 g of dihydrotestosterone acetate and 250 mg of toluenesulfonic acid in 100 ml of anhydrous ethanol was refluxed for 30 min and then made alkaline with sodium ethoxide (in ethanol). Work-up and recrystallization as for the dimethy ketal (above) gave 2.5 g of diethyl ketal: white prisms; mp 133–135°; λ_{max} 5.77, 7.97, 9.42, 9.63 μ.

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.61; H, 10.50.

17β-Acetoxy-3-methoxy-2-(5α-androstene). A.—A solution of 1.2 g of dihydrotestosterone acetate 3,3-dimethyl ketal in 20 ml of xylene was refluxed under nitrogen for 6 hr. Chromatography of the xylene residue on neutral alumina (20 g Woelm grade I; 20-mm-i.d. column; eluted with 150 ml of methylene chloride) gave crude enol ether which was recrystallized from methanol and from acetone (pyr) to give 0.15 g of the Δ^2-enol ether: mp 127–129°; λ_{max} 5.72, 5.93, 7.97, 8.14, 9.60, 12.67 μ.

B.—When 680 mg of the dimethyl ketal was heated with 100 mg of powdered Pyrex glass at 220°[13] for 1 hr and the pyrolysis product purified as in A, there was obtained 70 mg of the Δ^2-enol ether, mp 126–129°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.11; H, 9.98.

Cholestanone 3-ethylene hemithioketal, α-O–β-S (mp 135–136°, Ia) and cholestanone 3-ethylene hemithioketal, β-O–α-S (mp 112–113°, Ia′) were prepared essentially as described in ref 3a. These tentative configurations were based on nmr studies,[3a,b] but the chemical-shift values have not been noted in the publications. We have observed for Ia δ 3.02 (t, CH_2S), 4.15 (*split* t, CH_2O); for Ia′ 3.01 (t, CH_2S), 4.17 (*clean* t, CH_2O). The splitting of the CH_2O triplet of the α-O–β-S isomer is the most striking difference in the nmr spectra. This was also observed for the isomeric dihydrotestosterone 3-ethylene hemithioketals and their 17-acetates (below), and is the basis for their stereochemical assignments, following Eliel, Pilato, and Badding.[3a]

5α-Dihydrotestosterone Acetate 3-Ethylene Hemithioketal, β-O–α-S (Ib′).—A mixture of 10 g of β-mercaptoethanol, 10 g of dihydrotestosterone acetate, 500 mg of toluenesulfonic acid, and 500 ml of benzene was refluxed for 3 hr with separation of water (Dean–Stark trap). After several washings with water the benzene solution was evaporated to a crystalline residue of mixed hemithioketals. Fractional crystallization from ether and from ethyl acetate gave numerous small portions with roughly 10° melting point ranges, covering 140–185° over-all. All portions of melting point above 160° were combined and recrystallized successively from ethyl acetate, methanol, and ethyl acetate to give 1.1 g of white prisms of isomer Ib′: mp 185–186°; $[\alpha]_D$ +3.5°; λ_{max} 5.73, 7.97, 9.34, 9.65, 10.96, 11.41, 11.66 μ; nmr δ 0.79 (18-H_3), 0.82 (19-H_3), 2.01 (17β-OAc), 3.03 (t, CH_2S), 4.12 (t, CH_2O).

Anal. Calcd for $C_{23}H_{36}O_3S$: C, 70.40; H, 9.24. Found: C, 70.64; H, 9.30.

5α-Dihydrotestosterone 3-ethylene hemithioketal, β-O–α-S, by saponification of Ib′ (2% KOH–methanol, 10-min reflux), was obtained as white prisms from ethyl acetate: mp 207–209°; $[\alpha]_D$ +10.6°; λ_{max} 2.83, 9.29, 9.65, 10.90, 11.40, 11.69, 11.78 μ; nmr δ 0.74 (18-H_3), 0.83 (19-H_3), 3.04 (t, CH_2S), 4.12 (t, CH_2O).

Anal. Calcd for $C_{21}H_{34}O_2S$: C, 72.00; H, 9.77. Found: C, 71.78; H, 9.92.

5α-Dihydrotestosterone 3-Ethylene Hemithioketal, α-O–β-S.—The hemithioketal portions of melting point below 160° were combined and recrystallized from methanol to give 5 g of prisms, mp 143–150°, which was then saponified (200 ml of 2% KOH–methanol, 10-min reflux). The 17β-ol obtained by dilution with water and removal of methanol under vacuum was recrystallized twice from ethyl acetate (few drops of water) to afford 3.2 g of white prisms: mp 152–153°; $[\alpha]_D$ +16°; λ_{max} 2.90, 9.28, 9.69, 10.40, 11.60, 11.80 μ; nmr δ 0.75 (18-H_3), 0.84 (19-H_3), 3.03 (t, CH_2S), 4.16 (*split* t, CH_2O).

Anal. Calcd for $C_{21}H_{34}O_2S$: C, 72.00; H, 9.77. Found: C, 71.58; H, 9.90.

Acetylation of the 17β-ol with pyridine–acetic anhydride gave **5α-dihydrotestosterone acetate 3-ethylene hemithioketal, α-O–β-S (Ib):** mp 145–146°; $[\alpha]_D$ +12°; λ_{max} 5.73, 7.97, 9.62, 11.72 μ; nmr δ 0.79 (18-H_3), 0.83 (19-H_3), 2.01 (17β-OAc), 3.20 (t, CH_2S), 4.16 (*split* t, CH_2O).

Anal. Calcd for $C_{23}H_{36}O_3S$: C, 70.40; H, 9.24. Found: C, 70.53; H, 9.41.

2-(2′-Cholesten-3′-yl)-3-(β-acetylthioethoxy)-2-cholestene (IIa). A.—To a stirred solution of 1.0 g of the α-O–β-S hemithioketal Ia[3a] in 4 ml of methylene chloride was added a solution of 1.0 g of toluenesulfonic acid in 11 ml of acetic anhydride. After 45 min, the suspension was cooled to 0°, further diluted with 20 ml of acetic anhydride containing 2 ml of pyridine and filtered. Washing on the filter with methanol (pyr) and air drying gave 0.9 g of pale yellow microgranules, mp 138–141°. Recrystallization from acetone gave the analytical sample: mp 140–143°; $[\alpha]_D$ +59°; λ_{max} 230 mμ (ε 8940); λ_{max} 5.88, 8.51, 8.79, 9.00 μ; nmr δ 2.31 (AcS), 3.05 (t, CH_2S), 3.72 (t, CH_2O), 5.31 (m, 2′-H).

Anal. Calcd for $C_{58}H_{96}O_2S$: C, 81.23; H, 11.28; S, 3.74. Found: C, 81.46; H, 11.38; S, 3.64.

B.—The process of A, applied on a one-tenth scale to the β-O–α-S hemithioketal Ia′ afforded 85 mg of dimer enol ether with infrared spectrum identical with the IIa obtained from Ia.

2-(2′-Cholesten-3′-yl)-3-methoxy-2-cholestene (IIa′). A.—To a stirred solution of 1.0 g of cholestanone dimethyl ketal[14] in 6 ml of methylene chloride was added 0.5 g of toluenesulfonic acid in 7 ml of acetic anhydride. After 20 min at 25° and 20 min at 0° the crystalline solid was filtered off, washing with small amounts of acetic anhyride and ether (pyr) to give 0.75 g of the dimer methyl enol ether. Recrystallization from ether (pyr) afforded 0.6 g of IIa′: white flakes; mp 163–165°; λ_{max} 230 mμ (ε 12,200); λ_{max} 8.10, 8.25, 8.73, 12.34 μ; nmr δ 3.42 (3-MeO), 5.30 (m, 2′-H).

Anal. Calcd for $C_{55}H_{92}O$: C, 85.84; H, 12.05. Found: C, 86.09; H, 11.87.

When cholestanone dimethyl ketal was kept at 25° in a 4% solution of anhydrous toluenesulfonic acid in benzene for 20 min, no significant amount of dimerization occurred. Conventional work-up, with constant excess of pyridine, gave only recovered ketal.

2-(2′-Cholesten-3′-yl)-3-ethoxy-2-cholestene (IIa″).—When 1.0 g of 3-ethoxy-3-cholestene[8] was reacted with toluenesulfonic acid in acetic anhydride plus methylene chloride as described above for IIa, a viscous oil separated from the mixture. After addition of 2 ml of pyridine, the mixture was hydrolyzed in ice and water containing 20 ml of pyridine and the oily product was extracted with methylene chloride. Evaporation gave the crude dimer ethyl enol ether IIa″, λ_{max} 229 mμ, which could not be induced to crystallize. Acid hydrolysis as described below afforded 0.4 g of the dimer ketone IIIa.

2α-(2′-Cholesten-3′-yl)-3-cholestanone (IIIa). A.—A solu-

(10) P. E. Shaw, F. W. Gubitz, K. F. Jennings, G. O. Potts, A. L. Beyler, and R. C. Clarke, *J. Med. Chem.*, **7**, 555 (1964), isolated this compound from a complex reaction mixture. The direct preparation seems not to have been described.

(11) In this section, toluenesulfonic acid as a reagent means *p*-toluenesulfonic acid monohydrate. However, it obviously becomes anhydrous acid in the presence of acetic anhydride and in those experiments where the monohydrate in benzene is boiled down to a small final volume.

(12) A. Ercoli and P. Ruggieri, *J. Amer. Chem. Soc.*, **75**, 650 (1953), describe this compound as an oil.

(13) Pyrolysis process of J. H. Fried, A. N. Nutile, and G. E. Arth, *ibid.*, **82**, 5704 (1960).

(14) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Phillipps, *J. Chem. Soc.*, 1529 (1958).

tion of 1.0 g of IIa and 0.3 ml of concentrated HCl in 20 ml of tetrahydrofuran and 10 ml of acetone was kept at 25° for 1 hr and then slowly diluted with 100 ml of water. The cream solid was filtered off, dried, and recrystallized from methylene chloride–ethyl acetate to give 0.75 g of IIIa: mp 206–208°; $[\alpha]_D$ +40° (reported[1] mp 209–211°, $[\alpha]_D$ +41°); λ_{max} 5.82, 8.40, 8.50, 10.40, 12.40 μ; nmr δ 1.06 (19-H_3), 2.92 (m, 2-H), 5.30 (m, 2′-H).

B.—Acid hydrolysis of the crystalline dimer methyl enol ether IIa′, as in A, gave a high yield of the same dimer ketone IIIa.

C. From Cholestanone, through Crude Hemithioketal.—A mixture of 2 g of cholestanone, 2 ml of β-mercaptoethanol, 0.2 g of oxalic acid, and 150 ml of benzene was refluxed for 5 hr with water separation. Washing with water, drying, and evaporation of the benzene solution gave the mixed hemithioketals Ia + Ia′. This crystalline mass was dissolved in 8 ml of methylene chloride, 2 g of toluenesulfonic acid in 22 ml of acetic anhydride was added, and all was stirred at 25° for 3 hr and then hydrolyzed in ice and water containing 40 ml of pyridine. Methylene chloride extraction and evaporation, followed by acid hydrolysis and recrystallization as in A, afforded 1.4 g of IIIa, mp 204–208°.

D. From Cholestanone, by Aldol Condensation.—A suspension of 0.8 g of toluenesulfonic acid in 50 ml of benzene was boiled down to 10 ml to obtain a yellow solution of the anhydrous acid. Then 1.5 g of cholestanone and 10 ml of benzene was added, and the solution was refluxed for 3 hr. The water-washed benzene solution gave a glassy residue on evaporation, and from this there was obtained, after several recrystallizations from ethyl acetate, 0.15 g of IIIa: mp 200–204°; $[\alpha]_D$ +37°; ir and nmr spectra identical with those of the dimer ketone obtained in A. Cholestanone (0.7 g) was recovered during the recrystallization. There undoubtedly were other dimer isomers present in the remaining 0.5 g of high-melting (185–200°) material, but only IIIa could be isolated relatively pure through seeding with the material from A.

2-[17′β-Acetoxy-2′-(5′α-androsten)-3′-yl]-17β-acetoxy-3-methoxy-2-(5α-androstene) (IIb′). **A.**—To a solution of 0.75 g of toluenesulfonic acid in 25 ml of acetic anhydride was added 3.1 g of dihydrotestosterone acetate 3,3-dimethyl ketal. The mixture was stirred at 25° for 20 min; 8 ml of pyridine was added, and then it was hydrolyzed in ice and water containing 70 ml of pyridine. The white solid was filtered off, stirred well with 50 ml of methanol, and refiltered to give 2.5 g of the dimer methyl enol ether. This was recrystallized from acetone (pyr) to afford 2.0 g of IIb′: mp 192–199°; $[\alpha]_D$ +46°; λ_{max} 228 mμ (ϵ 6270); λ_{max} 5.75, 8.00, 9.53, 9.64 μ; nmr δ 0.80 (18-H_3, 18′-H_3, 19-H_3, 19′-H_3), 2.01 (17β-OAc), 3.41 (3-MeO), 5.30 (m, 2′-H).

Anal. Calcd for $C_{43}H_{64}O_5$: C, 78.14; H, 9.76. Found: C, 78.34; H, 9.90.

The methanol wash liquor from the crude dimer was acidified and worked up in conventional fashion to give 0.3 g of dihydrotestosterone acetate (identified by ir).

B.—On an appropriately smaller scale, 100 mg of 17β-acetoxy-3-methoxy-2-(5α-androstene) was treated with toluenesulfonic acid as in A to give 50 mg of dimer methyl enol ether, ir identical with that of IIb′ obtained in A.

C.—When dihydrotestosterone acetate 3,3-dimethyl ketal was kept for 1.5 hr at 25° in a 4% solution of anhydrous toluenesulfonic acid in benzene the yield of IIb′ was 30%. Boiling of a similar reaction mixture for 10 min raised the yield to 45%, apparently as a result of more monomeric enol ether first being formed.

Dimer 3-Ethyl Enol Ether (IIb″). **A.**—When 4.0 g of 17β-acetoxy-3-ethoxy-3-(5α-androstene)[8] was treated with toluenesulfonic acid and acetic anhydride as described for IIb′, there was obtained 3.5 g of crude dimer enol ether, mp 145–160°. Recrystallization from ether (pyr) gave 3.1 g of cream prisms of IIb″: mp 167–171°; $[\alpha]_D$ +49°; λ_{max} 230 mμ (ϵ 5700); λ_{max} 5.73, 8.01, 8.92, 9.63 μ; nmr δ 0.80 (18-H_3, 18′-H_3, 19-H_3, 19′-H_3), 1.09 and 3.53 (t, q, 3-EtO), 2.02 (17β-OAc), 5.29 (m, 2′-H).

Anal. Calcd for $C_{44}H_{66}O_5$: C, 78.29; H, 9.86. Found: C, 77.86; H, 9.98.

The same starting material, kept at 25° for 1.5 hr in 3% anhydrous toluenesulfonic acid in benzene, gave a 60% yield of dimer IIb″.

B.—When 1.0 g of 17β-acetoxy-3-ethoxy-2-(5α-androstene)[8] was treated with toluenesulfonic acid in acetic anhydride as in A, there was obtained 0.8 g of dimer whose ir and nmr spectrum were identical with those of IIb″ obtained in A.

C.—Reaction as in A, performed on 0.5 g of dihydrotestosterone acetate 3,3-diethyl ketal, gave 0.3 g of dimer ethyl enol ether IIb″.

2α-[17′β-Acetoxy-2′-(5α-androsten)-3′-yl]-17β-acetoxy-5α-androstan-3-one (IIIb). **A.**—When 0.5 g of dihydrotestosterone acetate 3-ethylene hemithioketal α-O-β-S (Ib) was treated with toluenesulfonic acid in acetic anhydride as in process A for IIb″ (above), the product was a viscous oil which could not be crystallized. Chromatography on acidic alumina (20 g, Woelm grade I; 20-mm i.d. column; eluted with 300 ml of 1:1 benzene–hexane) gave 0.32 g of pale yellow oil whose ir spectrum was appropriate for the dimer β-acetylthioethyl enol ether IIb: λ_{max} 5.74, 5.88, 7.99, 8.77, 9.51, 9.63 μ. The 0.32 g of IIb, in 10 ml of acetone and 0.3 ml of concentrated HCl, was kept at 5° for 30 min and filtered to give 0.25 g of cream prisms. Recrystallization from acetone afforded 0.2 g of white prisms of IIIb: mp 258–261° dec; $[\alpha]_D$ +21°; λ_{max} 5.74, 5.80, 8.00, 9.66 μ; nmr δ *ca.* 0.80 (18-H_3, 18′-H_3, 19′-H_3), 1.07 (19-H_3), 2.01 (17β-OAc), 2.90 (q, J_1 = 6, J_2 = 12, 2-H), 5.23 (m, 2′-H).

Anal. Calcd for $C_{42}H_{62}O_5$: C, 77.97; H, 9.66. Found: C, 78.06; H, 9.62.

The N-acetyloxime of IIIb (standard oximation in pyridine followed by pyridine–acetic anhydride acetylation) was white flakes: mp 190–192°; $[\alpha]_D$ +41°; λ_{max} 5.73, 8.00, 9.52, 9.63, 10.80 μ; nmr δ 0.81 (18-H_3, 18′H_3, 19′-H_3), 0.97 (19-H_3), 2.02 (17β-OAc), 2.16 (3-AcON=), 2.98 (q, 2-H), 5.37 (m, 2′-H).

Anal. Calcd for $C_{44}H_{65}O_6N$: C, 75.07; H, 9.31; N, 1.99. Found: C, 75.24; H, 9.49; N, 1.86.

B.—The reaction described in A, performed on the β-O-α-S hemithioketal Ib′, gave intermediate oily dimer enol ether IIb and final dimer ketone IIIb exactly as isolated in A.

C and D.—Acid hydrolysis, as in A, of the dimer methyl enol ether IIb′ and dimer ethyl enol ether IIb″ gave high yields of the dimer ketone IIIb, with physical properties exactly as described in A.

E.—A solution of 3.0 g of dihydrotestosterone acetate and 1.4 g of anhydrous toluenesulfonic acid in 20 ml of benzene was refluxed for 4 hr. After washing with water and evaporation of the benzene solution, the glassy residue was recrystallized from methanol and three times from acetone, seeding with IIIb, to afford 0.5 g of white prisms, mp 250–260° dec, ir similar to that of IIIb. Conversion of the 0.5 g to N-acetyloxime and two recrystallizations from methanol gave 0.25 g of white flakes: mp 192–192°; ir spectrum identical with that of the acetyloxime described in A.

Chemical Shifts of Starting Materials.—Interpretations of dimer nmr spectra were based on the spectra of steroid ketone, ketal, and enol ether starting materials. Some of these have not been reported and so all of the meaningful shifts (in $CDCl_3$ with *ca.* 1% pyridine) are here appended: **cholestanone**, 0.70 (18-H_3), 1.03 (19-H_3); **dihydrotestosterone acetate**, 0.82 (18-H_3), 1.02 (19-H_3), 2.02 (17β-OAc); **cholestanone dimethyl ketal**, 0.68 (18-H_3), 0.82 (19-H_3 + other), 3.11 and 3.16 (3-MeO, 3-MeO); **dihydrotestosterone acetate dimethyl ketal**, 0.82 (18-H_3, 19-H_3), 2.04 (17β-OAc), 3.18 and 3.22 (3-MeO, 3-MeO); **17β-acetoxy-3-ethoxy-2-(5α-androstene)**, 0.80 (18-H_3, 19-H_3), 1.28 and 3.71 (t, q, 3-EtO), 2.03 (17β-OAc), 4.54 (m, 2-H); **3-ethoxy-3-cholestene**, 0.70 (18-H_3), 1.29 and 3.70 (t, q, 3-EtO), 4.51 (m, 4-H); **17β-acetoxy-3-ethoxy-3-(5α-androstene)**, 0.82 (18-H_3, 19-H_3), 1.28 and 3.71 (t, q, 3-EtO), 2.05 (17β-OAc), 4.52 (m, 4-H).

Registry No.—Ia, 2760-91-0; Ia′, 2760-93-2; Ib, 16158-92-2; Ib′, 16158-93-3; IIa, 16159-07-2; IIa′, 16158-94-4; IIb′, 16203-49-9; IIb″, 16203-48-8; IIIa, 16203-50-2; IIIb, 16158-95-5; N-acetyl oxime of IIIb, 16158-96-6; 5α-dihydrotestosterone acetate 3,3-diethyl-ketal, 16158-97-7; 17β-acetoxy-3-methoxy-2-(5α-androstene), 16158-98-8; 5α-dihydrotestosterone 3-ethylenehemithioketal β-O-α-S, 16158-99-9; 5α-dihydrotestosterone 3-ethylenehemithioketal, α-O-β-S, 16159-00-5; 5α-dihydrotestosterone acetate 3,3-dimethyl ketal, 16159-01-6; cholestanone, 566-88-1; dihydrotestoster-

one acetate, 1164-91-6; cholestanone dimethyl ketal, 16159-03-8; 17β-acetoxy-3-ethoxy-2-(5α-androstene), 16159-04-9; 17β-acetoxy-3-ethoxy-3-(5α-androstene), 16159-05-0; 3-ethoxy-3-cholestene, 16159-06-1.

Acknowledgment.—Assistance from Dr. Fortune Kohen and Dr. A. P. Shroff in obtaining and interpreting the nmr spectra was extremely helpful during this investigation.

Steroids. VIII. The Beckmann Rearrangement of 2-Oximinocholesta-4,6-dien-3-one. The Synthesis of Some 2,3-Secocholesta-4,6-dienes[1a]

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Received December 19, 1967

The structure of an unusual dimeric Beckmann rearrangement product (III) derived from 2-oximinocholesta-4,6-dien-3-one (I) has been elucidated. A number of 2,3-secocholesta-4,6-dienes have been synthesized from I, making use of the Beckmann rearrangement as the ring-cleavage step.

The Beckmann rearrangement has been employed in the synthesis of a wide variety of aza steroids from various simple saturated and unsaturated steroidal ketoximines.[2] The Beckmann rearrangement of steroidal α-oximino ketones has been much less thoroughly investigated. This reaction appears to have been examined only with 16-oximino 17-ketones[3] and with 2,4-bisoximino 3-ketones;[4] it serves as a useful route to 16,17-seco steroids[3] and 2,3-seco-A-nor steroids,[4] respectively. We now report the behavior of the conjugated α-oximino ketone, 2-oximinocholesta-4,6-dien-3-one,[1a] (I) under Beckmann rearrangement conditions.

As reported previously, oximino ketone I reacts with acetic anhydride in pyridine to give an acetate (II) which can be hydrolyzed back to I without rearrangement or ring cleavage.[1a] On the other hand, the reaction of I with tosyl chloride in pyridine afforded a crystalline product, mp 197–198°, which was not the tosylate of I. It was assigned the unusual dimeric structure III on the basis of the spectral and chemical evidence discussed below.

The dimeric formula $C_{54}H_{82}O_3N_2$ fitted well with the results of both elemental analysis and molecular weight determinations. The infrared spectrum of III showed carbonyl bands at both 5.70 and 5.97 μ, as well as a series of bands at 6.17, 6.23, and 6.33 μ attributable to conjugated olefinic and imine functions; significantly, no nitrile absorption in the 4.4–4.5-μ region was observed.

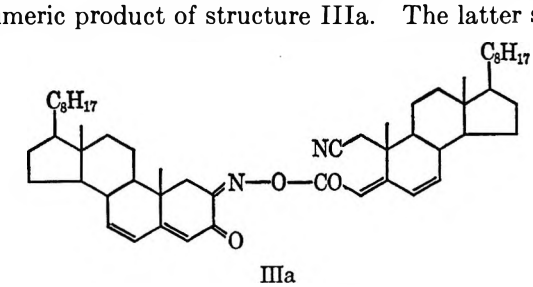
In the course of determining whether or not the dimer contained a readily reduced carbonyl group, it was allowed to react with sodium borohydride in methanol solution. Two crystalline products, mp 167 and 235°, were isolated in 41 and 37% yield, respectively, after preparative thin layer chromatography. It was soon shown that the reagent in this reaction was acting not as a reducing agent, but simply as a source of methoxide ion. The same products were obtained in approximately the same yields when dimer III was treated with a solution of sodium methoxide in methanol.

The product, mp 235°, was identified readily as the original oximino ketone I. The second product, mp 167°, analyzed for $C_{28}H_{43}O_3N$; it was assigned structure IV on the basis of its spectral and chemical properties. The infrared spectrum of IV showed an ester carbonyl at 5.78, a cyano group at 4.40, and conjugated olefin bands at 6.14 and 6.25 μ; no hydroxyl absorption in the 3-μ region was observed. The nmr spectrum of IV showed the methoxyl of the ester function as a singlet at τ 6.27, as well as a multiplet at 3.29–4.31 corresponding to three olefinic protons. Reaction of dimer III with sodium hydroxide yielded a mixture of oximino ketone I and the cyano acid V, mp 218°. Acid V was converted by diazomethane into the cyano ester IV.

The proposed mechanism for the conversion of oximino ketone I into the oxime imidate ester III, and fragmentation of III into I and IV by methoxide ion, is shown in Scheme I.

The interception of imino derivatives in the course of Beckmann rearrangements is well known.[5] An example of a Beckmann rearrangement in which an equivalent of unrearranged oxime is incorporated into the isolated product has been provided by Hill, who described the conversion of A into B shown in Scheme II.[6]

A rather analogous process can be envisaged for the Beckmann rearrangement of oximino ketone I to give a dimeric product of structure IIIa. The latter struc-



IIIa

(1) (a) Part VII: M. P. Cava, E. J. Glamkowski, and Q. A. Ahmed, *J. Org. Chem.*, **32**, 2644 (1967). (b) To whom all inquiries should be addressed: Department of Chemistry, Wayne State University, Detroit, Mich. 48202.

(2) (a) T. A. Jacobs and R. B. Brownfield [*J. Amer. Chem. Soc.*, **82**, 4033 (1960)] cover the literature up to 1960; (b) C. W. Shoppee and G. Kruger, *J. Chem. Soc.*, 3641 (1961); (c) C. W. Shoppee, G. Kruger, and R. N. Mirrington, *ibid.*, 1050 (1962); (d) C. W. Shoppee, R. E. Lack, and B. C. Newman, *ibid.*, 3388 (1964); (e) C. W. Shoppee, R. W. Killick, and G. Kruger, *ibid.*, 2275 (1962); (f) C. W. Shoppee, R. E. Lack, and S. K. Roy, *ibid.*, 3767 (1963); (g) C. W. Shoppee, R. E. Lack, R. N. Mirrington, and C. R. Smith, *ibid.*, 5868 (1965); (h) C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *ibid.*, 3392 (1964); (i) N. J. Doorenbos and R. E. Havranek, *J. Org. Chem.*, **30**, 2474 (1965); (j) R. Mazur, *ibid.*, **28**, 248 (1963); (k) L. Knof, *Ann.*, **642**, 194 (1961); (l) J. A. Zderic and J. Iriarte, *J. Org. Chem.*, **27**, 1756 (1962); (m) P. Bladon and W. McMeekin, *J. Chem. Soc.*, 3504 (1961); (n) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961); (o) H. Singh and V. V. Parashar, *Tetrahedron Lett.*, 983 (1966).

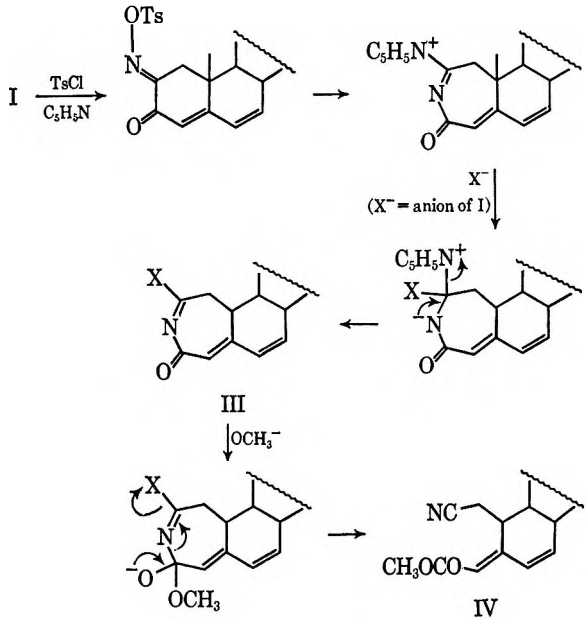
(3) (a) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938); and, more recently, (b) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).

(4) (a) M. P. Cava, E. J. Glamkowski, and P. M. Weintraub, *ibid.*, **31**, 2755 (1966); (b) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1445 (1965).

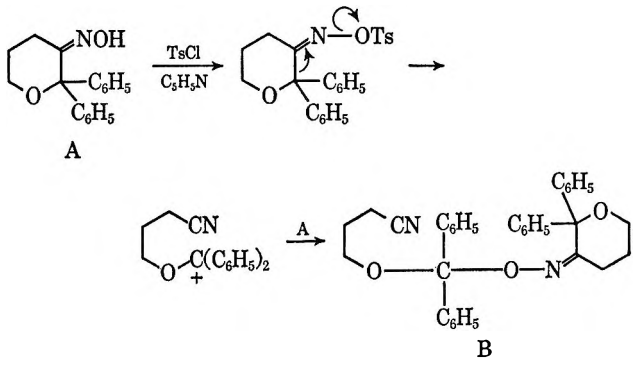
(5) For some examples, see W. Z. Heldt, *J. Amer. Chem. Soc.*, **80**, 5880 (1958), and references cited therein.

(6) R. K. Hill, *J. Org. Chem.*, **27**, 30 (1962).

SCHEME I



SCHEME II

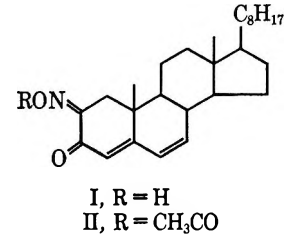


ture for the rearrangement product would be in accord with its transformation into compounds IV and V by base cleavage. It must be discarded in favor of III, however, since the infrared spectrum of the actual dimer unambiguously shows the absence of a cyano group in the molecule.

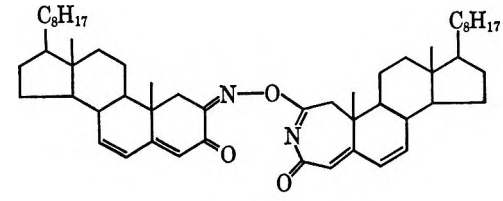
The reaction of oximino ketone I with thionyl chloride does not give the dimeric compound III. The product of second-order Beckmann cleavage, cyano acid chloride VI, is formed instead.[7] Although compound VI was not isolated in a state of purity, the crude material showed bands at 4.43 and 5.65 μ, characteristic of the cyano and the conjugated acid chloride functions, respectively. Furthermore, unpurified VI reacted with water and with methanol to give acid V and methyl ester IV, respectively, in yields based on I of well over 50%; no starting material was detected in these reactions.

Acid chloride VI was treated also with ammonia, aniline, phenylmagnesium bromide, and methylmagnesium bromide to give the corresponding 2,3-seco steroids (VII, VIII, IX, and X) in satisfactory yields. Dehydration of amide VII with refluxing thionyl chloride gave the dinitrile XI.

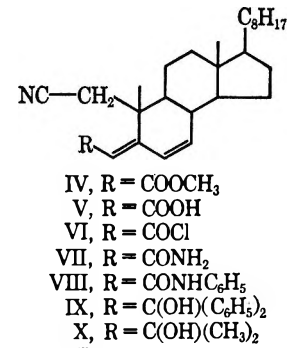
Cyano ester IV and dinitrile XI both underwent catalytic reduction in the presence of palladium to yield single crystalline tetrahydro derivatives (XII and XIII) in good yield. These compounds were shown to have the 5α configuration, resulting from delivery of hydrogen at the less hindered side of the molecule, by direct correlation with a cholestane derivative of known configuration at C-5. Thus, reaction of pure 2-oximinocholestan-3-one (XIV)[1a,8] with thionyl chloride gave the cyano acid chloride (XV), which was treated directly with sodium methoxide to give ester XII, identical with the reduction product of the unsaturated cyano ester IV. Similarly, the reaction of acid chloride XV with ammonia gave the saturated amide XVI; dehydration of XVI with thionyl chloride gave dinitrile XIII, identical with the reduction product of the unsaturated dinitrile XI.



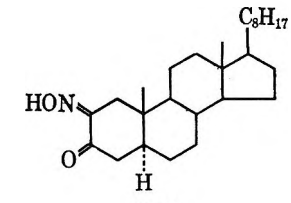
I, R = H
II, R = CH_3CO



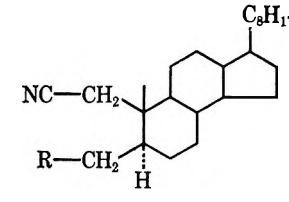
III



IV, R = $COOCH_3$
V, R = COOH
VI, R = COCl
VII, R = $CONH_2$
VIII, R = $CONHC_6H_5$
IX, R = $C(OH)(C_6H_5)_2$
X, R = $C(OH)(CH_3)_2$
XI, R = CN



XIV



XII, R = $COOCH_3$
XIII, R = CN
XV, R = COCl
XVI, R = $CONH_2$

Experimental Section[9]

Reaction of 2-Oximinocholesta-4,6-dien-3-one (I) with Tosyl Chloride in Pyridine.—A solution of oximino ketone I[1a] (3.00 g)

(7) The reaction of 1-nitroso-2-naphthol with phosphorous pentachloride to give *o*-cyanocinnamoyl chloride is closely analogous to this reaction: W. Borsche and W. Sander, *Ber.*, **47**, 2815 (1914).

(8) M. P. Cava, P. M. Weintraub, and E. J. Glamkowski, *J. Org. Chem.*, **31**, 2015 (1966).

(9) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer (potassium bromide disks). Ultraviolet absorption spectra were determined in 95% ethanol using a Perkin-Elmer Model 4000 Spectracord. Optical rotations were measured in chloroform solution, unless otherwise indicated. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and by Dr. A. Bernhardt, Mülheim, Germany. The statement that a solution was worked up on the usual manner should be taken to mean that it was washed successively with water and aqueous sodium chloride, then dried over anhydrous sodium sulfate, and finally evaporated to dryness on a steam bath with the aid of a rotary evaporator. The identity of products with authentic samples was checked by mixture melting point determinations and infrared spectral comparisons.

and tosyl chloride (4.50 g) in dry pyridine (50 ml) was stirred for 24 hr at room temperature. The reaction mixture was poured into cold water (500 ml) and the precipitated product was extracted into two 350-ml portions of ether. The ether extract was washed with aqueous sodium bicarbonate and worked up in the usual manner. Crystallization from ether–methanol gave the Beckmann dimer III (1.90 g, 63%), mp 195–197°. The pure dimer (1.83 g, 61%), mp 197–198°, was obtained by recrystallization from the same solvent mixture: $[\alpha]^{25}D$ −131° (c 2.62); λ_{max} 5.70, 5.97, 6.17, 6.23, and 6.30 μ; λ_{max} (sh) 220 mμ (ε 20,900) and 308 mμ (ε 30,200).

Anal. Calcd for $C_{54}H_{82}O_3N_2$: C, 80.59; H, 9.95; N, 3.48; S, 0.00. Found: C, 80.54; H, 9.91; N, 3.42; S, 0.00.

Sodium Hydroxide Cleavage of Beckmann Dimer III. 2,3-Secocholesta-4,6-diene-2-nitril-3-oic Acid (V).—A solution of dimer III (0.100 g) in 1:1 ether–methanol (50 ml) was combined with 10% methanolic sodium hydroxide (15 ml), and the mixture was stirred for 20 hr at room temperature. The solution was evaporated, diluted with water (20 ml), and extracted with three 20-ml portions of ether. The ether extract was worked up in the usual manner to give crude oximino ketone I (0.041 g, 40%), mp 221–231°; recrystallization from ethanol afforded pure I (0.035 g, 34%), mp 235° dec, identical with an authentic sample.

Acidification (HCl) of the alkaline aqueous phase from the hydrolysis fraction gave crude acid V (0.040 g). Two recrystallizations from ethanol gave pure V (0.031 g, 31%): mp 218°; $[\alpha]^{26}D$ −32.3° (c 1.12, tetrahydrofuran); λ_{max} 3.80, 4.40, 5.89, 6.10, and 6.22 μ; λ_{max} 259 mμ (ε 16,400).

Anal. Calcd for $C_{27}H_{41}O_2N$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.83; H, 10.15; N, 3.37.

Sodium Methoxide Cleavage of Beckmann Dimer III. Methyl Ester (IV) of Acid V.—A solution of dimer III (0.100 g) and sodium methoxide (0.013 g) in 1:1 ether–methanol (50 ml) was stirred under nitrogen for 20 hr at room temperature. Evaporation of the solvent gave a residue which was shaken with water and ether. Work-up of the ether extract in the usual manner gave a residue which was separated into two constituents by preparative tlc on a silica gel plate (1:1 benzene–ethyl acetate eluent). The slower moving band (R_f 0.59) afforded oximino ketone I (0.035 g, 34%), identical with an authentic sample. The faster moving band (R_f 0.91) gave crystals of methyl ester IV (0.045 g, 47%): mp 166° from ether–methanol; $[\alpha]^{26}D$ −3.3° (c 1.44); λ_{max} 4.44, 5.78, 6.12, and 6.25 μ; λ_{max} 268 mμ (ε 18,600).

Anal. Calcd for $C_{28}H_{43}O_2N$: C, 79.01; H, 10.18; N, 3.29. Found: C, 79.01; H, 10.37; N, 3.25.

When the reaction described above was run using sodium borohydride (0.100 g) instead of sodium methoxide, the same work-up yielded oximino ketone I (37%) and ester IV (41%) as the only products found.

Ester IV was also prepared (77% yield, recrystallized) by reaction of acid V with diazomethane in ether.

Cleavage of 2-Oximinocholesta-4,6-dien-3-one (I) to Acid Chloride VI.—Thionyl chloride (4 ml) was added to a solution of oximino ketone I (0.200 g) in methylene chloride (5 ml) and the mixture was stirred for 24 hr at room temperature. The solvent and excess thionyl chloride were then removed completely by evaporation under reduced pressure. The quantity of crude acid chloride VI obtained in this way was used directly in each of the reactions described below.

Reactions of Acid Chloride VI. A. Reaction of VI with Sodium Methoxide.—Acid chloride VI was stirred at room temperature for 15 min with a solution of sodium methoxide (0.10 g) in methanol (10 ml). The mixture was then diluted with water (10 ml) and the resulting precipitate was crystallized from 1:1 ether–methanol to give crude methyl ester IV (0.173 g, 96%), mp 157–164°. Recrystallization afforded the pure ester IV (0.160 g, 77%), mp 167°, identical with material prepared as described above.

B. Reaction of VI with Water.—Acid chloride VI was stirred with water for 5 hr at room temperature. Crystallization of the precipitate from ethanol afforded acid V, mp 218°, identical with material prepared from dimer III.

C. Reaction of VI with Ammonia. 2,3-Secocholesta-4,6-diene-2-nitril-3-amide (VII).—Dry gaseous ammonia was bubbled through a solution of acid chloride VI in dry ether (20 ml) at 0° for 10 min. The precipitate was filtered and washed well with ether. The combined filtrate and ether washings were worked up in the usual manner. The resulting crystalline residue (0.131 g) was recrystallized from petroleum ether (30–60°) to give amide VII (0.120 g, 65%): mp 209°; $[\alpha]^{25}D$ −3.2° (c 3.63); λ_{max} 3.01, 3.15, 4.51, 5.94, and 6.05 mμ; λ_{max} 249 mμ (ε 20,650).

Anal. Calcd for $C_{27}H_{42}ON_2$: C, 78.97; H, 10.31; N, 6.82. Found: C, 78.78; H, 10.35; N, 6.81.

D. Reactions of VI with Aniline. N-Phenyl-2,3-secocholesta-4,6-diene-2-nitril-3-amide (VIII).—Acid chloride VI was stirred with redistilled aniline (2 ml) for 30 min at room temperature. The mixture was then heated on a steam bath for 15 min, cooled, and diluted with water. Crystallization of the precipitate from acetone afforded shining colorless crystals of VIII (0.130 g, 60%): mp 215°; $[\alpha]^{25}D$ −11.0° (c 1.43); λ_{max} 3.20, 4.45, 5.97, 6.15, 6.25, 6.51, 13.29, and 14.49 μ; λ_{max} 225 mμ (ε 7364) and 286 mμ (ε 21,030).

Anal. Calcd for $C_{33}H_{46}ON_2$: C, 81.43; H, 9.53; N, 5.76. Found: C, 81.44; H, 9.56; N, 5.78.

E. Reaction of VI with Phenylmagnesium Bromide. 3,3-Diphenyl-3-hydroxy-2,3-secocholesta-4,6-diene-2-nitrile (IX).—An ethereal solution containing phenylmagnesium bromide (0.265 g) was added to a solution of acid chloride VI in dry ether (10 ml), and the mixture was refluxed for 45 min. The reaction mixture was then decomposed by stirring for 2 hr at room temperature with saturated aqueous ammonium chloride (50 ml). The mixture was filtered, the precipitate being washed well with ether. The combined ether solutions were worked up in the usual manner to give, after crystallization from ether–petroleum ether, white rosettes of alcohol IX (0.150 g, 56%): mp 215°; $[\alpha]^{26}D$ +70.9° (c 1.18, tetrahydrofuran); λ_{max} 249 mμ (ε 20,640).

Anal. Calcd for $C_{39}H_{51}ON$: C, 85.19; H, 9.35; N, 2.55. Found: C, 84.99; H, 9.09; N, 2.64.

F. Reaction of VI with Methylmagnesium Bromide. 3,3-Dimethyl-3-hydroxy-2,3-secocholesta-4,6-diene-2-nitrile (X).—The reaction of acid chloride VI with methylmagnesium bromide (0.160 g) was carried out as in part E above, except that a 90-min reaction time was used; the work-up was similar. The crude product (0.070 g) was chromatographed in ether over neutral alumina (grade IV, 1 g) to give colorless crystals of alcohol X (0.056 g, 30%): mp 145°; $[\alpha]^{26}D$ +7.2° (c 1.42); λ_{max} 2.91, 4.43, 6.06, and 6.11 μ; λ_{max} 241 mμ (ε 16,360).

Anal. Calcd for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; N, 3.29. Found: C, 82.02; H, 11.19; N, 3.32.

Dehydration of Amide VII. 2,3-Secocholesta-4,6-diene-2,3-dinitrile (XI).—Amide VII (0.200 g) was refluxed for 1 hr with thionyl chloride (0.6 ml). Evaporation of the excess thionyl chloride left a residue which was taken up in ether and worked up in the usual manner. The resulting crude dinitrile was triturated with petroleum ether to remove a brown impurity, and then crystallized twice from ether–petroleum ether to give the pure dinitrile (0.077 g, 40%): mp 116°; $[\alpha]^{26}D$ +6.5° (c 0.65); λ_{max} 4.43, 4.52, 6.14, and 6.33 μ; λ_{max} 265 mμ (ε 20,280).

Anal. Calcd for $C_{27}H_{40}N_2$: C, 82.59; H, 10.27; N, 7.14. Found: C, 83.04; H, 10.15; N, 7.01.

Methyl 2-3-Secocholestane-2-nitril-3-oate (XII). A. By Reduction of Ester IV.—A solution of ester IV (0.195 g) in pure ethyl acetate (30 ml) was stirred with 10% palladium-on-charcoal catalyst (0.10 g) for 7 min in an atmosphere of hydrogen (atmospheric pressure); during this time 2 molar equiv of hydrogen were absorbed. Work-up in the usual manner gave a product which was separated from a small amount of an oily polar impurity (R_f 0.11) by preparative tlc (silica, 1:1 benzene–methanol; R_f of major product = 0.85). Crystallization from methanol–ether gave the reduced ester XII as white rosettes (0.160 g, 81%): mp 91°; $[\alpha]^{25}D$ +23.6 (c 1.90); λ_{max} 4.42 and 5.72 μ; no uv maxima above 210 mμ.

Anal. Calcd for $C_{28}H_{47}O_2N$: C, 78.27; H, 11.03; N, 3.26. Found: C, 78.50; H, 10.70; N, 3.14.

B. From 2-Oximinocholestan-3-one (XIV) by Beckmann Cleavage.—Thionyl chloride (4 ml) was added to a solution of oximino ketone XIV[1a,6] (0.200 g) in methylene chloride (5 ml), and the mixture was stirred for 24 hr at room temperature. The solution was then evaporated and kept under reduced pressure until all thionyl chloride was removed. A solution of sodium methoxide (0.10 g) in methanol (10 ml) was added. After a short time the neutral product was worked up in the usual manner to give the cyano ester XII (0.176 g, 85%), mp 91–91.5°, identical with material obtained from ester IV as described above (section A).

2,3-Secocholestane-2,3-dinitrile (XIII). A. By Reduction of Dinitrile XI.—A solution of dinitrile XI (0.093 g) in pure ethyl acetate (20 ml) was stirred with 10% palladium-on-charcoal catalyst (0.05 g) for 23 min under hydrogen at atmospheric pressure;

2 molar equiv of hydrogen were absorbed. Work-up in the usual manner gave a product which was separated from a small amount of an oily polar impurity (R_f 0.12) by preparative tlc (silica, 1:1 benzene–ethyl acetate, R_f (major product) 0.90). Crystallization from petroleum ether gave nitrile XIII (0.067 g, 71%), mp 116°. Recrystallized XIII had mp 118–119°; $[\alpha]^{25}D$ +19.9° (c 1.00); λ_{max} 4.42, 6.81, 6.91, 7.20, and 7.25 μ.

Anal. Calcd for $C_{27}H_{44}N_2$: C, 81.75; H, 11.18; N, 7.06. Found: C, 81.87; H, 11.25; N, 6.94.

B. From 2-Oximinocholestan-3-one (XIV) by Beckmann Cleavage.—Oximino ketone XIV (0.200 g) was cleaved with thionyl chloride exactly as described for the synthesis of cyano ester XII. The resulting acid chloride XV was dissolved in methylene chloride (20 ml) and the solution was saturated with gaseous ammonia at 0°. Work-up in the usual manner, followed by crystallization from 1:1 chloroform–petroleum ether, gave brilliant colorless crystals of the cyano amide XVI (0.170 g, 86%): mp 261°; $[\alpha]^{26}D$ +33.6° (c 1.03); no uv maxima above 210 mμ.

Anal. Calcd for $C_{27}H_{46}ON_2$: C, 78.20; H, 11.18; N, 6.76. Found: C, 78.30; H, 11.02; N, 6.80.

A solution of amide XVI (0.100 g) in thionyl chloride (3 ml) was refluxed for 18 hr. Evaporation of the excess thionyl chloride, followed by crystallization of the residue from petroleum ether, afforded dinitrile XIII (0.060 g, 66%), mp 118–119°, identical with material obtained from dinitrile XI as described above (section A).

Registry No.—I, 13341-55-4; III, 16426-16-7; IV, 16426-17-8; V, 16426-18-9; VII, 16426-19-0; VIII, 16426-20-3; IX, 16426-21-4; X, 16426-22-5; XI, 16426-23-6; XII, 16426-24-7; XIII, 16426-25-8; XVI, 16426-26-9.

Acknowledgment.—This investigation was supported by Public Health Service Research Grants CY-4498 and CA-04498, National Institutes of Health.

The Alkaloids of *Cassytha americana* (*C. filiformis* L.)[1]

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Thirteen alkaloids have been isolated from Brazilian *Cassytha americana* (*C. filiformis* L., Lauraceae). The structures of 1,2,9,10-bismethylenedioxy-3-methoxydibenzo[*de,g*]quinolin-7-one and 1,2,9,10-bismethylenedioxydibenzo[*de,g*]quinolin-7-one are suggested for the new oxoaporphine bases cassamedine and cassameridine. The plant also yielded ten previously known aporphine bases.

Recent investigations have shown the parasitic genus *Cassytha* (Lauraceae) to be a rich source of aporphine alkaloids. Aporphines have been reported from the following species: *Cassytha filiformis*,[2] *C. melantha*,[3] *C. glabella*,[3] *C. pubescens*,[4] and *C. racemosa*.[5] The vine, *C. filiformis*, is a species which is widely distributed throughout the tropics. Plant material from Taiwan yielded the new aporphine cassyfiline (I),[1,6] whereas material from New Guinea and Australia gave cassythidine (III).[2] We now report the results of an investigation of the alkaloids of *Cassytha americana* of Brazilian origin. After the study was essentially complete, we learned that *C. americana* was apparently synonomous with *C. filiformis*.[7] Our work has resulted in the isolation of thirteen tertiary bases, two of which, cassamedine (IV) and cassameridine (V), are new oxoaporphines.

Separation of the Bases.—As described in detail in the Experimental Section, the bases were separated first into alkali-soluble and alkali-insoluble fractions. The latter were further fractionated by differential acid buffer extraction and chromatography. The yields of pure compounds were generally low, owing to experimental difficulties encountered in the separation steps. Thin layer chromatography indicated, however, the absence of significant quantities of alkaloids other than those identified.

The Alkali-Soluble Aporphines.—The largest portion of the total alkaloids was alkali soluble and consisted of a mixture of cassyfiline (I), actinodaphnine (VI), and N-methylactinodaphnine (VII). Compound VI was the major component of the mixture, although an efficient procedure for its separation was not devised. Compound VII has been described as a transformation product of VI,[8] but it had not been encountered as a naturally occurring alkaloid prior to the completion of our investigation. Very recently, however, it has been reported to be the major alkaloid of both *Cassytha melantha* and *C. glabella* and has been given the name cassythicine.[3]

The Alkali-Insoluble Aporphines.—The alkali-insoluble alkaloids consisted mainly of a mixture of seven aporphines. These included the cryptophenolic bases launobine (VIII) and bulbocapnine (IX), as well as the closely related nonphenolic bases O-methylcassyfiline (II), cassythidine (III), dicentrine (X), neolitsine (XI), and (+)-nornuciferine (XII). Compound XII could be separated from the natural alkaloid mixture only in the form of (+)-nuciferine (XIII) after N-methylation with formaldehyde and sodium borohydride. Thin layer chromatography showed definitely that no XIII was present before N-methylation.

(1) The plant material used in this investigation was collected near Porto Seguro in the State of Bahia, Brazil, by Dr. Aparicio Duarte whose assistance is gratefully acknowledged. A reference specimen, R. B. 130345, has been filed in the Herbarium of the Botanical Garden at Rio de Janeiro.

(2) (a) M. Tomita, S. T. Lu, and S. J. Wang, *J. Pharm. Soc. Jap.*, **85**, 827 (1965); (b) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **19**, 297 (1966).

(3) S. R. Johns, J. A. Lamberton, and A. S. Sioumis, *ibid.*, **19**, 2339 (1966).

(4) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *ibid.*, **19**, 2331 (1966).

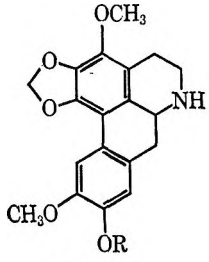
(5) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *ibid.*, in press.

(6) Alkaloid I is named cassyfiline in ref 1a and cassythine in ref 1b in which an independent isolation and structure determination are described. In view of the earlier publication of ref 1a, the name cassyfiline will henceforth be used in this paper.

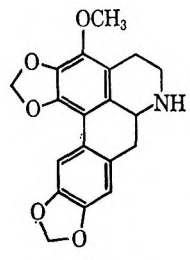
(7) The preferred binomial is *Cassytha filiformis* L. with *C. americana* Nees. and *C. capillaris* F.-Vill. occasionally given as synonyms.

(8) M. Tomita, M. Kozuka, E. Nakagawa, and Y. Mitsunori, *J. Pharm. Soc. Jap.*, **83**, 763 (1963).

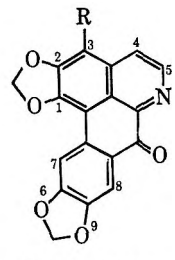
Compound XII has been isolated from natural sources previously only as (−)-nornuciferine.[9]



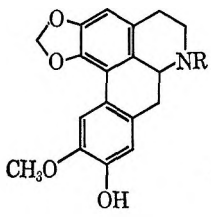
I, R = H
II, R = CH_3



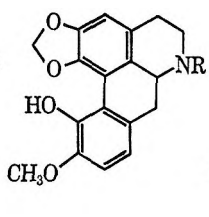
III



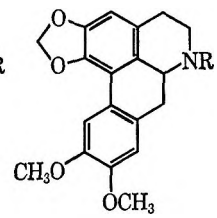
IV, R = OCH_3
V, R = H



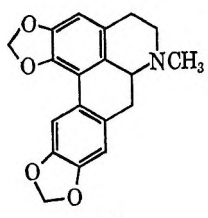
VI, R = H
VII, R = CH_3



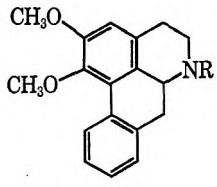
VIII, R = H
IX, R = CH_3



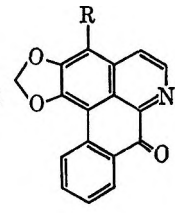
X, R = CH_3
XIX, R = H



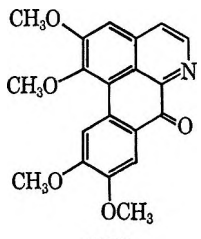
XI



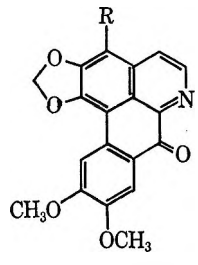
XII, R = H
XIII, R = CH_3



XIV, R = H
XV, R = OCH_3



XVI



XVII, R = OCH_3
XVIII, R = H

The Oxoaporphine Bases.—The alkali-insoluble alkaloid mixture contained an orange compound, mp 278°, which was readily separable from the major bases because of its sparing solubility in benzene. This new compound, cassamedine, has been assigned the oxoaporphine structure IV on the basis of the following evidence. Elemental analysis was in fair agreement with the composition $C_{19}H_{11}O_6N$; the mass spectrum of IV confirmed the molecular weight (349) and indicated no ready skeletal fragmentation, in accord with a completely aromatic structure. Its infrared spectrum showed a highly conjugated carbonyl band at 1650 cm^{-1}, but no NH or OH absorption. The complex ultraviolet absorption spectrum of the compound in neutral and acidic ethanol solution was indicative of the oxoaporphine chromophore found in liriodenine (XIV);[10] the spectrum was unchanged by the addition of alkali, showing the absence of a cryptophenolic hydroxyl.

The nmr spectrum of cassamedine IV showed signals due to two unsplit methylenedioxy groups at δ 6.62 and 6.23[11] and a methoxyl at 4.48, as well as five aromatic protons at 7.83, 8.19, and 8.85 (two protons). The signals at δ 6.62 and 4.48 are analogous to those (6.72 and 4.55) observed in the spectrum of atherospermidine (XV);[12] consequently, they have been assigned to a 1,2-methylenedioxy group and a 3-methoxy group, respectively. The aromatic protons may be assigned by comparison with those of O-methylatheroline (XVI). In the latter compound, the signals at δ 7.08, 7.63, 8.76, 7.93, and 8.65 have been attributed to the protons at C-3, C-4, C-5, C-8, and C-11, respectively.[13] In IV the two lowest field protons at δ 8.85 are therefore those at C-5 and C-11; the 8.19 proton must be that at C-8; and the 7.83 proton must be that at C-4. The signal at δ 6.23 is assigned to the 9,10-methylenedioxy group.

Since IV is the aromatic oxoaporphine corresponding to III, it should be possible to prepare IV from III by oxidation. We were unable to carry out this reaction because of the small amount of III at our disposal and the poor yield of oxoaporphine to be expected in this reaction.[14] On the other hand, oxidation of II afforded, in 2% yield, the corresponding orange oxoaporphine (XVII). As expected, the ultraviolet spectra of IV and XVII were practically identical in both neutral and acid solution, thus providing further support for the assignment of structure IV to cassamedine.

Cassameridine (V) was first detected as an impurity in IV, the mass spectrum of which showed the presence of a small amount of a compound of mol wt 319, corresponding to a demethoxycassamedine. Careful chromatography of IV eliminated this extraneous 319 peak and afforded a small amount (*ca.* 1 mg) of V as a bright yellow solid. Oxidation of O-methylactinodaphnine (XIX) afforded, in 2% yield, an aromatic oxoaporphine (XVIII) having practically the same ultraviolet spectrum as V in both neutral and acid solution, thus suggesting structure V for cassameridine. We were unable to attempt the direct preparation of V by the oxidation of neolitsine (XI), owing to the small amount of XI at our disposal. The confirmation of structure IV and V for cassamedine and cassameridine by total synthesis is in progress.

Experimental Section

All melting points are uncorrected. Optical rotations were determined in chloroform at room temperature unless otherwise stated. Infrared spectra were measured in KBr disks. Ultraviolet absorption spectra were run in 95% ethanol. Nmr spectra were taken on a Varian A-60 spectrometer. Microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Comparison of isolated compounds with authentic samples where available was made by mixture melting point determination, tlc, and ir and uv spectroscopy.

(9) S. M. Kupchan, B. Dasgupta, E. Fujita, and M. L. King, *Tetrahedron*, **19**, 227 (1963).

(10) A. W. Sangster and K. L. Stuart, *Chem. Rev.*, **65**, 69 (1965).

(11) Nmr values are expressed as parts per million downfield from tetramethylsilane.

(12) I. R. C. Bick and G. K. Douglas, *Tetrahedron Lett.*, 1629 (1964).

(13) I. R. C. Bick and G. K. Douglas, *ibid.*, 4655 (1965).

(14) M. Tomita, T. H. Yang, H. Furukawa, and H. M. Yang, *J. Pharm. Soc. Jap.*, **82**, 1574 (1962).

Extraction of *Cassytha americana* and Isolation of Crude Bases.—The alcoholic extract from 41.8 kg of plant material was concentrated to a thick syrup and extracted, with stirring and gentle heating, with 12.1 of ammoniacal (10%) ethyl acetate. The ethyl acetate was decanted from the nonalkaloidal residue and extracted with fifteen 500-cc portions of 5% H_2SO_4. The combined acid extracts were washed twice with 1-l. portions of benzene and the benzene extracts were discarded. The aqueous extracts were adjusted to pH 10 with ammonia and extracted with chloroform until alkaloid negative. The chloroform was dried over Na_2SO_4 and concentrated to yield 80 g of total nonquaternary bases.

Alkali Separation of the Alkaloids.—The crude base mixture (80 g) was dissolved in 2 *N* H_2SO_4 and nonalkaloidal impurities were removed by chloroform extraction. The bases were then extracted with chloroform after basification with ammonia. Separation into alkali-insoluble (14.4 g) and alkali-soluble (30.2 g) fractions was accomplished by distributing the bases between chloroform and 2% aqueous NaOH; the bases were recovered from the latter by saturating it with solid NH_4Cl and then extracting with chloroform.

Alkali-Insoluble Bases.—The mixture of "nonphenolic" bases was triturated with benzene and the insoluble orange solid (100 mg) (*vide infra*) was filtered off. The benzene solution was then extracted successively with McIlvaine buffer solutions of pH 6.6, 6.0, 5.0, 4.0, 3.6, and 2.2. The base fractions were recovered from the buffer solutions by basification with aqueous NaOH followed by extraction with benzene. Screening of the extracts was done by thin layer chromatography on neutral alumina using chloroform as solvent; the spots were visualized with iodine vapor.

Neolitsine (XI).—The pH 2.2 (0.75 g) and pH 3.6 (1 g) fractions were chromatographed in benzene solution over neutral Gr II alumina. Elution with benzene gave in the earlier fractions neolitsine, crystallizing from acetone as colorless needles (36 mg): mp 145–146°; $[\alpha]_D$ +55°; λ_{max} 284 mμ (log ε 4.19) and 311 (4.33); identical with an authentic sample (lit.[15] mp 149–150°; $[\alpha]_D$ +56.5°).

Dicentrine (X).—The middle benzene eluates from the above fractions afforded dicentrine, crystallizing from ethanol as pale yellow needles (450 mg): mp 167–168°; $[\alpha]_D$ +55.3° (ethanol); λ_{max} 282 mμ (log ε 4.19) and 306 (4.23); identical with an authentic sample {lit.[16] mp 168–169°; $[\alpha]_D$ +56° (ethanol)}.

Cassythidine (III).—The later benzene eluates from the above fractions afforded, after crystallization from ethanol, cassythidine as a microcrystalline solid (22 mg): melting point and mixture melting point with an authentic sample, 206–208°; $[\alpha]_D$ +15.8°; λ_{max} 235 mμ (log ε 4.42), 286 (4.20), and 310 (4.26) (lit.[2] mp 206–207°; $[\alpha]_D$ +15°).

Launobine (VIII).—The pH 5.0 fraction (1.8 g) was chromatographed in benzene over neutral Gr IV alumina. Elution with benzene and crystallization of the residue from methylene chloride furnished a microcrystalline solid (12 mg): mp 197°; $[\alpha]_D$ +228.7°; λ_{max} 270 mμ (log ε 4.25) and 307 (3.88); identical with an authentic sample (lit.[16] mp 214–215°; $[\alpha]_D$ +192.7°).

Anal. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.47; H, 5.60; N, 4.24.

Bulbocapnine (IX).—Preparative thin layer chromatography of pH 4.0 fraction (2.1 g) on neutral alumina with chloroform as developing solvent gave only partial resolution of the constituents. Elution of a fast-moving band afforded, after crystallization from ethanol, colorless needles (2 mg) of bulbocapnine, mp 202°, identical with an authentic sample.

O-Methylcassyfiline (II).—A slow moving compound from the above preparative tlc was obtained as a gum which was found to be highly soluble in the common organic solvents, but a few crystals, mp 150–152° (lit.[1,2] 150–151°, amorphous), could be obtained from ether: λ_{max} 236 mμ (log ε 4.43), 283 (4.31), 302 (4.30), and 312 (4.27). The compound was identical with an authentic sample of O-methylcassyfiline prepared from cassyfiline.

(+)-Nuciferine (XIII).—The pH 5.0 material remaining after the separation of VIII launobine was dissolved in methanol (10 ml) and stirred for 30 min with 37% formalin (0.5 ml), then for a further 30 min after adding sodium borohydride (50 mg). Buffer separation of the product and chromatography of the pH 2.2 fraction yielded (+)-nuciferine as colorless prisms from acetone (15 mg): mp 164°; $[\alpha]_D$ +159.3°; λ_{max} 230 mμ (log ε 4.36), 272 (4.27) and 310 (3.46). It was identical in all respects with an authentic sample of synthetic (+)-nuciferine.

Cassameridine (V).—The benzene-insoluble orange solid (100 mg) (*vide supra*) was dissolved in chloroform and adsorbed on neutral Gr III alumina (5 g) and dried. This material was added to fresh alumina (10 g) and the mixture was eluted with chloroform–benzene (1:3; 200 ml). Evaporation of the eluent gave, after crystallization from ethanol, a yellow microcrystalline solid (1 mg), mp 300°. It formed a red solution in mineral acid and exhibited a green fluorescence in $CHCl_3$ solution: λ_{max} 251 mμ (log ε 4.46), 274 (4.40), 323 (4.08), 353 (3.91), 388 (3.85), and 440 (3.73); $\lambda_{max}^{ethanol-HCl}$ 261 mμ (log ε 4.62), 290 (4.59), 385 (4.31), and 500 (3.62).

Cassamedine (IV).—Elution of the above column with chloroform–benzene (1:1; 200 ml) afforded after crystallization from chloroform–ethanol, an orange microcrystalline solid: mp 278°; λ_{max} 252 mμ (log ε 4.47), 281 (4.53), 324 (4.12), 364 (3.97) and 460 (3.76); $\lambda_{max}^{ethanol-HCl}$ 272 mμ (log ε 4.49), 286 (4.50), 408 (4.10), and 534 (3.40); nmr (in CF_3COOH), δ 7.83, 8.85 (2 H), 8.19, 4.48 (3 H), 6.62 (2 H), and 6.23 (2 H); ν_{max} 1650 cm^{-1}.

Anal. Calcd for $C_{19}H_{11}O_6N$: C, 65.33; H, 3.17; N, 4.01; mol wt., 349. Found: C, 64.61; H, 3.25; N, 4.29; mol wt (mass spectroscopy), 349.

Chromium Trioxide–Pyridine Oxidation of O-Methylcassyfiline (II).—O-Methylcassyfiline was prepared by methylation of cassyfiline (100 mg) in methanol (5 ml) with an excess of ethereal diazomethane for 2 days at 0°. A solution of the product in pyridine (2 ml) was treated with chromium trioxide (200 mg) in pyridine (3 ml) in the cold for 1 hr. Ethanol (2 ml) followed by water (10 ml) was added and the solution was extracted thoroughly with chloroform. The chloroform extract was extracted repeatedly with 5% aqueous HCl, basified, extracted with chloroform, and dried (K_2CO_3) and the solvent was removed. The orange residue was adsorbed on neutral Gr III alumina (5 g) and eluted with chloroform–benzene (1:1, 100 ml). The residue from the eluate was crystallized from chloroform–ethanol to give the orange microcrystalline XVII (2 mg), mp 274–275°. The mixture melting point with cassamedine IV was depressed and ir comparison showed that the compounds were different: λ_{max} 252 mμ (log ε 4.38), 282 (4.44), 281 (4.41), 406 (3.99), and 539 (3.39). The compound gave a red solution in mineral acid and its chloroform solution exhibited a green fluorescence.

Chromium Trioxide–Pyridine Oxidation of O-Methylactinodaphnine (XIX).—Actinodaphnine (*vide infra*) (100 mg) was methylated with excess diazomethane and the resulting O-methylactinodaphnine was oxidized with chromium trioxide–pyridine reagent as described for the oxidation of II. Crystallization from ethanol gave XVIII as a yellow microcrystalline solid (2 mg): mp 300°; λ_{max} 250 mμ (log ε 4.69), 272 (4.62), 313 sh (4.17), 351 (4.22), 392 (4.39), and 438 (4.29); $\lambda_{max}^{ethanol-HCl}$ 260 mμ (log ε 4.69), 292 (4.62), 382 (4.30), and 506 (3.64).

Alkali-Soluble Bases.—The alkali-soluble bases were dissolved in chloroform and the buffer separation was carried out as in the case of the alkali-insoluble bases. Tlc screening of the extracts was carried out on silica gel plates with 5% methanol in chloroform as solvent.

Cassyfiline (Cassythine) (I).—The pH 4.0 fraction (1.9 g) was crystallized directly from chloroform–ethanol to yield cassyfiline (430 mg): mp 211–213°; $[\alpha]_D$ +28.3°; λ_{max} 283 mμ (log ε 4.28) and 303 (4.27); identical with an authentic sample (lit.[2] mp 217–219°; $[\alpha]_D$ +24°).

The pH 5.0 fraction (2.1 g) was dissolved in chloroform and adsorbed on neutral Gr IV alumina. Elution of the column with benzene gave cassyfiline (230 mg).

Actinodaphnine (VI).—Further elution of the above column with chloroform–benzene (1:4) yielded actinodaphnine, crystallizing from ethanol as colorless prisms (112 mg): mp 202–203°; $[\alpha]_D$ +37.9° (ethanol); λ_{max} 284 mμ (log ε 4.12) and 307 (4.17); identical with an authentic sample {lit.[16] mp 210–211°; $[\alpha]_D$ +33° (ethanol)}.

The pH 6.6 fraction was found to be mostly actinodaphnine containing a small amount of I.

Cassythicine (N-Methylactinodaphnine) (VII).—The pH 2.2 (0.7 g) and pH 3.6 (1.4 g) fractions were chromatographed in chloroform–benzene (1:1) solution on neutral Gr IV alumina. Elution of the column with benzene and crystallization of the residue from ethyl acetate furnished colorless prisms of cassythicine (395 mg): mp 204–205°; $[\alpha]_D$ +53.1 (ethanol); λ_{max} 283 mμ (log ε 4.23) and 307 (4.27) {lit.[8] mp 210–211°; $[\alpha]_D$

(15) W. A. Hui, S. N. Loo, and H. R. Arthur, *J. Chem. Soc.*, 2285 (1965).
(16) M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, **64**, 59 (1964).

57.0° (ethanol)}. The compound was identical with an authentic sample prepared by the N-methylation of actinodaphnine VI with 37% formalin and $NaBH_4$ in methanol solution. With excess of ethereal diazomethane it afforded dicentrine, mp and mmp 166–167°.

Registry No.—IV, 16408-75-6; V, 16408-76-7; XVII, 16408-77-8; XVIII, 16408-78-9.

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Coumarins. V. The Acid-Catalyzed Reaction of Phenols with β-Oxonitriles[1]

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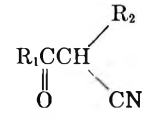
Benzoylacetonitrile (Ia) and acetoacetonitrile (Ib) were found to undergo carbon–carbon condensation with phenols providing a new route to coumarins, whereas carbon–oxygen condensation occurred with α-ethylacetoacetonitrile (Ic). The aluminum chloride catalyzed reaction of *meta*- and *para*-substituted phenols with Ia in the presence of dry hydrogen chloride yielded the corresponding iminocoumarins II and/or coumarins IV. Phenol as well as *o*-cresol gave predominantly β-(*p*-hydroxyphenyl)cinnamonitriles V. In contrast, Ib reacts with phenols in polyphosphoric acid or its ethyl ester to furnish 4-methylcoumarins in appreciable yields. The oxonitrile Ic on treatment with phenols in the presence of aluminum chloride and hydrogen chloride gave rise to both *cis*- and *trans*-β-aryloxy-α-ethylcrotononitriles VIIa and b in good yields. Mechanisms to account for the results are proposed.

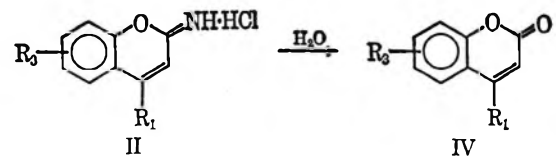
Previous papers in this series have demonstrated that anhydrous aluminum chloride, accompanied by dry hydrogen chloride, is an efficient reagent for nuclear addition reactions of phenols to α,β-unsaturated nitriles[3] and to 3-butenenitrile.[4] These studies have now been extended to β-oxonitriles. Whereas coumarins may be obtained by the acid-promoted condensation of phenols with β-keto esters (the von Pechmann reaction), little is known of a similar reaction with β-oxonitriles. It has been shown that benzoylacetonitriles condense with polyhydric phenols, such as resorcinol, in the presence of concentrated sulfuric acid to give the corresponding coumarins.[5,6] Mentzer and coworkers[7] have reported that the same acid-catalyzed reaction of resorcinol with α-aryl-β-ketonitriles yields 3-aryl-4-alkyl-7-hydroxycoumarins; no yields are given. While the reaction of the more active phenols, such as phloroglucinol, with 2-phenylacetoacetonitrile in trifluoroacetic acid is claimed[8] to give isoflavone in excellent yields, Cook and coworkers,[9] more recently, have noted that under identical conditions resorcinol reacts with α-(*p*-methoxyphenyl)acetoacetonitrile to provide the corresponding coumarin, which may be also secured by use of hydrogen fluoride as the condensation catalyst. No method of preparing coumarins by the acid-catalyzed reaction of phenols with aliphatic β-oxonitriles, such as acetoacetonitrile and its ethyl derivative, has yet appeared in the literature.

We have examined the condensation of phenols with β-oxonitriles Ia–c using anhydrous aluminum chloride, polyphosphoric acid (PPA), or its ethyl ester (PPE).[10]



Ia, R_1 = Ph; R_2 = H
b, R_1 = CH_3; R_2 = H
c, R_1 = CH_3; R_2 = C_2H_5

When equimolar amounts of resorcinol and benzoylacetonitrile (Ia) were treated with 2 equiv of anhydrous aluminum chloride in isopropyl ether saturated with dry hydrogen chloride, a nitrogenous product was obtained in nearly quantitative yield. The analytical data agreed with the formula $C_{15}H_{12}ClNO_2$, which is in accord with the structure of the coumarin derivative IIa



II IV

(1) This investigation was supported mainly by Asahi Glass Co., Ltd., for which we are grateful.

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(3) Part I: K. Sato, T. Amakasu, and S. Abe, *J. Org. Chem.*, **29**, 2971 (1964).

(4) Part IV: T. Amakasu, *Bull. Chem. Soc. Jap.*, **41**, 451 (1968).

(5) (a) B. N. Ghosh, *J. Chem. Soc.*, **109**, 105 (1916); (b) G. Bargellini and G. Forti-Forli, *Gazz. Chim. Ital.*, **41**, 747 (1911); (c) A. Sonn, *Chem. Ber.*, **51**, 821, 1829 (1918).

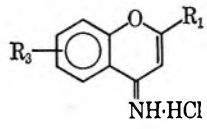
(6) W. Baker, *J. Chem. Soc.*, **127**, 2349 (1925).

(7) C. Mentzer, P. Gley, D. Molho, and D. Billet, *Bull. Soc. Chim. Fr.*, **5**, 13, 271 (1946).

(8) L. L. Wood and J. Sapp, *Texas J. Sci.*, **16**, 383 (1964); *Chem. Abstr.*, **62**, 6454 (1965).

(9) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

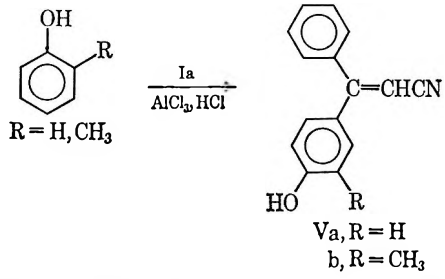
(10) T. Amakasu and K. Sato, *ibid.*, **31**, 1433 (1966).



III

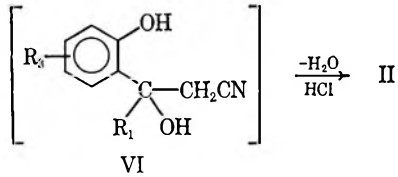
or the isomeric flavone III (R_1 = Ph; R_3 = 7-OH). When heated with water or dilute hydrochloric acid the salt IIa underwent readily hydrolysis to 4-phenylumbelliferone (IVa, R_3 = 7-OH), which on treatment with hot acetic anhydride was quantitatively converted into the acetate IVi (R_3 = 7-AcO). Resorcinol monomethyl ether behaved analogously when treated with Ia under the same conditions and gave the corresponding coumarin IVb as well as IIb.

In contrast, under such similar conditions as described above (procedure A, see Experimental Section) cresols failed to react with Ia. However, when Ia was treated with excess *m*-cresol without an inert solvent in the presence of aluminum chloride and excess dry hydrogen chloride, the iminocoumarin salt IIc was obtained; with *p*-cresol, 6-methyl-4-phenylcoumarin (IVd) was directly isolated in 30% yield. On the other hand, phenol on a similar treatment with Ia underwent intermolecular dehydration at the *para* position leading to β-(*p*-hydroxyphenyl)cinnamonitrile (Va). The reaction also proceeded smoothly with *o*-cresol to furnish Vb in 60% yield. The results, along with the elemental analysis and the infrared spectra, confirm the structure V for the β-arylcinnamonitriles.



Although acetoacetonitrile (Ib) will readily polymerize in the cold on treatment with aluminum chloride, it was found to undergo such a condensation as Ia yielding the corresponding coumarins IV (R_1 = CH_3), when treated with phenols in PPA or PPE. Resorcinol and its monomethyl ether react with Ib in PPE at 110–145° to furnish 4-methylumbelliferone (IVe) and its methyl ether (IVf), respectively, in good yields. Coumarins of type IV (R = CH_3) could also be prepared by the PPA-catalyzed condensation of cresols at 75–90°, but even under these conditions phenol failed to react with Ib.

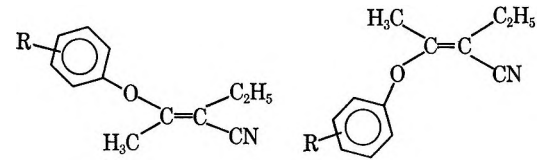
The results, summarized in Table I, suggest that the reactions proceed through addition of phenols to β-oxonitriles as indicated below. In those cases where the



VI

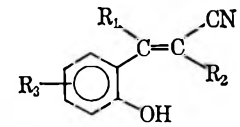
addition product (*i.e.*, VI) is derived by *ortho* nuclear addition, dehydration of VI would be followed[11] by intramolecular cyclization to an iminocoumarin II. The ultraviolet data of coumarins IV (Table I) may distinguish[12] clearly between coumarins IV and chromones.

When 5 equiv of *p*-cresol was warmed with ethylacetoacetonitrile (Ic) in the presence of 2.2 equiv of aluminum chloride and excess of dry hydrogen chloride, a liquid, bp 119° (3 mm), and white crystals, mp 51–52°, were obtained. Both of the products were shown by elemental analyses to have the identical formula $C_{13}H_{15}NO$, which is in accord with the crotononitrile structure VIIa and VIIb (R = 4-CH_3). Their infrared



VIIa VIIb

spectra showed cyano and conjugated olefin absorptions, respectively, at 2170–2200 and 1635–1641 cm^{-1} in addition to enolic ether bands at 1209–1255 cm^{-1}. Neither one of the spectra contained absorptions attributable to potential hydroxyl groups (see Experimental Section). This definitely excludes the possibility of structures such as VIII and reveals that VIIa and VIIb are geometrical



VIII

isomers. In addition, the ultraviolet spectrum of the former showed a strong absorption at 283 mμ (ε 1200) as well as a very weak band at 332 mμ (ε 12) while that of the latter indicated the lack of a weak absorption in high region. Finally, the nmr spectra clearly distinguish between the two isomers, the most significant feature being the appearance of the β-methyl proton signal of VIIa, at lower field. In the crotononitriles, as previous workers[13] have reported, the *cis*-methyl protons are at lower field by 0.15 ppm than those *trans* to the nitrile group. The same situation, adequately explained on the basis of diamagnetic anisotropic shielding[13] due to the nitrile triple bond, exists in the present case where the β-methyl protons in the former lie 0.22 ppm below those in the latter. Thus, we conclude that the *cis*-crotononitrile structure VIIa must be assigned to the former and the *trans* isomer VIIb to the latter.

It is noteworthy that phenol similarly yields isomers VIIa and VIIb (R = H), whereas only the *cis* compound VIIa (R = 2-CH_3) is formed from *o*-cresol. The following discussion is presented to account for the stereochemical course of the reaction listed in Table II.

It is suggested that the most likely pathway for the formation of the vinyl ethers VIIa,b involves an addition–elimination mechanism. Anhydrous aluminum chloride is believed to coordinate not only with a cyano[14]

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TABLE I

THE ACID-CATALYZED REACTION OF PHENOLS WITH β-OXONITRILES Ia AND Ib

Phenol	Oxonitrile	Procedure[a]	Reaction temp, °C	Time, hr	Product composition, % II	IV	V
Resorcinol	Ia	A	50–60	5	94		
Resorcinol monomethyl ether	Ia	A	60–65	5	20	10	
m-Cresol	Ia	A′	70–75	5	41		
p-Cresol	Ia	A′	70–75	3		30	
o-Cresol	Ia	A′	70–75	1			60
Phenol	Ia	A′	70–75	7			43
Resorcinol	Ib	B	110–115	5		80	
Resorcinol monomethyl ether	Ib	B	140–145	5		70	
m-Cresol	Ib	C	70–80	1.5		10	
p-Cresol	Ib	C	90–95	1.5		20	

Compd[b] IV	R_1	R_2	Recrystn solvent[c]	Mp, °C Obsd	Mp, °C Lit	Infrared, cm^{-1} C=O	Ultraviolet λ_{max} mμ (ε)[m]
a	Ph	7-OH	A	249–250	245[d]	1690	241 (10,500)[n]
					256.5–257[e]		259 ± 3 (7,700)[o]
							375 (11,500)
b	Ph	7-OCH_3	A	110.5–111	110[f]	1725	233 ± 3 (12,600)[o]
							259 ± 1 (8,000)
							331 (12,900)
c	Ph	7-CH_3	B	97	96[g]	1740	290 (12,000)
d	Ph	6-CH_3	B	135	131[h]	1740	284 (14,700)
e	CH_3	7-OH	B	185	185[i]	1680	222 (14,000)[n,p]
							254 ± 2 (2,300)[o]
							326 (12,700)
f	CH_3	7-OCH_3	A	158.5–159	159[j]	1730	222 (16,400)
							252 ± 2 (2,300)[o]
							324 (13,900)
g	CH_3	7-CH_3	A	132	132[k]	1700	222 (19,500)[q]
							282 (10,500)
							319 (900)
h	CH_3	6-CH_3	B	151	150[l]	1710	218 (24,000)[q]
							276 (11,500)
							324 (5,700)

[a] See Experimental Section. [b] See Experimental Section for the characterization data of II and V. [c] A, ethanol; B, aqueous ethanol. [d] See ref 5c. [e] L. L. Wood and J. Sapp, *J. Org. Chem.*, **27**, 3703 (1962). [f] R. Robinson and M. R. Turner, *J. Chem. Soc.*, **113**, 859 (1918) [g] See ref 11a. [h] A. Robertson and W. F. Sandrock, *ibid.*, 1180 (1932). [i] D. Chakravarti and C. B. Bera, *J. Indian Chem. Soc.*, **21**, 109 (1944). [j] H. von Pechmann and C. Duisberg, *Chem. Ber.*, **16**, 2119 (1883). [k] K. Fries and W. Klostermann, *ibid.*, **39**, 871 (1906). [l] K. Fries and W. Kostermann, *Ann. Chem.*, **362**, 1 (1908). [m] The spectra were measured at concentration of 6–6.2 mg/l. of Spectrograde ethanol. [n] See ref 12c. [o] Flat. [p] See ref 12b. [q] See ref 12a.

TABLE II

THE ALUMINUM CHLORIDE CATALYZED CONDENSATION OF PHENOLS WITH α-ETHYLACETOACETONITRILE (Ic)[a]

No.	Phenol	Total yield, %	Product composition, mole fraction VIIa	VIIb	Bp (mm), °C VIIa	VIIb
1	Phenol	60	0.75	0.25	107 (1)	125 (1)
2	*o*-Cresol	33	1		113 (2)	
3	*p*-Cresol	70	0.75	0.25	119 (3)	140 (3)

No.	$n^{25}D$ VIIa	$n^{25}D$ VIIb	d^{25} VIIa	d^{25} VIIb	C, % Calcd	C, % Found VIIa	C, % Found VIIb	H, % Calcd	H, % Found VIIa	H, % Found VIIb
1	1.5355	1.5378	1.0439	1.0577	76.97	77.66	76.84	7.00	6.61	6.95
2	1.5365		1.0250		77.58	77.22		7.51	7.51	
3	1.5341	*b*	1.0069	*b*	77.58	77.70	77.30	7.51	7.36	7.24

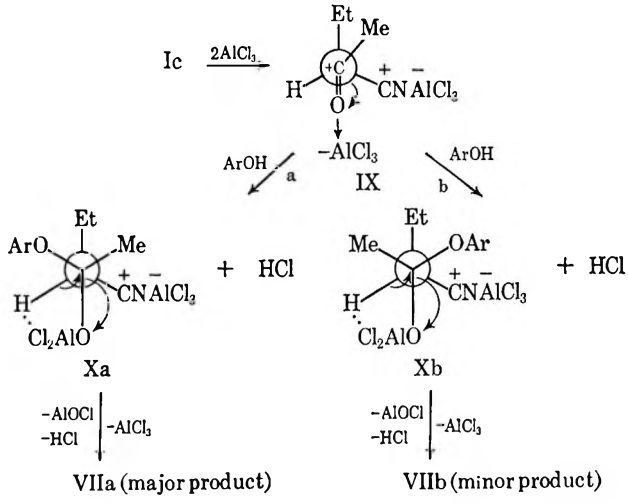
[a] The reaction was carried out at 40–50° for 4 hr according to the procedure A′; see Experimental Section. [b] Mp 51–52°, recrystallized from ligroin.

group but also with the carbonyl group[15] of a ketone. The observation that use of at least two molecular proportions of aluminum chloride is required in order to obtain good yield of VIIa,b supports this suggestion. The mechanism for the steric course of the reaction presented in Scheme I can account for the results (Table II).

Treatment of Ic with aluminum chloride might provide the complex IX containing two electrophilic centers, of which the one with less steric interference appears to be the carbonyl carbon rather than the cyano carbon. The subsequent addition reaction of phenol with IX may take place *via* two routes a and b (Scheme I) where the incoming nucleophile (ArO:) is expected to attack preferentially on the side near the α hydrogen, leading to hemiketal complex Xa rather than on the side adjacent to the more bulky nitrile

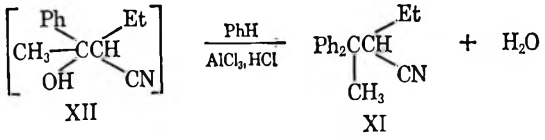
(15) (a) C. Mentzer, D. Molho, and D. Xuong, *Bull. Soc. Chim. Fr.*, **15**, 263 (1948); (b) J. Colonge and L. Pichat, *ibid.*, **16**, 177 (1949); (c) M. H. Dilke, D. D. Eley, and M. G. Cheppard, *Trans. Faraday Soc.* **46**, 261 (1950); (d) J. Broome and B. R. Brown, *Chem. Ind.*, (London), 1307 (1956).

SCHEME I



group, which would result in the formation of the isomeric complex Xb. The intermediates Xa and Xb could then undergo "*cis* elimination," to form VIIa as major product and VIIb as minor product. The data in Table II, except in the case of *o*-cresol, are consistent with this view. This exception, probably attributable to the presence of the methyl substituent at a position *ortho* to the hydroxyl group, suggests that steric constraint is operative.

On the other hand, condensation of benzene with Ic in a similar manner readily resulted in formation of the saturated nitrile XI, which could arise by formation of XII followed by reaction with a second mole of benzene.



The enol content of α-substituted β-oxonitrile Ic was shown by means of nmr spectra to be negligible whereas the enol content in Ia and Ib is about 11[16] and 38%,[17] respectively. In contrast with their enolization character, it is of potential interest to note that Ic may predominantly undergo the carbon–oxygen condensation reaction with phenols to the vinyl ethers VIIa and b while the electrophilic attack by either Ia or b on their nuclei brings about the condensation which can provide a new route to the synthesis of coumarins.

Experimental Section

All melting points, determined on a Shimadzu Type MM-2 micro hot stage, and boiling points are uncorrected. Infrared and ultraviolet spectra were recorded, respectively, on a Hitachi Model EPI-S2 and a Hitachi Model EPS-3T spectrophotometers. The nmr spectra were taken in deuteriochloroform or carbon tetrachloride on a Varian A-60 and JEOL Model JNM 4H-100 instruments with tetramethylsilane as an internal standard.

Materials.—Benzoylacetonitrile (Ia) was prepared from ω-bromoacetophenone and potassium cyanide according to the procedure of Shriner and Fuson.[18] Monoetherification of resorcinol with dimethyl sulfate was carried out by the method of Kinugawa and coworkers.[19] α-Ethylacetoacetonitrile (Ic) was obtained by the sodium-induced dimerization of acetonitrile followed by ethylation with ethyl bromide.[20] The nmr spectrum of Ic showed a triplet at τ 8.97 (CH_3 of ethyl group), a multiplet centered at 8.20 (CH_2), and a singlet at 7.63 (CH_3 of acetyl group), but no singlet due to an enolic proton at lower field. Other materials were obtained from commercial sources.

Acetoacetonitrile (Ib).—This material was prepared by a simplification of the procedure of Dahn and Hauth[17] as follows. *t*-Butyl α-cyanoacetoacetate (21.6 g, 0.118 mol), prepared by acetylation of *t*-butyl cyanoacetate[21] anion with acetyl chloride, was refluxed in 260 ml of benzene for several hours. To this mixture was then added dropwise a solution of *p*-toluenesulfonic acid (1 g) in 75 ml of benzene. After the mixture was heated under refluxing until the generated crystals disappeared (about 3 hr); removal of the solvent followed by fractional distillation gave 8.4 g (84%) of Ib, bp 47–50° (0.5 mm), the infrared spectrum of which was identical with that of the authentic sample.[17]

The Acid-Catalyzed Reaction of Phenols with β-Oxonitriles. General Procedure A.—To a stirred suspension of anhydrous aluminum chloride (0.1 mol) in isopropyl ether (15 ml) was added dropwise at 20–30° a solution of the phenol (0.05 mol) and Ia (0.05 mol) in the solvent (60 ml). The mixture, into which dry hydrogen chloride was continuously passed, was gradually heated and kept under the conditions presented in Table I. Then the resulting mixture was chilled and poured over water containing crushed ice and concentrated hydrochloric acid. After it was stirred for 0.5 hr, filtration and drying gave the crude product II, which was purified by recrystallization from an appropriate solvent. Substitution of isopropyl ether for such an inert solvent as *sym*-tetrachloroethane afforded a lower yield of II. The alternative procedure of adding the catalyst to a stirred solution of the phenol and Ia in the solvent provided the same results as have been presented above. Analytical data for the hitherto unknown compound II are individually described below. The coumarin IV[22] was isolated by concentration of the aqueous layer followed by extraction with ether. Removal of the solvent from the separated organic layer resulted in recovery of the starting materials.

Procedure A′.—The procedure involves no use of such an inert solvent as described above. Finely powdered anhydrous aluminum chloride (0.1–0.11 mol) was added slowly to a vigorously stirred mixture of the phenol (0.25 mol) and I (0.05 mol) at 5–10°. Dry hydrogen chloride was passed into the viscous slurry, which then was heated in a steam or oil bath and kept under the conditions shown in Table I. Unless otherwise specified, the subsequent work-up followed the above procedure.

Coumarins IIc, IVc, and IVd were isolated by means of the following work-up 1, while crotononitriles VIIa and b were isolated by work-up 2.

Work-Up 1.—After treatment of the resulting mixture with cold water, the organic layer was separated. The aqueous layer was extracted with ether, which was then combined with the separated organic materials. Filtration gave a crystals mass, which was recrystallized from such a solvent as anhydrous ethanol–ether to provide IIc. Saturation of the filtrate with dry hydrogen chloride afforded additional amount of IIc. A small amount of IV was obtained by concentration of the aqueous layer followed by extraction with ether. *p*-Cresol yielded the corresponding crude II, mp 112–113°, the infrared spectrum of which showed the absorptions due to functional groups. Attempts, however, to isolate the pure product by repeated recrystallization were unsuccessful, leading to IVd.

Work-Up 2.—The compounds VIIa and VIIb were isolated by this procedure. Such an extract as shown above was washed with dilute sodium hydroxide solution and water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was fractionated by distillation to give the products VIIa and b. Results with individual compounds are presented in Table II. Infrared spectra of compounds VIIa and VIIb

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(18) R. L. Shriner and R. C. Fuson, "Preparation of Organic Intermediates," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 98.

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(20) E. Mohr, *J. Prakt. Chem.*, **90**, 189 (1914).

(21) R. E. Ireland and M. Chaykovsky, *Org. Syn.*, **41**, p 5 (1961).

(22) The formation of IV along with II would presumably depend upon the individual stability of II to the contact time with aqueous solution during workup.

are summarized as follows:[23] VIIa (R = H), ν_{max}^{film} 2230 (A), 1648 (B), 1596, 1490 (C), 1257, 1220 (D), and 930, 760, 700 cm^{-1} (E); VIIb (R = H), ν_{max}^{film} 2220 (A), 1647 (B), 1594, 1490 (C), 1250, 1210 (D), and 940, 759, 696 cm^{-1} (E); VIIa (R = 2-CH_3), ν_{max}^{film} 2250 (A), 1650 (B), 1590, 1496 (C), 1262, 1237 (D), and 930, 780, 752 cm^{-1} (E); VIIa (R = 4-CH_3), ν_{max}^{film} 2200 (A), 1635 (B), 1600, 1498 (C), 1255, 1223 (D), and 930, 832, 819 cm^{-1} (E); λ_{max}^{EtOH} 238 mμ (ϵ 1200)[23] and 322 (12); VIIb (R = 4-CH_3), ν_{max}^{KBr} 2170 (A), 1641 (B), 1604, 1504 (C), 1220, 1209 (D), and 940, 829, 820 cm^{-1} (E); λ_{max}^{EtOH} 241 mμ (ϵ 1500).

The nmr spectrum of VIIa (R = 4-CH_3) showed a triplet at τ 8.83 (J = 7.2 cps, methyl protons of ethyl group), singlets at 7.95 (β-methyl protons) and 7.65 (aromatic methyl protons), and two doublets at 3.11 and 2.80 (J = 9.0 cps, aromatic protons) while that of VIIb (R = 4-CH_3) exhibited the corresponding peaks at τ 8.83 (J = 6.6), 8.17 and 7.71, and 3.16 and 2.91 (J = 8.4 cps).

Procedure B.—A solution of 0.05 mol of the phenol and 0.05–0.06 mol of acetoacetonitrile (Ib) in 52 g of PPE was stirred and heated under the conditions shown in Table I. In the case of resorcinol, the resulting mixture was decomposed with cold water and extracted with such a solvent as ethyl acetate or ether. After the extract was washed with water and dried over magnesium sulfate, removal of the solvent gave a mass of crystals (7 g, 80%). Recrystallization from aqueous ethanol afforded 4-methylumbelliferone (IVe), mp 185°. On the other hand, the mixture from resorcinol monomethyl ether obtained as described above on treatment with cold water and filtration gave a crude solid (11 g), mp 136–142°, which was recrystallized from ethanol to give 6.7 g (70%) of white crystals (IVf): mp 158.5–159°; ν_{max}^{KBr} 1730 (C=O), 1625, 1610, 1510 (C=C), 1287, 1265, 1213, 1070 (C–O–C), and 858 cm^{-1} (aromatic).

Procedure C.—A mixture of 0.05 mol of the phenol, 0.05–0.06 mol of Ib, and 60 g of PPA was heated with mechanical stirring under the conditions given in Table I. The mixture was poured onto an ice–water slurry (200–300 ml), stirred vigorously for 0.5 hr, and filtered. Purification was effected by recryrstallization from an appropriate solvent. The filtrate was saturated with ammonium sulfate and extracted with ether. After drying, the ether was evaporated *in vacuo* and the residue was recrystallized from the appropriate solvent (Table I).

2-Imino-4-phenylumbelliferone Hydrogen Chloride (IIa).—This compound was prepared by means of the procedure A. Recrystallization from acetic acid or ethanol gave the pure compound IIa: mp 222–223°; ν_{max}^{KBr} 3000 (N–H), 1670 (C=N), and 1560 cm^{-1} (δ N–H).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.81; H, 4.43. Found: C, 66.04; H, 4.46.

Methyl Ether of IIa (IIb).—The compound IIb was synthesized together with IVb by means of the procedure A. Recrystallization from ethanol afforded the analytical sample: mp 201.5–202°; ν_{max}^{KBr} 2900 (N–H), 1675 (C=N), and 1550 cm^{-1} (δ N–H).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.87. Found: C, 66.96; H, 4.99.

2-Imino-7-methyl-4-phenylcoumarin Hydrogen Chloride (IIc).—The crude salt IIc was prepared, through work-up 1, by using the procedure A′. Attempts to isolate the analytical sample by repeated recrystallization from such an anhydrous solvent as ethanol–ether failed although the infrared spectrum showed ν_{max}^{KBr} 2850 (N–H), 1670 (C=N), and 1550 cm^{-1} (δ N–H); the melting point was 205–210°. Attempted recrystallization from such an aqueous solvent as aqueous ethanol provided quantitatively IVc.

β-(p-Hydroxyphenyl)cinnamonitrile (Va).—This compound was prepared by means of the procedure A′. The reaction was carried out under the conditions presented in Table I, using 28.2 g (0.3 mol) of phenol and 10 g (0.06 mol) of Ia. After the extract was shaken with 1 N sodium hydroxide solution, concentration of the separated alkaline layer followed by filtration gave 7.3 g of white crystals, which were presumed to be the sodium salt of Va. A solution of the crystals in 20 ml of water was acidified with hydrochloric acid. The precipitate (5.7 g, 43%) was filtered and washed with water. Recrystallization from aqueous ethanol afforded white crystals (needles): mp 162°; ν_{max}^{KBr} 3350 (OH), 2250 (CN), 1620 (alkenic C=C), 1595, 1520 (aromatic C=C), 1260 (C–O), 840, 805 (*para* substituted), and 775, 700 cm^{-1} (aromatic).

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01. Found: C, 81.21; H, 4.97.

Compound IV was not found in the ethereal layer.

β-(4-Hydroxy-3-methylphenyl)cinnamonitrile (Vb).—The procedure for the preparation of Va was followed using the same molar ratios of the reagents and the conditions listed in Table I. Acidification of the sodium salt of Vb with hydrochloric acid afforded crude Vb (10.8 g) which was recrystallized from aqueous acetic acid: mp 135°; ν_{max}^{KBr} 3380 (O–H), 2250 (CN), 1615 (alkenic C=C), 1570, 1515 (aromatic C=C), 1280 (C–O), 1120, 830, 805 (1,2,4 trisubstituted), and 780, 700 cm^{-1} (monosubstituted).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.96; H, 5.56.

α-Ethyl-β,β-methylphenylhydrocinnamonitrile (XI).—This compound was prepared according to the procedure A′ using 0.5–0.7 mol of benzene, 0.1 mol of Ic, and 0.22 mol of anhydrous aluminum chloride. The reaction was carried out in the presence of dry hydrogen chloride at 40–50° for 5 hr. After the resulting mixture was treated with ice–water, the separated aqueous layer extracted with benzene and organic solution were combined. Removal of benzene followed by fractional distillation furnished 11.7 (47%) of a yellow viscous oil after recovery of Ic (40%): bp 159° (3 mm); $n^{20}D$ 1.5774; ν_{max}^{film} 3070, 3020 (C–H), 2260 (CN), 1609, 1500 (C=C), 1453, 1390 (C–H deformation), and 1033, 765, 705 cm^{-1} (aromatic).

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68. Found: C, 86.62; H, 7.59.

Conversion of II into IV.—Compound IIa (0.6 g) in 6 ml of water was heated on a steam bath for 3 hr. Upon cooling to room temperature, the solution was filtered to give 0.5 g (95%) of IVa, mp 246–247°. One recrystallization from ethanol gave pure material, mp 249–250° (lit.[5c] 245°). Use of dilute hydrochloric acid smoothly effected partial hydrolysis. Its methyl ether IIb as well as IIc even upon heating with aqueous ethanol for a few minutes was converted into the corresponding coumarin IVb.

7-Acetoxy-4-phenylcoumarin (IVi).—A mixture of IVa (0.6 g) and acetic anhydride (1.2 g) was refluxed for 0.5 hr and was poured into cold water (10 ml). The precipitate was filtered and washed thoroughly with water. The crude product, 0.6 g, was recrystallized from aqueous ethanol to provide 0.3 g of white crystals: mp 120–121° (lit.[24] 120°); ν_{max}^{KBr} 1765 (C=O of acetate), 1730 (C=O of lactone), 1620 (C=C), 1268, 1205, 1142, 1110 (C–O–C), and 868, 820, 780, 710 cm^{-1} (aromatic); λ_{max}^{EtOH} 286 mμ (ϵ 13,300, flat).

Registry No.—IIa, 16299-16-4; IIb, 16299-17-5; IIc, 16299-18-6; IVa, 2555-30-8; IVb, 2555-31-9; IVc, 7758-71-6; IVd, 16299-22-2; IVe, 90-33-5; IVf, 2555-28-4; IVg, 14002-90-5; IVh, 14002-89-2; IVi, 16299-27-7; Va, 16281-90-6; Vb, 16299-28-8; VIIa (R = H), 16299-29-9; VIIb (R = H), 16299-30-2; VIIa (R = 2-CH_3), 16299-31-3; VIIa (R = 4-CH_3), 16299-32-4; VIIb (R = 4-CH_3), 16299-33-5; XI, 16299-34-6.

Acknowledgment.—The authors wish to express their gratitude to Mrs. N. Monte, T. Takahashi, S. Tokita, and T. Itakura for capable technical assistance in these experiments.

(23) The absorptions, A, B, C, D, and E are due to CN, alkenic C=C aromatic C=C, conjugated C–O–C bands, and aromatic C–H deformations, respectively. The ultraviolet spectra were determined at concentration of 1.5×10^{-3} mol/l.

(24) H. von Pechmann and E. Hanke, *Chem. Ber.*, **34**, 354 (1901).

The Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. II. 4-Methyl-, 5-Methyl-, 6-Methyl-, and 4,5,6-Trimethyl-3-pentadecylcatechol[1]

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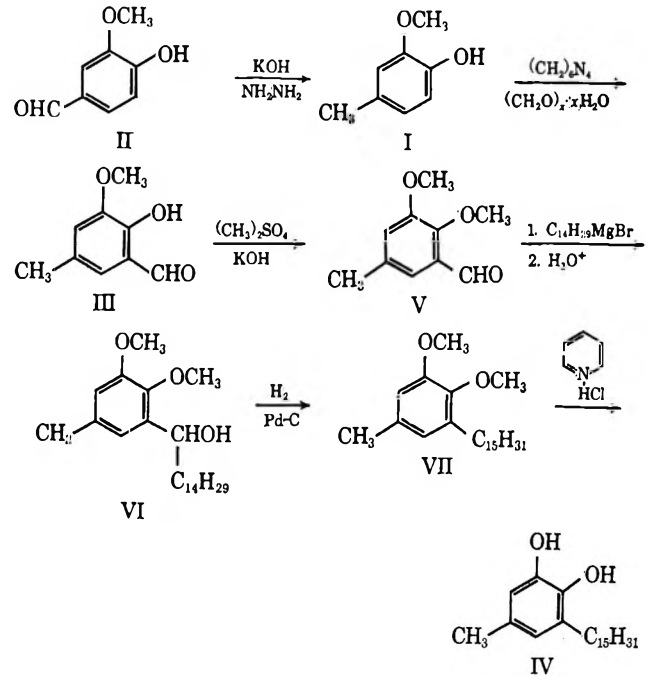
Urushiol, the allergenic principle of poison ivy, is an oil composed of four compounds, all having the carbon skeleton of 3-pentadecylcatechol. As part of an investigation of the possible role of the unsubstituted positions on the catechol ring in the allergenic activity of these compounds, a series of ring-methylated homologs of 3-pentadecylcatechol have been synthesized and are being clinically tested. Successful synthetic routes to 4-methyl-, 5-methyl-, 6-methyl-, and 4,5,6-trimethyl-3-pentadecylcatechol are reported.

It has been suggested[2] that a critical step in the biochemical mechanism of the poison ivy allergy may be the oxidation of the catecholic components of poison ivy urushiol to the corresponding *o*-benzoquinones. Antigen formation might then occur by reaction of protein nucleophilic groups with the *o*-quinones *via* a 1,4-dipolar addition. Supporting evidence for the above view was obtained by the synthesis and biological testing of 4,5-dimethyl-3-pentadecylcatechol.[2] Preliminary clinical tests revealed that the simultaneous blocking of both the 4 and 5 positions, the normal sites for 1,4 addition to the quinone, resulted in the loss of most, but not all activity. This result made it advisable to synthesize and test other ring-methylated homologs of 3-pentadecylcatechol. Of particular interest were the three monomethyl homologs and the fully substituted compound, 4,5,6-trimethyl-3-pentadecylcatechol.

The 5-Methyl Homolog.—As previously reported,[2] the successful synthesis of 4,5-dimethyl-3-pentadecylcatechol was accomplished by the preparation of 5,6-dimethyl-*o*-vanillin, followed by conversion of that compound into the desired catechol by established means. The most critical steps in this route were the preparation of 4,5-dimethyl guaiacol and its formylation to 5,6-dimethyl-*o*-vanillin. Since the synthesis in good yield of 4-methyl guaiacol (I) from vanillin (II) has been reported in the literature,[3] it appeared that 5-methyl-*o*-vanillin (III) could also be synthesized by formylation and that III could be converted into 5-methyl-3-pentadecylcatechol (IV) by the sequence of reactions shown in Scheme I.

SCHEME I



The preparation of 4-methyl guaiacol (I), as reported by Lock,[3] was accomplished in 90% yield by the Wolff–Kishner reduction of vanillin (II). It was found, however, as part of the present investigation, that this reduction could be carried out on a large scale more easily by means of the Huang-Minlon modification of the Wolff–Kishner reaction,[4] which led to a comparable yield (89%). Formylation of compound I was then carried out in strong acid using a mixture of hexamethylenetetramine and paraformaldehyde as the formylating reagent.[5] The reaction proceeded without difficulty to give 5-methyl-*o*-vanillin (III) in about 50% yield, which was comparable with the yield of 5,6-dimethyl-*o*-vanillin obtained in the synthesis of 4,5-dimethyl-3-pentadecylcatechol.[2] Although there were three unsubstituted sites on the guaiacol ring at which formylation might have occurred, only the desired product would have been the result of formylation *ortho* to the free hydroxyl, whereas the other possible products would have resulted from *meta* substitution. Nonetheless it seemed prudent to seek confirmation that the formylation reaction had produced the proper vanillin. Since the phenolic hydroxyl of *o*-vanillins should be hydrogen bonded to the adjacent aldehyde carbonyl, it was predicted that the peak in the nmr spectrum for the hydroxyl proton would appear at lower field than the corresponding peaks for *meta* and *para* compounds. In the nmr spectrum of *o*-vanillin the hydroxyl peak is at τ −0.52 to −0.74, depending on concentration, which is downfield from the aldehyde proton peak at τ −0.15. In vanillin (*para*) and isovanillin (*meta*) the hydroxyl peaks at τ 1.25–1.42 and 1.95, respectively, are upfield from the aldehyde proton. The spectrum of III confirmed *ortho* formylation as the hydroxyl and aldehyde proton peaks were found at τ −0.51 and −0.02, respectively.

The methylation of the vanillin to give 5-methyl-*o*-veratraldehyde (V) was then carried out in 87% yield using dimethyl sulfate in aqueous potassium hydroxide. The over-all yield to this stage was just about 40%. The remainder of the synthesis was easily accomplished

(1) This investigation was supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health and by a predoctoral training grant (T1-GM-1130), National Institutes of General Medical Sciences, U. S. Public Health Service, to J. S. B. during 1963–1964.

(2) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **32**, 1084 (1967).

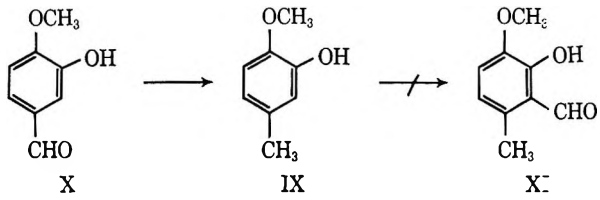
(3) G. Lock, *Monatsh.*, **85**, 802 (1954).

(4) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(5) Farbenfabriken Bayer A.-G., British Patent 794,885 (May 14, 1958).

without any unusual difficulties in quite satisfactory yield (about 50%). The side chain was introduced by the reaction of V with tetradecylmagnesium bromide to yield the carbinol (VI), which was then directly hydrogenolyzed over palladium-on-charcoal catalyst, without complete purification, to give 5-methyl-3-pentadecyl veratrole (VII). The final step was cleavage of the veratrole (VII) by means of refluxing pyridine hydrochloride[6] to give 5-methyl-3-pentadecylcatechol (IV) in 88% yield and nearly 20% yield overall from vanillin.

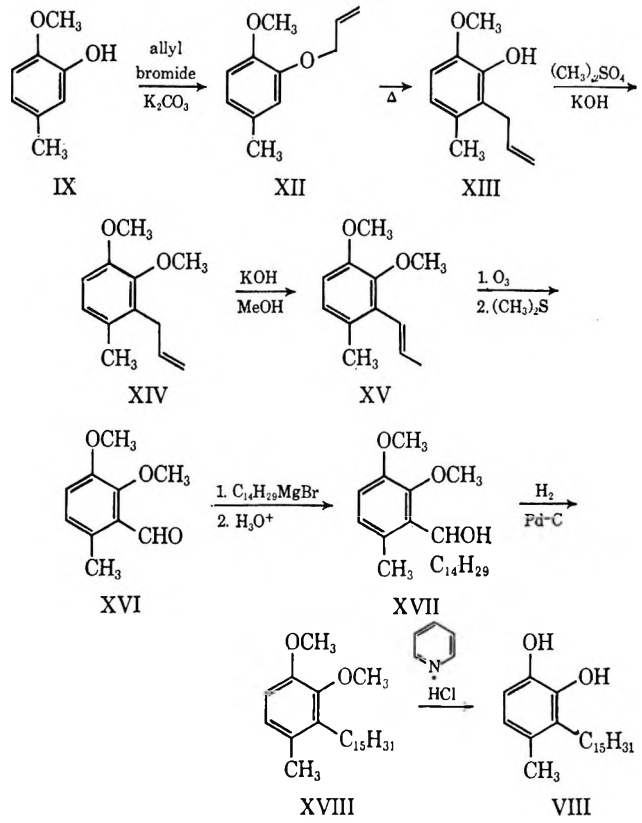
The 4-Methyl Homolog.—Since the synthesis of both 4,5-dimethyl- and 5-methyl-3-pentadecylcatechol had been successfully accomplished by similar routes involving the formylation of appropriate guaiacols to give *o*-vanillins, it was assumed that the synthesis of 4-methyl-3-pentadecylcatechol (VIII) could also be carried out in this fashion. Once again employing the Huang-Minlon modification of the Wolff–Kishner reduction, 5-methyl guaiacol (IX) was readily prepared from isovanillin (X) in 96% yield. However, the direct formylation of IX using hexamethylenetetramine and paraformaldehyde repeatedly failed to yield the desired compound (XI). Only a small amount of an uncharacterized amorphous yellow substance could be isolated. Other methods of formylation[7,8] also failed to produce the desired product (XI).



The route by which 4-methyl-3-pentadecylcatechol was finally prepared employed a Claisen rearrangement as a means for introducing useful functionality into the appropriate position of 5-methyl guaiacol (IX).

After conversion of IX into its allyl ether (XII) had been readily accomplished in 92% yield according to the procedure of Allen and Gates,[9] the thermal rearrangement of XII was then carried out by heating the neat liquid to 255° under a nitrogen atmosphere[9] to give 5-methyl-6-allyl guaiacol (XIII) in about 70% yield. Evidence of the successful rearrangement was provided by the shift upfield in the nmr spectrum of the allylic methylene doublet from τ 5.58 to 6.60 and the appearance of the hydroxyl group absorption in the infrared spectrum at 2.80 μ and in the nmr as a sharp singlet at τ 4.33. After methylation of XIII to the corresponding veratrole XIV in 87.5% yield, isomerization of the allyl group to give 4-methyl-3-propenylveratrole (XV) was accomplished by heating the allyl compound under nitrogen with saturated methanolic potassium hydroxide.[10] The most significant feature of the nmr spectrum of the isomerized compound was the complete disappearance of the two-proton allylic methylene doublet at τ 6.60, which was replaced by the three-proton doublet of the new allylic methyl group at τ 8.12. Recovery of the propenyl compound XV was nearly quantitative (96%). Ozonization of XV was carried out in methanolic solution at −30 to −40°, after which reductive decomposition of the ozonide using dimethyl sulfide yielded 6-methyl-*o*-veratraldehyde (XVI) in 82% yield. Vapor phase chromatography of this substance confirmed the absence of any 2′,3′-dimethoxy-6′-methylphenylacetaldehyde, the compound which would have been formed by ozonolysis of any unisomerized 3-allyl-4-methylveratrole (XIV) (Scheme II).

SCHEME II



The remainder of the synthesis was carried out by the customary route without difficulty. The reaction of the aldehyde (XVI) with tetradecyl Grignard reagent yielded the carbinol (XVII), which was converted into 4-methyl-3-pentadecylveratrole (XVIII) by hydrogenolysis over palladium-on-carbon catalyst. The combined yield for these two steps was 48%. Finally, pyridine hydrochloride cleavage of the methoxyls gave 4-methyl-3-pentadecylcatechol (VIII) in just over 70% yield. For the entire eight-step synthesis, the yield of VIII from isovanillin was about 15%.

The 6-Methyl Homolog.—The most direct approach to the synthesis of 6-methyl-3-pentadecylcatechol (XIXa) appeared to be the introduction, into the 6 position of 3-pentadecylcatechol, of a functional group which might subsequently be converted into a methyl group, presumably by reduction. One such method was the Mannich reaction which could be used to introduce an N,N-dimethylaminomethylene moiety at the unsubstituted ring site adjacent to the phenolic hydroxyl to yield 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXa). Hydrogenolysis of the benzylic amino group would then be expected to yield XIXa.

(6) E. Wenkert, E. M. Loesser, S. N. Mahaptera, F. Schenker, and E. M. Wilson, *J. Org. Chem.*, **29**, 438 (1964).

(7) A. Russell and L. H. Lockhart, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 463.

(8) J. C. Duff, *J. Chem. Soc.*, 547 (1941).

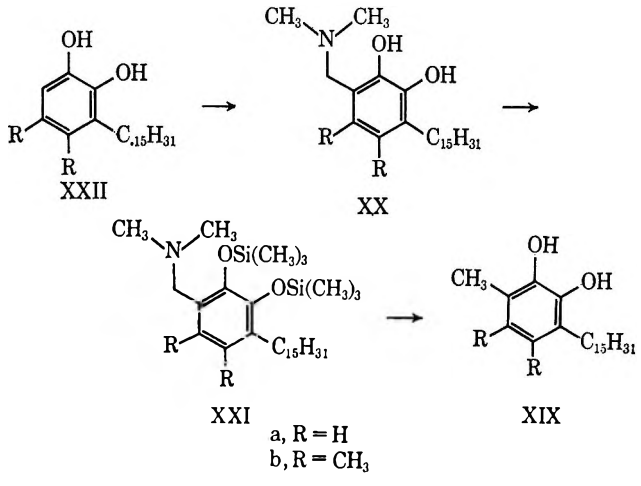
(9) C. F. H. Allen and J. W. Gates, Jr., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 418.

(10) D. S. Tarbell, *Org. Reactions*, **2**, 1 (1944).

A similar synthesis had already been achieved by Gulati,[11] who converted 3-pentadecylphenol into 6-methyl-3-pentadecylphenol.

The Mannich reaction of 3-pentadecylcatechol with dimethylamine and formaldehyde in ethanol solution led to recovery of XXa in about 89% yield (Scheme III). The structure of this compound was apparent from its nmr spectrum which had a typical AB-type quartet at τ 3.65 for the two adjacent aromatic protons, a singlet for the aminomethylene at τ 6.47, and another singlet at τ 7.70 for the aminomethyl groups in the ratio 1:1:3. The hydroxyls appeared far downfield at τ 1.6, presumably because of hydrogen bonding with the amino nitrogen.

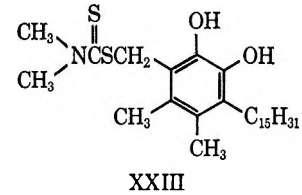
SCHEME III



It was expected that hydrogenolysis of the Mannich base (XXa) would then produce 6-methyl-3-pentadecylcatechol in good yield, but such was not the case. When hydrogenolysis was attempted at 60 psi over Raney nickel or platinum oxide catalysts, there was no observable uptake of hydrogen. When palladium-on-carbon catalyst was used in ethanol, some hydrogenolysis took place, but the yield of 6-methyl-3-pentadecylcatechol was only 12%. Similar difficulties had been encountered by other workers who attempted the preparation of methyl phenols by the hydrogenolysis of phenolic Mannich bases.[12,13] Their solution to this problem was to perform the hydrogenolysis over copper chromite catalyst at elevated temperatures and pressures. While use of these conditions might also have led to the successful preparation of 6-methyl-3-pentadecylcatechol, a less drastic alternative also seemed promising. It was observed that the failure of this reduction to proceed in good yield was in sharp contrast with the hydrogenolysis of N,N-dimethylbenzylamine to toluene, which is rapid with several catalysts and in a variety of solvents. This contrast made it appear that the hydrogen bonding between the amino and hydroxyl groups was in some way largely responsible for the difficulty. Therefore, it seemed that the use of some easily removed hydroxyl protecting group, which could be introduced without altering the N,N-dimethylamino moiety, might facilitate hydrogenolysis. This was accomplished by converting the Mannich base into its bistrimethylsilyl derivative (XXIa) in 76% yield using hexamethyldisilizane in refluxing pyridine.[14] Once the hydroxyls had been derivatized in this manner and could no longer hydrogen bond with the nitrogen atom, hydrogenation proceeded smoothly in absolute ethanol over palladium on charcoal. After completion of the hydrogenation and removal of the catalyst by filtration, hydrolysis of the protecting groups was accomplished by adding water to the ethanolic solution and refluxing. The yield of 6-methyl-3-pentadecylcatechol from the trimethylsilyl derivative of the Mannich base was 78% and the yield, over-all, from 3-pentadecylcatechol was 53%.

The Trimethyl Homolog.—In a similar fashion to the work with the 6-methyl compound, the original plan for the synthesis of 4,5,6-trimethyl-3-pentadecylcatechol (XIXb) called for the conversion of 4,5-dimethyl-3-pentadecylcatechol into the corresponding 6-(N,N-dimethylamino)methyl compound (XXb), followed by appropriate steps to bring about reduction of the Mannich base. Although the Mannich reaction with dimethylamine and formaldehyde led to isolation of XXb, the yield was not high (about 46%). As was expected, hydrogenolysis of the unprotected phenolic Mannich base proved impractical and the bistrimethylsilyl derivative (XXIb) was prepared, but the yield of the silylation reaction was only about 62%. When the hydrogenolysis of this compound was carried out over palladium-on-carbon catalyst, even after 48 hr the yield of the reduction was only 26%, giving an over-all yield from 4,5-dimethyl-3-pentadecylcatechol (XXIIb) of only about 7%. This corresponds to less than a 1% yield from readily available starting materials since the yield in the synthesis of XXIIb was about 13%.

Having found that hydrogenolysis of the amine (XXIb) proceeded so poorly, presumably because of the considerable crowding around the hexasubstituted aromatic ring, it seemed that synthesis of 4,5,6-trimethyl-3-pentadecylcatechol might be better accomplished if it were possible to prepare a similar intermediate which could be converted into XIXb by hydrogenolysis of a more easily broken bond, such as the one between carbon and sulfur. This goal was achieved by the reaction of 4,5-dimethyl-3-pentadecylcatechol with a mixture of carbon disulfide, formaldehyde, and dimethylamine in ethanol to give 6-(N,N-dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII) in 82% yield.[15] Successful substitution for the lone aromatic proton of 4,5-dimethyl-3-pentadecylcatechol was indicated by the absence of a peak in the τ 3–5 region of the nmr spectrum. Desulfurization of XXIII was accomplished using a tenfold excess by weight of Raney nickel W-7 catalyst in reflux-



XXIII

(11) A. S. Gulati, Ph.D. Dissertation, University of Poona, 1963.

(12) W. T. Caldwell and T. R. Thompson, *J. Amer. Chem. Soc.*, **61**, 765 (1939).

(13) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bills, *J. Org. Chem.*, **26**, 4669 (1961).

(14) S. H. Langer, P. Pantages, and I. Wender, *Chem. Ind.* (London), 1664 (1958).

(15) U. S. Rubber Co., Netherlands Patent Appl. 6,408,883 (Feb 2, (1965).

ing dioxane[16] to give 4,5,6-trimethyl-3-pentadecylcatechol in over 75% yield. Evidence of complete desulfurization was provided by the loss of the thiocarbonyl absorption at 7.65 μ in the infrared spectrum and the presence in the nmr spectrum of a peak at τ 7.92 equivalent to three nuclear methyl groups. This compound was identical with the one obtained by hydrogenolysis of XXIb, but the yield was 62% from 4,5-dimethyl-3-pentadecylcatechol. Thus, the synthesis of the trimethyl homolog *via* the dithiocarbamoyl intermediate resulted in an eightfold improvement in the over-all yield.

Experimental Section[17]

5-Methyl-*o*-vanillin (III).—A mixture of 183.6 g of 4-methylguaiacol (prepared from vanillin in 89% yield by the Huang-Minlon modification of the Wolff–Kishner reduction), 78.6 g of paraformaldehyde, and 78.6 g of hexamethylenetetramine was melted and heated to 110°. To this molten mixture was added 300 ml of glacial acetic acid, followed by slow addition of 150 ml of a 1:1 solution of sulfuric acid and water. Addition of the sulfuric acid caused rapid reflux and considerable darkening of the reaction mixture. The resulting solution was then heated at reflux for 30 min, after which it was poured into 1500 ml of water. This mixture was steam distilled and the product separated from the steam distillate as yellow plates. Recrystallization from ligroin (bp 60–90°) gave 5-methyl-*o*-vanillin as yellow needles, mp 40.0–41.5°. The yield was 110.1 g (49.9%). The significant peaks in the infrared spectrum were hydroxyl at 2.84 μ and carbonyl at 6.00 μ. In the nmr spectrum in acetone solution, the hydroxyl proton produced a sharp singlet at τ −0.51 and the hydrogen on the carbonyl carbon produced a sharp singlet at τ −0.02.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.96; H, 5.97.

5-Methyl-*o*-veratraldehyde (V).—To 110.1 g of melted 5-methyl-*o*-vanillin (III) were simultaneously added 80 g of potassium hydroxide in 175 ml of water and 100 ml of dimethyl sulfate. The mixture was then refluxed for 2.5 hr, after which 500 ml of water was added and the reaction vessel was cooled in an ice bath. The product, which separated as a tan solid, was filtered, washed with water, and then recrystallized from ligroin. The yield of 5-methyl-*o*-veratraldehyde was 104.2 g (87.2%). The hydroxyl peak at 2.84 μ was absent in the spectrum and the carbonyl peak was at 5.85 μ.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.52; H, 6.55.

5-Methyl-3-(1′-hydroxy)pentadecylveratrole (VI).—To a solution of tetradecylmagnesium bromide in 150 ml of anhydrous ether prepared in the usual manner from 3.8 g of magnesium metal and 41.6 g of 1-bromotetradecane was added 18.0 g of the above 5-methyl-*o*-veratraldehyde in 100 ml of ether. The reaction mixture was heated at reflux for 18 hr under a nitrogen atmosphere and then was cooled in an ice bath and hydrolyzed by addition of 150 ml of 10% sulfuric acid. After separating the two phases, the aqueous layer was washed with 200 ml of ether, and the combined ether solutions were dried over magnesium sulfate. Removal of solvent gave a yellow oil which was dissolved in boiling 95% ethanol. On chilling of the ethanolic solution, octacosane precipitated as silvery plates and was filtered. Solvent was again removed to give 36 g of crude 5-methyl-3-(1′-hydroxy)-pentadecylveratrole as a yellow oil. This material was used in the next step without further purification.

5-Methyl-3-pentadecylveratrole (VII).—The crude 5-methyl-3-(1′-hydroxy)pentadecylveratrole obtained in the previous step was dissolved in 100 ml of ethyl acetate to which was added 5 drops of sulfuric acid and 0.35 g of 10% palladium-on-charcoal catalyst. Hydrogenation was carried out in a Parr shaker at approximately 60° and at an initial hydrogen pressure of 60 psi. Hydrogenation was continued for 24 hr and then the solution was allowed to cool and was diluted with 200 ml of ether. After the catalyst had been removed by filtration, the solvent was evaporated and vacuum distillation of the residual oil was carried out at 0.4-mm pressure to give 20.3 g (56.2%) of 5-methyl-3-pentadecylveratrole as a colorless oil (bp 206–209°). On cooling, the oil formed a white solid which was recrystallized from an ethanol–acetone mixture (mp 35.2–36.2°). The nmr spectrum of this compound consisted of a two-proton singlet at τ 3.61 (aromatic H), a six-proton singlet at τ 6.30 (–OCH_3), and a three-proton singlet at τ 7.80 (nuclear –CH_3), as well as the characteristic peaks for the pentadecyl side chain. In the infrared, the low intensity peaks indicative of a 1,2,3,5-tetrasubstituted benzene appeared at 5.15, 5.25, and 5.80 μ.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.51; H, 11.44.

5-Methyl-3-pentadecylcatechol (IV).—A solution of 50 g of 5-methyl-3-pentadecylveratrole (VII) in 250 g of pyridine was heated at reflux, and dry hydrogen chloride gas was bubbled through the refluxing solution. In approximately 1 hr all of the pyridine had been converted into pyridine hydrochloride, and the temperature of the reaction mixture rose to about 220°. After refluxing at that temperature for 2.5 hr, the solution was allowed to cool and 250 ml of ether was added as well. The layers were then separated, the aqueous layer was extracted with two 250-ml portions of ether, and the combined ether solutions were washed with two 200-ml portions of water. After treatment with decolorizing charcoal and drying over magnesium sulfate, the solvent was removed *in vacuo* to give a white solid. After recrystallization from ligroin, the yield of 5-methyl-3-pentadecylcatechol (mp 74.5–76.0°) was 41.2 g (89.5%). The significant peak in the infrared spectrum of this compound was that for the hydroxyl groups at 2.85 μ.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 78.95; H, 10.98.

5-Methylguaiacol Allyl Ether (XII).—To a solution of 41.4 g of 5-methylguaiacol (IX) (prepared from isovanillin in 96% yield by the Huang-Minlon modification of the Wolff–Kishner reduction) in 75 ml of acetone was added 42 g of anhydrous potassium carbonate and 40 g of allyl bromide. The mixture was refluxed with rapid stirring for 8 hr, after which 200 ml of water was added. As soon as all solids had dissolved, the phases were separated and the aqueous layer was extracted with two 100-ml portions of ether. The organic solutions were then combined, washed with two 100-ml portions of 10% sodium hydroxide, and dried over anhydrous potassium carbonate. After evaporating the solvent, the residual oil was distilled at 10 mm to yield 49.2 g (92%) of 5-methylguaiacol allyl ether as a colorless oil, bp 128–132°. The infrared spectrum contained no peak for hydroxyl and had a new peak at ~10.6 μ. The following peaks appeared in the nmr spectrum: singlet (3) at τ 3.37 (aromatic H); multiplet (1) at τ 3.7–4.3 (–CH_2CH=CH_2); multiplet (2) at τ 4.5–5.0 (–CH_2CH=CH_2); doublet (2) at τ 5.58 (–CH_2CH=CH_2); singlet (3) at τ 6.33 (–OCH_3); singlet (3) at τ 7.80 (nuclear –CH_3).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.92.

5-Methyl-6-allylguaiacol (XIII).—Using an oil bath set at 235°, 48.0 g of the above 5-methylguaiacol allyl ether was heated under an inert atmosphere of nitrogen. When the temperature of the liquid reached 210°, slow evolution of bubbles began. At 225° rapid reflux started, the internal temperature rose quickly to 255°, and the bath was removed. When the temperature began to fall, heating was resumed and the temperature of the liquid was kept at 245° for 1 hr. After cooling to room temperature, 100 ml of ether was added, and the ethereal solution was extracted with three 100-ml portions of 10% sodium hydroxide. The alkaline solution was then acidified with hydrochloric acid and extracted with two 150-ml portions of ether. These were combined, dried over magnesium sulfate, and concentrated to give a clear, brown oil. Distillation of that oil at 10 mm yielded 33.4 g (69.5%) of 5-methyl-6-allyl guaiacol as a colorless oil, bp 135–142°. In the infrared, there was now a hydroxyl peak at 2.80 μ and a peak at 10.4 μ. In the 5–6-μ region, low intensity peaks appeared at ~5.4 and ~5.8 μ, with the shorter wavelength peak the more intense of the two. In the nmr, the allylic methylene doublet was shifted upfield to τ 6.60 and there was a sharp singlet at τ 4.33 (–OH).

(16) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).

(17) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 Infracord and were measured in carbon tetrachloride solution unless otherwise specified. The nmr spectra were obtained with a Varian A-60 or A-60A spectrometer using tetramethylsilane as an internal standard and carbon tetrachloride as solvent, unless otherwise indicated. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 7.91.

3-Allyl-4-methylveratrole (XIV).—To 31.3 g of the above 5-methyl-6-allylguaiacol heated to 100° were added simultaneously 11.2 g of potassium hydroxide in 25 ml of water and 25.2 g of dimethyl sulfate. After the addition was complete, the mixture was refluxed with rapid stirring for 3 hr, then cooled and the layers separated. The aqueous layer was extracted with two 75-ml portions of ether, and the combined organic fractions were dried over magnesium sulfate and the solvent removed *in vacuo* to give a yellow oil. Distillation of this oil at 10 mm yielded 29.5 g (87%) of 3-allyl-4-methylveratrole as a colorless liquid, bp 133–140°. The hydroxyl peak at 2.80 μ was no longer apparent in the infrared. In the nmr the singlet at τ 4.33 was gone, and the two methoxyls appeared as sharp singlets at τ 6.25 and 6.28.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.76; H, 8.28.

3-Propenyl-4-methylveratrole (XV).—Methanol was distilled from a rapidly stirred mixture of 29.0 g of 3-allyl-4-methylveratrole (XIV) and 90 ml of saturated methanolic potassium hydroxide until the temperature of the liquid reached 100°. Distillation was then discontinued, and the mixture was refluxed at 110–120° for 6 hr. It was then cooled, 100 ml of water was added, and the layers were separated. The aqueous phase was extracted with two 75-ml portions of ether, the combined ether extracts were dried over magnesium sulfate, and the solvent was evaporated. Vacuum distillation at 15 mm yielded 27.9 g (96%) of 3-propenyl-4-methylveratrole as a colorless liquid, bp 142–151°. In the nmr the two proton allylic doublet at τ 6.60 was replaced by a three-proton doublet at τ 8.12. There were overlapping multiplets in the τ 3–4 region.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.94; H, 8.38.

6-Methyl-*o*-veratraldehyde (XVI).—A solution of 26.9 g of the above 3-propenyl-4-methylveratrole in 500 ml of methanol was chilled to approximately −40°. A stream of ozone enriched oxygen (2%) was then bubbled through the solution at a rate of 0.08 ft³/min for 1.5 hr, during which time the temperature of the solution was held at −30 to −40°. When the ozonization had been completed, the temperature of the solution was brought to 0°, and the reaction mixture was decanted into an erlenmeyer flask cooled in an ice bath. After rinsing the ozonization vessel with 100 ml of methanol and adding this to the original solution, 10 g of dimethyl sulfide was added, and the mixture was stirred at approximately 0° for 2 hr. Next, the solvent was stripped to leave a residual oil which was suspended in 200 ml of water. This was extracted with three 200-ml portions of ether, the combined ethereal fractions were dried over magnesium sulfate, and the solvent was removed under vacuum. Distillation of the residual oil at 10 mm yielded 20.7 g (82%) of 6-methyl-*o*-veratraldehyde as a pale yellow oil (bp 127–133°). On cooling, the oil became a cream solid which was recrystallized from ligroin as white needles (mp 53.5–54.5°). The significant absorption in the infrared was a carbonyl peak at 5.94 μ. When subjected to vapor phase chromatography on an SE-30 column, the product gave a single sharp peak.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.21; H, 6.62.

4-Methyl-3-(1′-hydroxy)pentadecylveratrole (XVII).—To a solution of tetradecylmagnesium bromide in 150 ml of ether, prepared in the customary fashion from 2.9 g of magnesium metal and 30.5 g of 1-bromotetradecane, was added 18.0 g of the above 6-methyl-*o*-veratraldehyde in 100 ml of ether. The mixture was refluxed for 18 hr, after which it was cooled in an ice bath and then hydrolyzed by addition of 200 ml of 10% sulfuric acid. The layers were separated, the aqueous layer was extracted with 150 ml of ether, and the combined ethereal solutions were dried over magnesium sulfate and then were concentrated to give a yellow liquid. This oil was dissolved in boiling ethanol which was then chilled to precipitate octacosane. After filtering, the solvent was removed to give 35 g of crude 4-methyl-3-(1′-hydroxy)-pentadecylveratrole, which was used in the next step without further purification.

4-Methyl-3-pentadecylveratrole (XVIII).—The above crude 4-methyl-3-(1′-hydroxy)pentadecylveratrole was dissolved in 100 ml of ethyl acetate containing 5 drops of sulfuric acid to which was added 0.35 g of 10% palladium-on-carbon catalyst. This mixture was shaken at about 60° for 48 hr under an initial hydrogen pressure of 60 psi. After that time the solution was diluted with 150 ml of ether, filtered, and washed with 100 ml of 10% sodium bicarbonate, followed by 100 ml of water. After drying with magnesium sulfate, the solvent was evaporated, and the residual oil was distilled at 0.4 mm to yield 17.3 g (48% yield, based on 6-methyl-*o*-veratraldehyde) of 4-methyl-3-pentadecylveratrole as a colorless oil (bp 213–217°). On cooling this oil changed to a white solid, recrystallizable from ethanol–acetone, mp 34.0–35.0°. The significant peaks in the nmr were aromatic H at τ 3.39, methoxyl at τ 6.25, and methyl at τ 7.82.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.32; H, 11.53.

4-Methyl-3-pentadecylcatechol (VIII).—A solution of 17.3 g of the above 4-methyl-3-pentadecylveratrole in 85 g of pyridine was heated to reflux, and a stream of dry hydrogen chloride gas bubbled through the mixture. After about 1 hr the temperature of the liquid reached 220°. Refluxing was continued at that temperature for 4 hr with the passage of HCl, then the mixture was cooled to 120°, and 100 ml of water was added. After cooling further with an ice bath, 150 ml of ether was added and the layers were separated. The aqueous layer was extracted with 200 ml of ether, and the combined ether layers were treated with decolorizing charcoal and then dried over magnesium sulfate. The solution was concentrated and the residual brown oil was distilled at 0.4 mm to yield 4-methyl-3-pentadecylcatechol as a pale yellow oil (bp 200–203°) which cooled to a white solid. After recrystallization from ligroin, the yield was 11.3 g (70.6%) of white solid, mp 55.0–56.5°.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.18; H, 11.51.

6-(N,N-Dimethylamino)methyl-3-pentadecylcatechol (XXa).—A solution of 48 g of 3-pentadecylcatechol in 300 ml of 95% ethanol was chilled in an ice bath and to it was added 42 ml of 25% dimethylamine in water, followed by 18 ml of 37% formaldehyde. After 1 hr, the ice bath was removed and the reaction mixture was stirred at room temperature for 18 hr. During that time a deep violet color developed and considerable solid separated from the solution. This solid was filtered, washed with ice-cold ethanol, and recrystallized from ethanol to give 50.4 g (89.2%) of 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol as cream plates (mp 46.0–46.8°). The significant peaks in the nmr were a quartet at τ 3.65 (aromatic H), a two-proton singlet at τ 6.47 (–N–CH_2), a six-proton singlet at τ 7.70 (–N–CH_3), and a broad two-proton singlet at about τ 1.6 (–OH).

Anal. Calcd for $C_{24}H_{43}NO_2$: C, 76.34; H, 11.48; N, 3.71. Found: C, 75.90; H, 11.39; N, 3.69.

Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXIa).—To a solution of 37.7 g of the above 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol in 150 ml of pyridine were added 40 g of hexamethyldisilizane and 10 drops of trimethylchlorosilane.[11] The solution was heated at reflux, causing evolution of ammonia which continued for about 45 min. The solution was then refluxed an additional 1 hr, after which the solvent was removed on the rotary evaporator to give a brown oil. Vacuum distillation of the oil at 0.5 mm yielded 39.6 g (76%) of the product (XXIa) as a colorless liquid, bp 237–243°. The absence of a hydroxyl peak at <3.0 μ in the infrared spectrum indicated complete conversion into the bistrimethylsilyl derivative.

6-Methyl-3-pentadecylcatechol (XIXa). A. By Hydrogenolysis of 6-(N,N-Dimethylamino)methyl-3-pentadecylcatechol (XXa).—A solution of 11.4 g of XXa in 100 ml of absolute ethanol was shaken with 1 g of 10% palladium-on-carbon catalyst at approximately 60° and under an initial hydrogen pressure of 60.2 psi for a total of 48 hr. The solution was then cooled and filtered to remove the catalyst, and the solvent was evaporated to give a dark oil which partially solidified. Recrystallization of this material from ligroin, followed by vacuum sublimation, gave 1.2 g of 6-methyl-3-pentadecylcatechol as a white solid (mp 63.5–64.5°). The yield was 12%. The nmr spectrum of this compound was composed of a sharp two-proton singlet at τ 3.50 (aromatic H), a broad two-proton singlet at τ 4.45 (–OH), and a sharp three-proton singlet at τ 7.80 (nuclear –CH_3), as well as appropriate peaks for the pentadecyl side chain.

B. By Hydrogenolysis of Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXIa).—To a solution of 37.7 g of XXIa in 150 ml of absolute ethanol were added 1 g of 10% palladium-on-carbon catalyst and 5 drops of sulfuric acid. The mixture was then hydrogenated on a Parr shaker for 20 hr at approximately 60° at an initial hydrogen pressure of 60 psi. When no further hydrogen uptake could be observed, the reaction

mixture was cooled and filtered. To this was added 25 ml of water, and the solution was refluxed with rapid stirring for 2 hr. The reaction mixture was then poured into 200 ml of water, and the resulting emulsion was extracted with three 100-ml portions of ether. The combined ether solutions were dried over magnesium sulfate, and the solvent was removed to give a dark oil. Vacuum distillation of this material at 0.2 mm yielded a pale yellow oil (bp 200–206°) which cooled to a cream solid. Recrystallization from ligroin gave 18.9 g (78%) of a white solid (mp 62.5–64.5°) which was indistinguishable on the basis of infrared and nmr spectra from the 6-methyl-3-pentadecylcatechol obtained by procedure A, *i.e.*, hydrogenolysis of the unsilylated Mannich base.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 78.73; H, 11.36.

6-(N,N-Dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol (XXb).—A solution of 17.4 g of 4,5-dimethyl-3-pentadecylcatechol in 100 ml of 95% ethanol was chilled in an ice bath, and to it was added 14.1 g of dimethylamine (25% in water), followed by 6.3 ml of 37% formaldehyde solution. After 1 hr the ice bath was removed, and the solution was stirred at room temperature for 16 hr. The product separated as a tan solid which was filtered and washed with cold ethanol. After recrystallization from ethanol, 9.4 g (46.5%) of 6-(N,N-dimethylamino)-methyl-4,5-dimethyl-3-pentadecylcatechol was obtained (mp 35.0–37.0°). In the nmr there was a broad two-proton singlet at τ 1.50 (-OH), a two-proton singlet at τ 6.40 ($-N-CH_2-$), a six-proton singlet at τ 7.70 ($-N-CH_3$), and a pair of singlets corresponding to a total of six protons at τ 7.92 and 7.96 (nuclear $-CH_3$), as well as the characteristic peaks for the pentadecyl side chain. There was no peak in the downfield region characteristic of hydrogens on a benzene ring.

Anal. Calcd for $C_{26}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 77.34; H, 11.48; N, 3.59.

Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-4,5-di-methyl-3-pentadecylcatechol (XXIb).—To a solution of 9.4 g of the above 6-(N,N-dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol in 50 ml of pyridine were added 8 g of hexamethyldisilizane and 5 drops of trimethylchlorosilane. This reaction mixture was refluxed for 2.5 hr, after which the solvent was removed under vacuum to give a brown oil. Vacuum distillation of this material at 0.4 mm yielded 8.5 g (62.5%) of the bistrimethylsilyl compound (XXIb) as a clear, colorless oil (bp 205–214°). The absence of a hydroxyl peak in the infrared spectrum at $<3.0\ \mu$ indicated that trimethylsilylation was complete.

6-(N,N-Dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII).—To a solution of 34.8 g of 4,5-dimethyl-3-pentadecylcatechol in 200 ml of 95% ethanol was added 8.3 g of carbon disulfide, 8.5 g of 37% formaldehyde, and 18.9 g of 25% dimethylamine. The resulting solution was refluxed for 2.5 hr, during which time considerable turbidity developed, and was then chilled in an ice bath to precipitate 6-(N,N-dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol. Recrystallization from ethanol–acetone gave a cream solid, mp 71.0–73.0°. The yield was 39.5 g (82%). In the infrared there was a peak for C=S at 7.65 μ. The significant peaks in the nmr were a two-proton singlet at τ 5.50 ($-S-CH_2-$), a pair of singlets equal to six protons at τ 6.66 and 6.84 ($-N-CH_3$), and a six-proton singlet at τ 7.95 (nuclear $-CH_3$).

Anal. Calcd for $C_{27}H_{47}NO_2S_2$: C, 67.31; H, 9.83; N, 2.91; S, 13.31. Found: C, 67.78; H, 9.96; N, 2.72; S, 13.07.

4,5,6-Trimethyl-3-pentadecylcatechol (XIXb). A. By Hydrogenolysis of 6-(N,N-Dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII).—A solution of 36.1 g of the above XXIII in 1200 ml of anhydrous dioxane was refluxed for 16 hr with Raney nickel W-7 catalyst prepared from 361 g of Raney nickel alloy.[18] The reaction mixture was then cooled and filtered to give a green solution to which was added 750 ml of ether. This solution was shaken with 750 ml of 5% aqueous hydrochloric acid, bleaching the organic layer to an orange color. The phases were then separated, and the aqueous layer was washed with 500 ml of ether. The organic portions were combined, dried over magnesium sulfate, and concentrated to give a red-brown oil. Vacuum distillation at 0.2–0.3-mm pressure yielded 20.5 g (75.7%) of 4,5,6-trimethyl-3-pentadecylcatechol as a colorless liquid (bp 210–223°), which rapidly gave a white solid (mp 78.0–79.0°) on cooling. The infrared spectrum of this compound lacked the thiocarbonyl peak at 7.65 μ. In the nmr the only peaks other than those for the pentadecyl side chain were a broad two-proton singlet at τ 6.49 (-OH) and a nine-proton singlet at τ 7.92 (nuclear $-CH_3$).

Anal. Calcd for $C_{25}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.59; H, 11.71.

B. By Hydrogenolysis of Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIb).—To a solution of 8.5 g of (XXIb) in 100 ml of absolute ethanol were added 0.85 g of 10% palladium-on-carbon catalyst and 5 drops of sulfuric acid, and the mixture was hydrogenated at approximately 60° at an initial hydrogen pressure of 60 psi. After 48 hr the reaction mixture was cooled and filtered and to it was added 10 ml of water. This solution was refluxed for 2 hr and then was poured into 150 ml of water and 100 ml of ether. After the layers had been separated, the aqueous phase was washed with two 100-ml portions of ether, and the combined ether solutions were dried over magnesium sulfate. Solvent was then removed, and the residual oil was distilled at 0.5 mm. The yellow distillate (bp 225–237°) solidified on cooling to give a tan solid. After recrystallization from ligroin 1.2 g (26%) of 4,5,6-trimethyl-3-pentadecylcatechol (mp 77.0–79.0°) was isolated. This material was identical in infrared and nmr spectra with the product obtained by procedure A.

Registry No.—III, 7452-10-0; IV, 16273-08-8; V, 5701-86-0; VII, 16273-09-9; VIII, 16273-11-3; XII, 16273-12-4; XIII, 16273-13-5; XIV, 16273-14-6; XV, 16273-15-7; XVI, 16273-16-8; XVIII, 16273-17-9; XIXa, 16273-18-0; XIXb, 16273-19-1; XXa, 16273-29-3; XXb, 16273-21-5; XXIa, 16273-23-7; XXIb, 16273-25-9; XXIII, 16273-27-1.

(18) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 176.

Syntheses of Medium-Ring Benzoic Acid Lactones

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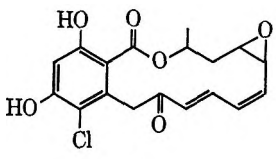
A study of synthetic reactions leading to medium-ring lactones of substituted benzoic acids is described. Ketones **4a–f** were converted *via* carbethoxylation and alkylation into the correspondingly substituted butanols **6a–f**. The alcohols were cyclized to yield enol ethers **7a–g**, which were used as substrates to study the per acid oxidation reaction. Enol ethers **7a, c, d, e,** and **g** on treatment with an excess of *m*-chloroperbenzoic acid generated the corresponding benzoic acid lactones **9a–f**. Similar treatment of **7b** and **7f** resulted in the formation of carbonates **8** and **16**, respectively. The influence of the conformation of the transitional intermediates and the extent of stabilization of the onium ions involved govern the course of the per acid reaction. A mechanism for the pathway leading to the carbonates is suggested. Carbonate **8** and lactone **9e** were transformed in alkaline medium *via* a transannular reaction into the cyclic ethers **11** and **18**, respectively. A rational pathway for the genesis of **11** and **18** is suggested.

Macrolides constitute a large group of naturally occurring compounds, having a broad spectrum of pharmacodynamic properties. To this class belongs a group of acetogenins, of relatively rare natural occurrence, biogenetically arising from the cyclization of a polyketo chain to a β-resorcylic acid nucleus, to yield what may be generally termed "β-resorcylic acid lactones." Radicicol[1] **1**, zearalenone[2] **2**, and two parent members lacking in the large ring found in isocoumarins[3] **3a** and **b** are the only examples known to date.



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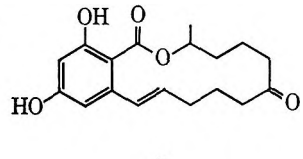

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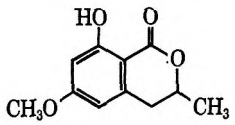
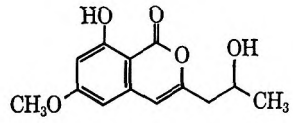


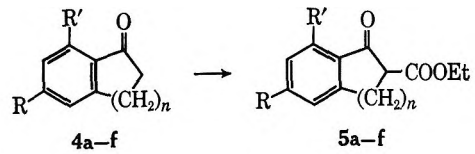
3a



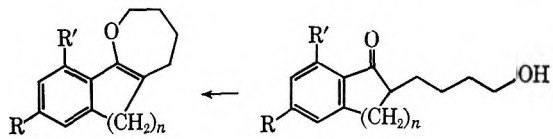
3b

In view of the antifungal properties[4] of radicicol and the anabolic and uterotrophic[5] action of zearalenone, it was of interest to explore synthetic methods potentially applicable to the synthesis of compounds of this group.

This article describes some of our work along these lines. Tetralone **4a** was carbethoxylated to yield the suitably substituted product **5a**. Condensation of **5a** with 4-bromobutyl 1-acetate[6] in dry *t*-butyl alcohol containing potassium *t*-butoxide yielded the alkylated acetoxy compound. Alkaline hydrolysis led through concomitant decarboxylation to the alcohol **6a**. Treatment of **6a** in dry benzene containing a catalytic amount of *p*-toluenesulfonic acid generated the enol ether **7a**.



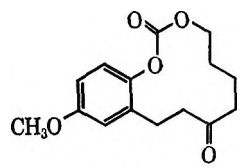
4a–f **5a–f**



7a–g **6a–g**

a, R = H; R′ = H; *n* = 2
b, R = OMe; R′ = H; *n* = 2
c, R = OMe; R′ = H; *n* = 3
d, R = OMe; R′ = H; *n* = 1
e, R = H; R′ = OMe; *n* = 1
f, R = OMe; R′ = OMe; *n* = 1
g, R = $OCOCH_3$; R′ = H; *n* = 2

Reaction[7] of **7a** in methylene chloride with an excess (3 mol) of *m*-chloroperbenzoic acid led to the formation of a compound whose spectral properties were in complete consonance with the structure **9a**.



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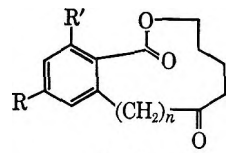


9a–f

a, R = H; R′ = H; *n* = 2
b, R = $OCOCH_3$; R′ = H; *n* = 2
c, R = OH; R′ = H; *n* = 2
d, R = OCH_3; R′ = H; *n* = 3
e, R = OCH_3; R′ = H; *n* = 1
f, R = H; R′ = OCH_3; *n* = 1

In a similar sequence of reactions, starting with methoxytetralone **4b**, the enol ether **7b** was prepared. The per acid oxidation of this compound generated a product, which showed in its infrared spectrum a carbonyl absorption at 1755 and 1700 cm^{-1}. The elemental analysis was consistent with the formula $C_{15}H_{18}O_5$ indicating one more oxygen than that required for the desired lactone. The ultraviolet spectrum was characteristic for that of an isolated aromatic ring (276 mμ,

(1) (a) R. N. Mirrington, E. Ritchie, C. W. Shoppee, and W. C. Taylor, *Tetrahedron Lett.*, 365 (1964); (b) F. McCapra, A. I. Scott, P. Delmotte, and J. Delmottee-Plaquee, *ibid.*, 869 (1964); (c) R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell, and W. C. Taylor, *Aust. J. Chem.*, **19**, 1265 (1966).

(2) (a) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966); (b) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Chem. Commun.*, 225 (1967); (c) N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967).

(3) (a) F. Sondheimer, *J. Amer. Chem. Soc.*, **79**, 5036 (1957); (b) E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, **49**, 1283 (1966).

(4) N. H. White, G. A. Chilvers, and O. Evans, *Nature*, **195**, 406 (1962).

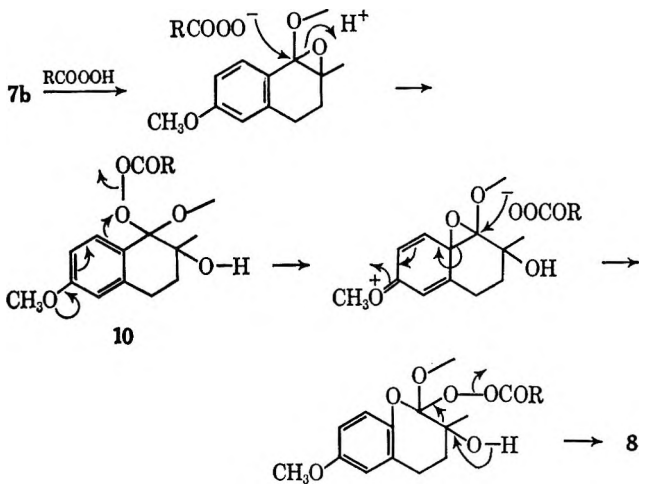
(5) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *ibid.*, **196**, 1318 (1962).

(6) J. B. Cloke and F. J. Pilgrim, *J. Amer. Chem. Soc.*, **61**, 2667 (1939).

(7) (a) I. J. Borowitz and G. J. Williams, *Tetrahedron Lett.*, 3813 (1965); (b) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

ϵ 2580). The structure **8** was assigned to this product and was corroborated by its nmr spectrum. A mechanism of formation of carbonate **8** is shown in Scheme I.

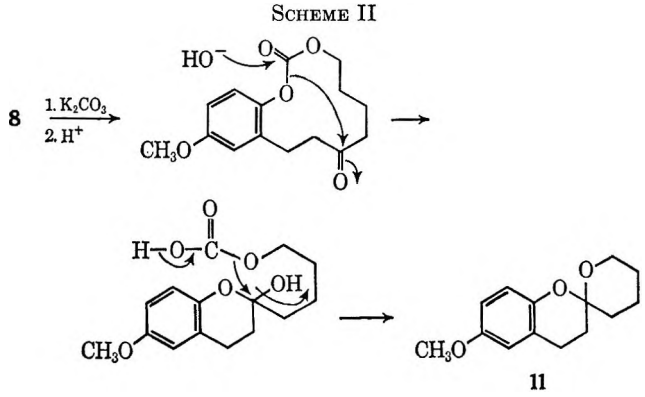
SCHEME I



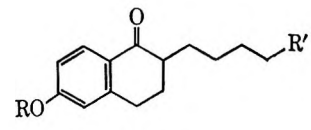
The positive character on the oxygen atom of the per ester **10**—an intermediate in the cleavage[7b] reaction—may be stabilized by participation of the methoxyl on the aromatic ring to divert the normal pathway as depicted above. That this indeed is the case is substantiated by the fact that the reaction yields almost exclusively a lactone, when the lone pair of electrons on the aromatic methoxyl group are made unavailable for such participation (see below).

Treatment of the carbonate **8** with methanolic potassium carbonate and subsequent acidification led quantitatively to a transformation product, the mass spectrum of which exhibited a molecular ion peak at *m/e* 234. The infrared showed weak aromatic absorption at 1605 cm^{-1}, and the hydroxylic and ketonic bands were absent. The ultraviolet spectrum confirmed the presence of an isolated aromatic ring (288 mμ, ϵ 2850). The nmr spectrum of the compound revealed signals at δ 7.0–6.58 (3 H, aromatic, multiplet), 4.15–3.35 (5 H, methoxyl singlet at δ 3.76, and two protons, carbinolic multiplet), 3.3–2.35 (2 H, benzylic, poorly resolved triplet), and 2.3–1.15 (8 H, methylenic multiplet). The above analytical data concur with the empirical formula $C_{14}H_{18}O_3$, and permit the assignment of structure **11** to this product. Its formation from progenitor **8** may be rationalized as in Scheme II.

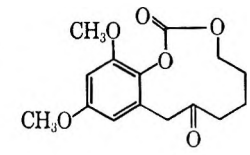
SCHEME II



A synthetic study leading to compounds of the type **1** and **2** must be adaptable to yield free phenols in view of their ubiquity in nature. An obvious detour was sought in the synthesis of the acetate **15** obtainable from methyl ether **6b**. Demethylation of methyl ether **6b** with 48% hydrobromic acid resulted in concomitant displacement of the terminal hydroxyl group by bromine to yield bromophenol **12**. Treatment of **12** with silver acetate in acetic acid followed by hydrolysis of acetate **13** generated diol **14**, in an over-all yield of 15% from ether **6b**. The yield of the diol **14** was highly ameliorated in the one-step reaction described below. The methyl ether **6b** when treated with potassium thiophenolate anion[8] in the presence of dry dimethyl sulfoxide at 120° (bath temperature) yielded the expected diol in excellent yield (85%). The diol was selectively



12, R = H; R′ = Br
13, R = H; R′ = $OCOCH_3$
14, R = H; R′ = OH
15, R = $COCH_3$; R′ = OH
20, R = $COCH_3$; R′ = $OCOCH_3$



16

acetylated[9] using 1.5 mol of acetic anhydride in a pyridine–acetic anhydride (50:1) mixture to yield the monoacetate **15**. Acid-catalyzed dehydration of acetate **15** led to the cyclic enol ether **7g**. The optimum yield of this reaction was 28%.

The diacetate **20** and diol **14** were detected in the crude reaction product. A possible explanation for the generation of diol **14** lies in the sensitivity of the phenolic acetate to the water produced in the reaction. The acetic acid thus generated may be instrumental in the production of diacetate by acetylating the starting alcohol.

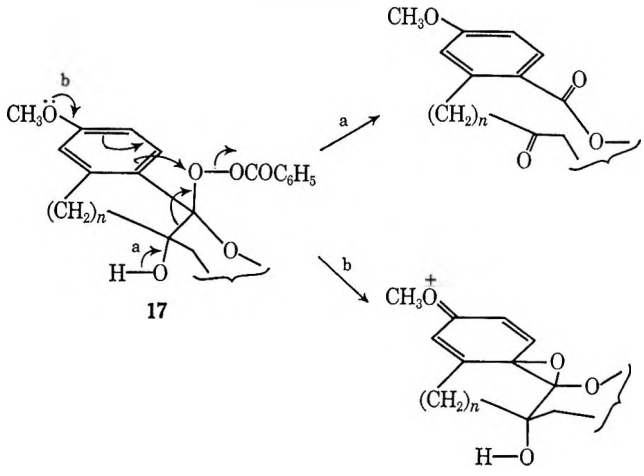
Reaction of enol ether **7g** with *m*-chloroperbenzoic acid yielded almost exclusively the lactone **9b**. This reaction coupled with the obtention of lactone as a sole product from the precursor **7a** clearly demonstrates that the presence of unshared electrons on methoxyl oxygen is essential for the stabilization (in formula **10**) *via* participation of the aromatic ring, to divert the reaction pathway from generating a lactone.

Employing the above sequence to benzocycloheptanone **4c** led to the synthesis of enol ether **7c**. The per acid oxidation of this enol ether, in contrast to that of **7b**, yielded lactone **9d**. Finally the enol ethers **7d** and **7e** were synthesized from ketones **4d** and **4e**. It was noted that these enol ethers were relatively unstable and slowly reverted to their progenitor under normal handling conditions. The reason for this unstability lies most likely in the strain exerted by the cyclopentadiene system generated in the enol ethers. The per acid oxidation of **7d** and **7e** proceeded in the normal manner to generate lactones **9e** and **9f**. Enol ether **7f** was obtained from ketone **6f** by treatment of the latter with *p*-toluenesulfonic acid in refluxing toluene–dimethylformamide (2:1). The per acid reaction with **7f** rather unexpectedly gave almost exclusively the carbonate **16**.

(8) G. Illuminati and H. Gilman, *J. Amer. Chem. Soc.*, **71**, 3349 (1949).
(9) O. V. Dominguez, J. R. Selly, and J. Gorki, *Anal. Chem.*, **35** (9), 1243 (1963).

It is noted that the products of oxidation of **7b**, **7c**, and **7d** varied from predominantly carbonate in the case of **7b** to mainly lactone with **7c**, and an intermediate mixture of lactone and carbonate with **7d**. These results strikingly indicate the critical spacial requirement of the per ester group in the transitional intermediate **17**,[10] for the preferential expulsion of benzoate *via* pathway b to generate the carbonate (*vide infra*) (Scheme III). Such stereochemistry is ideally offered by the tetrahydronaphthalene system produced from **7b**, in contrast to its higher (from **7c**) and lower (from **7d**) homologs.

SCHEME III



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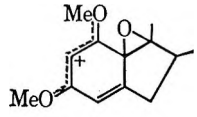
A second factor responsible for controlling the reaction course must involve the degree of stabilization resulting from the alkoxy substituents present in the *ortho* and/or *para* positions. Whereas **7d** reacts apparently by both pathways a and b to yield a mixture, in the case of **7f**, the conformational destabilization is balanced by the increased stabilization of the positive charge as shown in **19** by two methoxyl functions.



19

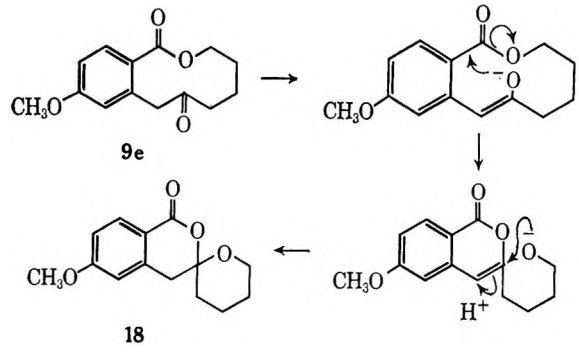
This is apparently sufficient to divert the reaction course *via* pathway b to produce carbonate **16**.

Treatment of lactone **9e** with sodium hydride in dry benzene led to a transannular reaction. The product **18** showed a molecular ion at *m/e* 248, which concurred with its elemental analysis to evolve the formula $C_{14}H_{16}O_4$. The ultraviolet spectrum (259 mμ, ε 15,600) was characteristic of a *p*-methoxybenzoic acid ester. The infrared and nmr spectra were in complete consonance with the structure assigned which follows from the mechanistic arguments outlined in Scheme IV.

This type of transannular reaction has been observed by Shoppee[1c] on alkaline treatment of radicicol derivatives.

(10) This postulate is further supported by the fact that no detectable amount of carbonate was formed from **7e**. In this case, the steric repulsion exerted by methoxyl in the *ortho* position clearly overbalances the electronic effect. However, the increased electronic stabilization as in **19** restores the generation of carbonate. Such competition between steric and electronic effect has also been observed by R. Huisgen [*Ber.*, **90**, 1946 (1957)] in the intensity variation of the ultraviolet spectra of 1,2-benzocycl-3-en-1-one.

SCHEME IV



18

Ultraviolet Spectra.—It is interesting to note that benzoic acid lactones when lactone is a part of a medium-size ring appear to follow the usual increment rule useful for simpler benzoic acid lactones.[11] Using 230 mμ as parent chromophore representing the electron-transfer (ET) band, the calculated and observed values of the ET bands are listed in Table I. An abnormality is noted in the unusually low intensity value of lactone **9f**. This marked[12] depression in intensity may be attributed to the increased loss of coplanarity.[13]

TABLE I

Compd	ET band		Benzenoid
	Calcd mμ	Obsd mμ (ε)	mμ (ε)
9a	233	233 (7,454)	279 (1,140)
9b	233	238 (9,280)	
9c	258	260 (14,250)	
9d	258	258 (17,400)	295 (3,247)
9e	258	260 (14,800)	
9f	240	239 (3,770)	292 (3,180)

Experimental Section[14a]

Ketones.—**3,4-Dihydro-2H-naphthalen-1-one**[14b] (**4a**) and **3,4-dihydro-6-methoxy-2H-naphthalen-1-one** (**4b**) used were those available commercially. **2,3,4,5-Tetrahydro-7-methoxy-1H-benzocyclohepten-1-one** (**4c**) was prepared as described,[15] mp 54.5–55.5. **5-Methoxyindan-1-one** (**4d**), mp 97–98° (lit.[16a] mp 102–103°), and **7-methoxyindan-1-one** (**4e**), mp 107–108° (lit.[16a] mp 109–110°), were prepared by ring closure of corresponding propionic acids as described for phenols.[16b] **5,7-Dimethoxyindan-1-one** (**4f**), mp 98–99° (lit.[16c] mp 98.5–99.5°), was prepared by hydrogen fluoride ring closure of the corresponding propionic acid.

Carbethoxylation of Ketones.—In a typical procedure, to a suspension of sodium hydride (10 g) washed free of oil in dry tetra-

(11) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press Ltd., Oxford, 1964, p 115.

(12) The value of the intensity of the *ortho*-substituted acids is usually about half that of their *para*-substituted counterparts [C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951)].

(13) E. A. Braude and E. S. Waight, *Progr. Stereochem.*, **1**, 144 (1954).

(14) (a) All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer with sodium chloride optics. Ultraviolet spectra were taken in ethanol with a Unicam Model SP 800. Nmr spectra were recorded on a Varian A-60A spectrometer. The mass spectra were recorded on Hitachi RMU-6D. Alumina (Woelm) and silica gel (Davison Grade 923, 100–200 mesh) were used for column chromatography. Silica gel G (according to Stahl, E. Merck Co., Germany) was used for thin layer chromatography. Petroleum ether refers to that fraction with bp 30–60°. Organic extracts were dried over magnesium sulfate and solvents were removed under vacuum. *t*-Butyl alcohol was dried by distilling over sodium, tetrahydrofuran was distilled over lithium aluminium hydride, and methylene chloride used for oxidation was distilled over potassium carbonate. (b) Nomenclature for all compounds was derived based on that described in "The Ring Index," American Chemical Society, Washington, D. C., 1960.

(15) W. J. Horton and L. L. Pitchforth, *J. Org. Chem.*, **25**, 131 (1960).

(16) (a) L. D. Louden and R. K. Razdan, *J. Chem. Soc.*, 4299 (1954); (b) W. S. Johnson, J. M. Anderson, and W. E. Shelborg, *J. Amer. Chem. Soc.*, **66**, 218 (1944); (c) R. Huisgen, G. Siedl, and I. Wimmer, *Ann. Chim.*, **677**, 21 (1964).

hydrofuran (100 ml) was added diethyl carbonate (26.8 g). The mixture was stirred and heated to reflux under an atmosphere of nitrogen. A solution of 6-methoxy-1-tetralone **4b** (20 g) in dry tetrahydrofuran (220 ml) was added dropwise. The refluxing was continued for 2 days. To the cooled reaction mixture glacial acetic acid (18 ml) was slowly added, and the reaction mixture taken in ether and washed several times with saturated sodium chloride solution. The solution was dried, the solvent removed, and the residue distilled (yield 79%): **3,4-dihydro-6-methoxy-2-carbethoxy-2H-naphthalen-1-one (5b)**, bp 150–104° (0.3 mm) [*Anal.* Calcd for $C_{14}H_{16}O_4$ (248): C, 67.63; H, 6.50. Found: C, 67.85; H, 6.42]; **3,4-dihydro-2-carbethoxy-2H-naphthalen-1-one (5a)**, bp 109° (0.2 mm), 85% [*Anal.* Calcd for $C_{13}H_{14}O_3$ (218): C, 73.02; H, 6.13. Found: C, 73.14; H, 6.40]; **2,3,4,5-tetrahydro-7-methoxy-2-carbethoxy-1H-benzocyclohepten-1-one (5c)**, bp 154° (0.5 mm), 69% [*Anal.* Calcd for $C_{15}H_{18}O_4$ (262): C, 68.68; H, 6.92. Found: C, 69.23; H, 6.74]; **5-methoxy-2-carbethoxyindan-1-one (5d)**, bp 153–156° (0.5 mm), 49% [*Anal.* Calcd for $C_{13}H_{14}O_4$ (222): C, 66.65; H, 6.02. Found: C, 66.71; H, 5.74]; **7-methoxy-2-carbethoxyindan-1-one (5e)**, bp 156–158° (0.5 mm) (lit.[17] bp 165° (0.2 mm), 55%, on keeping the compound crystallized, mp 54–57°; **5,7-dimethoxy-2-carbethoxyindan-1-one (5f)**, crystallized from acetone–hexane, mp 91–92°, 55% [*Anal.* Calcd for $C_{14}H_{16}O_5$ (264): C, 63.62; H, 6.10. Found: C, 63.36; H, 6.27].

Preparation of 4-Hydroxybutyl Ketones.—A characteristic procedure was as follows. Potassium (3.2 g) was dissolved in dry *t*-butyl alcohol (200 ml). Tetralone **5a** (8.16 g) dissolved in the same solvent (100 ml) was slowly added. The solution was refluxed in nitrogen atmosphere for 30 min, and cooled to room temperature. With stirring 4-bromobutyl 1-acetate[6] was added, and the mixture refluxed overnight. After cooling, glacial acetic acid (24 ml) was added, and most of the solvent was removed. The residue was taken in chloroform and washed several times with saturated salt solution and dried; the solvent was removed. The excess bromobutyl acetate was removed by distillation (at 0.3 mm). The residue was used directly for saponification. The product was dissolved in ethanol (30 ml), a solution of potassium hydroxide (6.8 g) in water (10 ml) was added, and the mixture was refluxed under nitrogen overnight. The mixture was cooled, diluted with ether, washed neutral with saturated sodium chloride solution, and dried, and the solvent removed to yield crude product (7.06 g). The material was filtered through neutral alumina (activity II) to yield **3,4-dihydro-2-(4-hydroxybutyl)-2H-naphthalen-1-one (6a)**, homogenous by tlc: ν_{max} (neat) 3410 (broad, OH) 1675 (ketone), 1600 cm^{-1} (aromatic); nmr showed signals at δ 7.99 (1 H, *ortho*[18] aromatic proton, quartet), 7.65–6.92 (3 H, aromatic multiplet), 3.61 (2 H, carbionolic triplet poorly resolved), 3.14–2.8 (2 H, benzylic triplet).

3,4-Dihydro-2-(4-hydroxybutyl)-6-methoxy-2H-naphthalen-1-one (6b) was similarly prepared from **5b** in 96% yield and crystallized from ether–petroleum ether: mp 57–59°; ν_{max} (Nujol) 3475 (OH), 1656 (ketone), 1598 cm^{-1} (aromatic); nmr exhibited signals at δ 7.98 (1 H, J = 8 Hz, doublet *ortho*[18] aromatic proton), 7.05–6.54 (2 H, aromatic protons), 3.9–3.5 (5 H, two carbinolic and three methoxyl at 3.83), 3.1–2.75 (2 H, benzylic, triplet).

Anal. Calcd for $C_{15}H_{20}O_5$ (248): C, 72.53; H, 8.12. Found: C, 72.30; H, 7.85.

2,3,4,5-Tetrahydro-2-(4-hydroxybutyl)-7-methoxy-1H-benzocyclohepten-1-one (6c) was obtained in 43% yield from **5c**. Mass spectrum showed *m/e* 262 (M), *m/e* 244 (M − 18); ν_{max} (neat) 3430 (hydroxyl), 1670 (carbonyl), 1600 cm^{-1} (aromatic); nmr showed signals at δ 7.65 (1 H, *ortho*[18] aromatic), 3.61 (2 H, carbinolic).

5-Methoxy-2-(4-hydroxybutyl)indan-1-one (6d) was prepared from the corresponding precursor and crystallized from ether–petroleum ether: mp 51–52° (58%); ν_{max} (Nujol), 3400 (hydroxyl), 1705 (ketone), 1612, 1600 cm^{-1} (aromatic); nmr showed peaks at δ 7.6 (1 H, J = 9 Hz, *ortho*[18] aromatic proton), 6.95–6.66 (2 H, aromatic protons), 3.81 (3 H, methoxyl singlet), 3.61 (2 H, carbinolic).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 71.96; H, 7.67.

7-Methoxy-2-(4-hydroxybutyl)indan-1-one (6e) was crystallized from ether–petroleum ether: mp 71–72° (30%); ν_{max} (Nujol) 3500 (hydroxyl), 1700 (ketone), 1600 cm^{-1} (aromatic); nmr, δ 7.7–6.5 (3 H, aromatic, multiplet), 3.86 (methoxyl, singlet), 3.6 (2 H, carbinolic).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 71.81; H, 7.45.

5,7-Dimethoxy-2-(4-hydroxybutyl)indan-1-one (6f) was obtained from **5f** in 50% yield. Crystallization from acetone–hexane gave a solid: mp 86–87°; ν_{max} (Nujol) 3490 (hydroxyl), 1675 (ketone), 1600 cm^{-1} (aromatic); nmr showed signals at δ 6.52–6.20 (2 H, aromatic), 3.88 and 3.86 (6 H, two methoxyl, singlets), 3.77–3.47 (2 H, carbinolic multiplet).

Anal. Calcd for $C_{15}H_{20}O_4$ (264): C, 68.15; H, 7.63. Found: C, 68.10; H, 7.48.

Preparation of Enol Ethers.—Enol ethers were generally prepared by refluxing for 20 hr a solution of corresponding 4-hydroxybutyl ketones in dry benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, and continuous removal of water with a Dean–Stark water separator. The work-up was effected by passing the reaction mixture through a 20-fold amount of alumina (neutral, activity II) and eluting the product with benzene–petroleum ether (1:1). In case of **6f** the solvent had to be changed to toluene–dimethylformamide (2:1). In most cases enol ethers were purified by distillation and/or purity checked by thin layer plates, and the structure was confirmed by disappearance of hydroxyl and ketonic absorption and the presence of an enolic double bond in the infrared. These were immediately utilized for the oxidation. Their physical constants are recorded in Table II.

TABLE II

Compd	Criteria of purity, bp (mm) or mp, °C	Enolic band, cm^{-1}	Yield, %
7a	98 (0.2)	1650	72
7b	134 (0.3)	1650	71
7c	141–143 (0.3)	1640	74
7d	52°	1580, 1575	31
7e	Homogenous by tlc	1625, 1600	41
7f	Homogenous by tlc	1625, 1605	21

Per Acid Oxidation.—A typical oxidation procedure for the above enol ethers was as follows. The *m*-chloroperbenzoic acid (8.1 g) was suspended in methylene chloride (freshly distilled over potassium carbonate, 25 ml). A solution of enol ether (**7a**, 2.69 g) in methylene chloride (12 ml) was added dropwise with stirring. An exothermic reaction ensued. The mixture was kept at boiling point during addition. It was then stirred at room temperature overnight and filtered, and the residue washed with methylene chloride. The organic layer was washed with 7% potassium carbonate, followed by saturated salt solution, and dried, and solvent was removed. The residue was passed through a 20-fold amount of alumina (neutral, activity II) in benzene–petroleum ether (1:1). The eluate was homogenous by the tlc and yielded **3,4,5,6,8,9-hexahydro-2-benzoxacycloundecane-1,7-dione (9a)**: bp 138–144° (0.2 mm); ν_{max} (neat) 1710 (broad carbonyl), 1600 cm^{-1} (aromatic); nmr, δ 8.03 (1 H, *ortho*[18] aromatic proton), 7.56–7.1 (3 H, aromatic proton), 4.38 (2 H, carbinolic, multiplet), 3.5–3.16 (2 H, benzylic, multiplet), 2.83–2.5 (4 H, α-ketomethylenes).

Anal. Calcd for $C_{14}H_{16}O_3$ (232): C, 72.39; H, 6.94. Found: C, 72.14; H, 6.82.

4,5,6,7,9,10-Hexahydro-12-methoxy-1,3-benzodioxacyclododecane-2,8-dione (8) was crystallized from methylene chloride–ether–petroleum ether to yield crystals: mp 90–91° (50%); ν_{max} (Nujol) 1755 (carbonate), 1700 (ketone), 1605 cm^{-1} (aromatic); nmr, δ 7.2–6.6 (3 H, aromatic), 4.3 (2 H, carbinolic, multiplet), 3.85 (methoxyl singlet), 3.2–2.2 (6 H, 2 benzylic, 4 α-ketomethylenic).

Anal. Calcd for $C_{15}H_{18}O_5$ (278): C, 64.73; H, 6.52. Found: C, 64.36; H, 6.35.

3,4,5,6,9,10-Hexahydro-12-methoxy-8H-2-benzoxacyclododecane-1,7-dione (9d) was crystallized from acetone–hexane: mp 92–93° (40%); ν_{max} (Nujol) 1700, 1675 (carbonyl), 1600 cm^{-1} (aromatic); nmr, δ 7.88 (1 H, *ortho*[18] aromatic proton), 6.87–6.62 (2 H, aromatic, multiplet), 4.4–4.17 (2 H, carbinolic, multiplet), 3.81 (3 H, methoxyl, singlet), 2.85 (2 H, benzylic, triplet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.54; H, 7.30. Found: C, 69.80; H, 7.35.

3,4,5,6-Tetrahydro-10-methoxy-8H-2-benzoxecin-1,7-dione (9e) was crystallized from acetone–hexane: mp 97–98° (58%);

(17) Z. Horii and T. Tanaka, *Chem. Ind.* (London), 1576 (1959).

(18) "*ortho* proton" refers to the proton *ortho* to the carbonyl substituent.

ν_{max} (Nujol) 1710, 1700 (carbonyls), 1605 cm^{-1} (aromatic); nmr, δ 8.06 (1 H, doublet, J = 7 Hz, *ortho*[18] aromatic proton), 6.95–6.57 (2 H, aromatic multiplet), 4.19 (2 H, carbinolic, multiplet), 3.93 (2 H, benzylic, singlet), 3.83 (3 H, methoxyl, singlet), 2.56 (2 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.94; H, 6.46.

3,4,5,6-Tetrahydro-12-methoxy-8H-2-benzoxecin-1,7-dione (**9f**) was crystallized from acetone–hexane: mp 123–124° (61%); ν_{max} (Nujol), 1725, 1700 (carbonyls), 1600, 1575 cm^{-1} (aromatic); nmr, δ 7.44–6.35 (3 H, aromatic), 4.4–4.1 (2 H, carbinolic poorly resolved triplets), 3.75 (3 H, methoxyl, singlet), 3.65 (2 H, benzylic, singlet), 2.6–2.25 (2 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.92; H, 6.49.

4,5,6,7-Tetrahydro-11,13-dimethoxy-9H-1,3-benzodioxacycloundecane-2,8-dione (**16**) was crystallized from acetone–hexane: mp 148–149° (54%); ν_{max} (Nujol) 1765 (carbonate), 1700 (ketone), 1610, 1600 cm^{-1} (aromatic); nmr, δ 6.48 (2 H, aromatic, multiplet), 4.3 (2 H, carbinolic, triplet), 3.85 (6 H, methoxyls), 3.60 (2 H, benzylic, singlet), 2.45 (2 H, α-ketomethylenic multiplet).

Anal. Calcd for $C_{15}H_{18}O_6$ (294): C, 61.21; H, 6.17. Found: C, 61.31; H, 6.36.

3,4-Dihydro-2-(4-bromobutyl)-6-methoxy-2H-naphthalen-1-one (**12**).—Methoxy ketone **6b** (15 g) was dissolved in 48% hydrobromic acid (300 ml) and the mixture was refluxed for 5 hr. The reaction mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with water and dried, and the solvent was removed. Residue crystallized from chloroform–hexane to give 11 g of **12**, mp 102–106°. An analytical sample from the same solvent mixture had mp 111–112°; $\nu_{max}^{CHCl_3}$ 3600, 3270 (hydroxyl), 1670 (ketone), 1600 cm^{-1} (aromatic); ultraviolet, 275 mμ (ϵ 15,300) neutral, 328 (29,000) alkaline; nmr δ 7.88 (1 H, *ortho*[18] aromatic proton, doublet, J = 7 Hz), 6.78 (2 H, aromatic), 3.39 (2 H, protons of C–Br carbon, triplet), 2.92 (2 H, benzylic, triplet).

Anal. Calcd for $C_{14}H_{17}O_2Br$ (297): C, 56.60; H, 5.72. Found: C, 56.83; H, 5.89.

3,4-Dihydro-2-(4-acetoxybutyl)-6-hydroxy-2H-naphthalen-1-one (**13**).—Bromo compound **12** (6 g) was dissolved in dry benzene, silver acetate (4.5 g) was added, and the mixture was refluxed with stirring for 6 hr. Another 4.5 g of silver acetate was added and refluxing continued for 16 hr. The mixture was cooled and filtered. The residue was washed with benzene and the solvent was removed. Residue was put on column of silica gel (180 g) in benzene. Elution with 10–20% ether–benzene yielded 1.7 g of solid, homogenous on tlc. An analytical sample from chloroform–hexane had mp 97–98°; $\nu_{max}^{CHCl_3}$ 3525, 3240 (nonbonded and bonded OH), 1720, 1660 (acetate and ketone), 1600 cm^{-1} (aromatic); ultraviolet, 275 mμ (ϵ 14,122); nmr, δ 7.88 (1 H, *ortho*[18] aromatic proton), 6.72 (2 H, aromatic protons), 4.03 (2 H, carbinolic, triplet), 2.88 (2 H, benzylic, triplet), 2.01 (acetate methyl singlet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.70; H, 7.25. Found: C, 70.01; H, 7.03.

3,4-Dihydro-2-(4-hydroxybutyl)-6-hydroxy-2H-naphthalen-1-one (**14**). **A. Hydrolysis of Acetate 13.**—To a solution of acetate **13** (2 g) in methanol (50 ml) was added a solution of potassium hydroxide (1.34 g) in water (20 ml). The solution was stirred at room temperature for 30 min. The mixture was concentrated to remove most of the methanol. The residue was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The usual work-up gave 1.6 g of solid. One crystallization from methanol–ether gave crystals: mp 171–172°; ν_{max} (Nujol) 3440 (hydroxyl), 1652 (ketone), 1605, 1575 cm^{-1} (aromatic); ultraviolet spectrum had maxima at 275 mμ (ϵ 15,000).

Anal. Calcd for $C_{14}H_{18}O_3$ (234): C, 71.77; H, 7.74. Found: C, 72.14; H, 7.56.

B. Demethylation of Ketone 6b.—To a solution of thiophenol (21.15 g) in dry dimethyl sulfoxide under nitrogen was added potassium *t*-butoxide (24.6 g). The mixture was stirred until the solution was complete. To this solution was added a solution of methyl ether **6b** (7.2 g) in dimethyl sulfoxide (35 ml). The reaction mixture was heated to 120° and kept at that temperature for 7.5 hr. It was then cooled and poured into water (400 ml) containing acetic acid (4.4 ml). The liberated semisolid was extracted with ethyl acetate, washed with water, and dried; the solvent was removed. The residue when suspended in ice cold ether and filtered gave diol **14**: yield 4.56 g; mp 171–174°. The filtrate was separated into acid and the neutral fractions. The former gave 1.2 g more of diol **14** of the same purity as above. This was identical in all respects with the product obtained from hydrolysis of acetate described earlier.

3,4-Dihydro-2-(4-hydroxybutyl)-6-acetoxy-2H-naphthalen-1-one (**15**).—To a solution of diol **14** (4.5 g) in dry pyridine (73.5 ml) was added a mixture of pyridine–acetic anhydride (25:1, 73.5 ml) and the solution stirred for 40 min. The reaction was quenched by adding water (20 ml) and most of the solvent was removed. The residue was stirred with 10 ml of 10% hydrochloric acid for 5 min. The organic material was extracted with ether, washed with water, and dried, and the solvent evaporated. The residue was chromatographed on silica gel (125 g) in benzene. Eluate with 10–20% ether–benzene was pooled to yield monoacetate **15** (3.5 g) homogenous by tlc. An analytical sample crystallized from ether–hexane had mp 56–58°; $\nu_{max}^{CHCl_3}$ 3610, 3470 (hydroxyl nonbonded and bonded), 1755 (phenolic acetate), 1670 (ketone), 1600 cm^{-1} (aromatic); ultraviolet maxima at 252 mμ (ϵ 13,900); nmr, δ 7.98 (1 H *ortho*[18] aromatic proton), 6.88 (2 H, aromatic, protons), 3.62 (2 H, carbinolic, triplet), 2.95 (2 H, benzylic, triplet), 2.27 (3 H, acetate methyl, singlet).

Anal. Calcd for $C_{16}H_{20}O_4$ (276): C, 69.70; H, 7.25. Found: C, 70.00; H, 7.14.

2,3,4,5,6,7-Hexahydro-9-acetoxynaphth[1,2-*b*]oxepin[14b] (**7g**).—A solution of monoacetate **15** (3 g) in dry benzene was refluxed to distill off some benzene. To this solution *p*-toluenesulfonic acid (0.15 g) was added. The solution was refluxed for 2 hr with a continuous water separator. The solution was cooled and diluted with petroleum ether and filtered through alumina (neutral, activity II, 50 g). The first 650 ml yielded in the eluate 1.3 g of enol ether **7g**: homogenous by tlc; $\nu_{max}^{CHCl_3}$ 1760 (phenolic acetate), 1655 cm^{-1} (enolic double bond); nmr, δ 7.2 (1 H, doublet, *ortho* proton), 6.65 (3 H, aromatic), 3.87 (2 H, carbinolic, triplet), 2.1 (3 H, acetyl methyl, singlet).

3,4,5,6,8,9-Hexahydro-11-acetoxy-2-benzoxacycoundecane-1,7-dione (**9b**).—To a suspension of *m*-chloroperbenzoic acid (2.7 g) in methylene chloride[18] (4 ml) was added dropwise a solution of enol ether **7g** (1.1 g) in methylene chloride (3.5 ml). An exothermic reaction ensued, and the mixture was kept at boiling point. The mixture was stirred for 2 hr at room temperature. The methylene chloride was removed and the residue was suspended in dry benzene and filtered. The precipitate was washed with benzene and the filtrate passed through a column of alumina (neutral, activity II, 40 g) in benzene. The first 200 ml of eluate yielded 1 g of crystalline solid. Crystallization from chloroform–hexane gave 0.6 g, mp 96–108°. An analytical sample had mp 109–110°; $\nu_{max}^{CHCl_3}$ 1760 (phenolic acetate), 1710 (ketone and lactone), 1605 cm^{-1} (aromatic); ultraviolet showed maxima at 238.5 mμ (ϵ 9280); nmr, δ 8.1 (1 H, *ortho*[18] proton, doublet, J = 7 Hz), 7.07 (2 H, aromatic), 4.33 (2 H, carbinolic, multiplet), 3.28 (2 H, benzylic, multiplet), 2.62 (4 H, α-ketomethylenic), 2.28 (3 H, acetyl methyl).

Anal. Calcd for $C_{16}H_{18}O_5$ (290): C, 66.20; H, 6.25. Found: C, 66.09; H, 6.21.

3,4,5,6,8,9-Hexahydro-11-hydroxy-2-benzoxacycloundecane-1,7-dione (**9c**).—To a solution of acetate **9b** (0.87 g) in methanol (6 ml) was added a solution of sodium carbonate (0.318 g) in water (3 ml). The mixture was stirred at room temperature for 10 min, then diluted with ether and washed with water. The aqueous layer was acidified with 3% hydrochloric acid (5 ml). The resulting mixture was extracted with ether, washed with water, and dried; the solvent was removed. Residue (0.65 g) crystallized from chloroform–hexane to yield 0.34 g solid, mp 145–150°. An analytical sample had mp 154–155°; $\nu_{max}^{CHCl_3}$ 3570, 3200 (nonbonded and bonded hydroxyl), 1692 cm^{-1} (carbonyl); ultraviolet, 260 mμ (ϵ 14,250) neutral, 300 (25,200) alkaline; nmr, δ 7.91 and 6.59 (3 H, aromatic), 4.33 (2 H, carbinolic), 3.2 (2 H, benzylic), 2.63 (4 H, α-ketomethylenic).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.50. Found: C, 67.79; H, 6.55.

3,4,3′,4′,5′,6′-Hexahydro-6-methoxyspiro[2H-1-benzopyran-2,2′(2H)-pyran] (**11**).—Carbonate **8** (0.3 g) was dissolved in methanol (10 ml), saturated with potassium carbonate, and left for 2 days at room temperature. The mixture was then diluted with ether and extracted with 2 *N* potassium carbonate (10 ml). The aqueous extract was cooled in ice and acidified with 10% sulfuric acid. The mixture was extracted with ether, washed with water, and dried; the solvent was evaporated. The residue (0.24 g) was put through alumina (neutral, activity II, 7.2 g) and

eluted with petroleum ether–benzene 4:1 (75%). The residue was distilled at 0.2-mm pressure. The distillate showed a single spot on tlc and a single peak in glpc (15% S.E. 30, 80–100 mesh, 248°, R_T 6.45 min). Mass spectrum showed a *m/e* 234 (M); ν (neat) 1605 cm^{-1} (aromatic); ultraviolet maxima at 288 mμ (ε 2850); nmr, δ 6.68 (3 H, aromatic, multiplet), 3.75 (5 H, methoxy and carbinolic), 3.3–2.58 (2 H, benzylic, multiplet).

1,4,3′,4′,5′,6′-Hexahydro-6-methoxyspiro[3H-2-benzopyran-3,2′(2H)-pyran]-1-one (18).—Sodium hydride (0.4-g oil suspension) was washed with hexane and suspended in tetrahydrofuran (15 ml). A solution of lactone **9e** (0.2 g) in dry tetrahydrofuran (5 ml) was added to the boiling suspension of sodium hydride. The mixture was refluxed overnight and cooled, acetic acid (1 ml) was added, and the mixture was diluted with ether, washed with water, and dried. Residue (0.5 g) was passed through alumina (neutral activity II, 4.5 g). Elution with petroleum ether–benzene gave crystals (0.118 g). Acetone–hexane gave crystals: mp 150–151°; ν_{max} (Nujol) 1700 (carbonyl), 1600, 1575 cm^{-1} (aromatic); ultraviolet, 259 mμ (ε 15,600); nmr, δ 7.99 (1 H, aromatic *ortho* to carbonyl, doublet, J = 8 Hz), 6.80 (2 H, aromatic), 3.81 (5 H, methoxyl, singlet and carbinolic), 3.05 (2 H, benzylic, doublet).

Anal. Calcd for $C_{14}H_{16}O_4$ (248): C, 67.73; H, 6.5. Found: C, 67.79; H, 6.33.

Registry No.—**5a**, 6742-26-3; **5b**, 16425-80-2; **5c**, 16425-81-3; **5d**, 16425-82-4; **5e**, 16452-35-0; **5f**, 16425-83-5; **6a**, 16425-84-6; **6b**, 16425-85-7; **6c**, 16425-86-8; **6d**, 16425-87-9; **6e**, 16425-88-0; **6f**, 16425-89-1; **6g**, 16425-62-0; **7a**, 16425-91-5; **7b**, 16425-92-6; **7c**, 16425-93-7; **7d**, 16425-94-8; **7e**, 16425-95-9; **7f**, 16425-96-0; **7g**, 16425-65-3; **8**, 16425-53-9; **9a**, 16425-54-0; **9b**, 16425-55-1; **9c**, 16425-56-2; **9d**, 16425-66-4; **9e**, 16425-57-3; **9f**, 16452-36-1; **11**, 16425-58-4; **12**, 16425-59-5; **13**, 16425-60-8; **14**, 16425-61-9; **15**, 16425-62-0; **16**, 16425-63-1; **18**, 16425-64-2.

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Terpene–Formaldehyde Reactions. III. Camphene[1]

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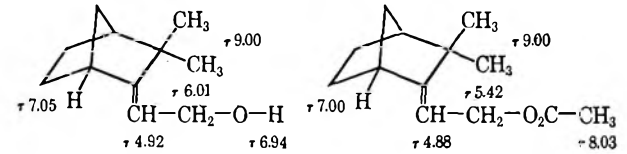
Boron trifluoride dihydrate catalysis of the camphene–formaldehyde reaction in solvent methylene chloride–acetic anhydride affords 8-hydroxymethyltricyclene acetate as the principal product (*ca.* 55%). The corresponding tricyclo alcohol is the main product when the reaction is carried out in solvent methylene chloride with stannic chloride as catalyst. In contrast to the foregoing, reaction of camphene with formaldehyde in solvent acetic acid, either in the absence of added catalyst or with added phosphoric acid, gives unrearranged 8-hydroxymethylcamphene acetate as the principal product together with smaller amounts of the parent alcohol and its formate. Depending upon conditions, the latter reactions afford yields of product that vary from *ca.* 47 to 94%.

As part of a general program concerned with the obtainment of primary alcohols from certain of the more readily available terpenes, it was of interest to make a thorough study of the camphene–formaldehyde reaction. Appropriate derivatives of primary alcohols derived from camphene, such as acrylic and methacrylic esters, could afford interesting and useful homo- and copolymers.

Earlier studies of the camphene–formaldehyde reaction have been limited to those carried out under simple thermal "noncatalyzed" conditions and those catalyzed by mineral acids;[3-8] there are no early reports on reactions effected in the presence of Lewis acid catalysts, conditions that afforded rather interesting results in the limonene–formaldehyde condensation.[1b]

This report supplements the preliminary account of observations made on the Lewis acid catalyzed camphene–formaldehyde reaction[1a] and also presents briefly pertinent results obtained in reexamination of the title reaction effected under thermal and mineral acid catalyzed conditions. The isolation, purification, analysis, and characterization of products formed in all reactions studied involved extensive use of the technique of glpc together with the methods of ir and nmr spectroscopy.

The thermal camphene–formaldehyde reaction is best done under atmospheric pressure in glacial acetic acid at reflux temperature (*ca.* 120°) as described by Langlois.[4] Under these conditions reaction for 2 days of a 2:1 mol ratio of camphene to formaldehyde gives a 94% yield of a 1:1 reaction product that comprises *ca.* 80% 8-hydroxymethylcamphene acetate (**1b**); the remainder consists mainly of 8-hydroxymethylcamphene (**1a**) and its formate. The pure alcohol **1a** is



1a **1b**

readily obtained, *via* preparative glpc, from the acetate **1b** by (a) lithium aluminum hydride reduction, (b) methanolysis, or (c) alkaline hydrolysis. Nmr and ir spectral data together with chemical properties support the structural assignments (see Experimental Section). Use of camphene that contains 20–25% tricyclene[8] affords an 84% yield of the 1:1 reaction product whose principal component (*ca.* 85%) is the acetate **1b**. A reduced yield of the 1:1 reaction product (*ca.* 47 *vs.*

(1) For two closely related reports from this laboratory on terpene–formaldehyde reactions, see (a) A. T. Blomquist and R. J. Himics, *Tetrahedron Lett.*, 3947 (1967); (b) A. T. Blomquist and R. J. Himics, *J. Org. Chem.*, **33**, 1156 (1968).

(2) Abstracted from portions of the dissertations presented by R. J. Himics and J. D. Meador to the Graduate School of Cornell University for the Ph.D. degree, Feb 1967.

(3) H. J. Prins, *Chem. Weekbl.*, **14**, 932 (1917); **16**, 1072 (1919); **16**, 1510 (1919); *Chem. Zentr.*, 168 (1918); *Chem. Abstr.*, **13**, 3155 (1919); **14**, 1662 (1920); **14**, 1119 (1920).

(4) G. Langlois, *Ann. Chim.*, **12**, 265 (1919).

(5) J. P. Bain, *J. Amer. Chem. Soc.*, **68**, 638 (1946).

(6) Y. Watanabe, *J. Chem. Soc. Jap.*, **81**, 827 (1960).

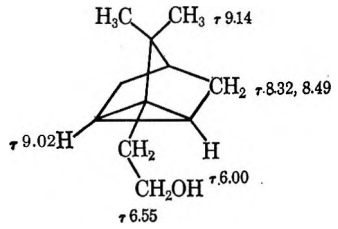
(7) S. Watanabe, S. Miki, T. Matsuzaki, Y. Nagaoka, and K. Suga, *Chiba Daigaku Kogakuba Kenkyu Hokoku*, **14** (26), 111 (1963); *Chem. Abstr.*, **62**, 7802 (1965).

(8) S. Ramaswami, S. K. Ramaswami, and S. Bhattacharyya, *J. Org. Chem.*, **29**, 2245 (1964).

94%) is observed when the condensation is carried out in a sealed autoclave and solvent acetic acid at 103–105° for 16 hr.[7] Again, little change in product yield is noted when camphene containing tricyclene (15%) is used (see Experimental Section).

The mineral acid catalyzed reaction of camphene with formaldehyde was best done with 85% phosphoric acid in solvent glacial acetic acid. Reaction at 23–29° for 24 hr gave 66% of a 1:1 product mixture that contained 79% of the acetate **1b**.[6]

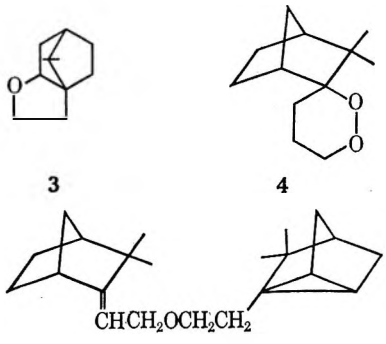
The use of Lewis acids as catalysts effects a substantial change in the nature of the principal reaction product that results from condensation of camphene with formaldehyde.[1a] Reaction of a 2:1 mol ratio of camphene and formaldehyde in solvent methylene chloride–actic anhydride for *ca.* 90 min at autogenous temperature (25–54°) in the presence of boron trifluoride dihydrate catalyst gives mainly (*ca.* 57%) 8-hydroxymethyltricyclene acetate (**2b**). The free alcohol, 8-hydroxymethyltricyclene (**2a**), is the principal product obtained when reaction is carried out in methylene chloride (2 days at 25–27°) with fuming stannic chloride added as catalyst: yield, 49% of a 1:1 reaction product that contained *ca.* 65–70% of the alcohol 2a.



2a

Nmr and ir spectra (including near-ir) together with elemental analyses and chemical properties support the assignments of structures **2a** and **2b** (see Experimental Section and also ref 1a). The acetate **2b** was observed to rearrange slowly to the acetate **1b** when heated in acetic acid at reflux temperature; about a 1:1 mol mixture of the isomeric acetates is formed from the acetate **2b** after a 4-day period of heating.

Three accessory products were isolated from the stannic chloride catalyzed reaction in solvent methylene chloride: (1) the tricyclo ether **3**, mp 129–130°; (2) the spiro-*m*-dioxane **4**, mp 44–44.5°; and (3) the unsymmetrical high-boiling ether **5** derived from the



3 **4**

5

alcohols **1a** and **2a**. The structural assignments of the three accessory products are supported by the ir and nmr data given in the Experimental Section. Hydrolysis of the *m*-dioxane **4** with aqueous acetic acid produces the acetate **1b** together with some of the alcohol **1a**. It was noted that the dioxane **4** is the principal product formed in the boron trifluoride etherate catalyzed reaction of camphene with formaldehyde in methylene chloride at 25° for 2.5 hr.

With the pure alcohol **1a** available in quantity it was of interest to examine very briefly the polymerization of 8-hydroxymethylcamphane methacrylate (**7**). Under carefully controlled conditions to avoid hydrogenolysis, catalytic hydrogenation of the alcohol **1a** in ethanol over platinum black gave the saturated primary alcohol 8-hydroxymethylcamphane (**6**) in high yield (95%), as a mixture of *endo* and *exo* isomers. The methacrylate derivative of the alcohol **6** (**7**) was easily prepared *via* transesterification with methyl methacrylate. Free-radical initiation of the ester **7**, either in bulk or emulsion, gave the homopolymer in high yield (90–95%), mp 207–215° and intrinsic viscosity of 6.91 dl/g of polymer (in benzene at 30°). Similarly, bulk copolymerization of the methacrylate **7** with styrene occurred smoothly (71%) to give a polymeric material that showed mp 196–205° and an intrinsic viscosity of 3.50 dl/g (in benzene at 30°).

Experimental Section[9,10]

Materials.—Pure camphene (*ca.* 95%), obtained from the Hercules Powder Co., was used in all studies unless otherwise indicated. Authentic tricyclene was obtained from Chemicals Procurement Laboratories, Inc. Fisher "trioxymethylene" (USP) was used as a formaldehyde source; the boron trifluoride catalysts were obtained from the General Chemical Division of the Allied Chemical Corp.

Thermal Reactions of Camphene with Paraformaldehyde. A. In a Sealed Autoclave.—A mixture of 57 g (0.42 mol) of camphene (purity *ca.* 95%), 6.6 g (0.22 mol) of paraformaldehyde, and 57 g of glacial acetic acid was heated with shaking for 16 hr at 103–105° in a 200-ml stainless steel bomb. After a conventional workup, distillation gave 28 g of camphene and two principal product fractions: (1) 14.4 g, bp 68–71° (0.25 mm), $n^{18}D$ 1.4825, and (2) 7.4 g, bp 70–77° (0.30 mm), $n^{18}D$ 1.4850. The two fractions corresponded to a 47.5% yield of an acetate such as **1b** but contained some of the free alcohol **1a** and the formate ester of **1a**.

The combined product fractions, 21 g, were heated for 2 hr at 100–105° with 20 g of acetic anhydride and 2 g of sodium acetate. Work-up of the cooled mixture gave three fractions of the acetate **1b**: (1′) 1.3 g, bp 59–64° (0.20 mm), $n^{19}D$ 1.4805; (2′) 7.3 g, bp 66–69° (0.30 mm), $n^{19}D$ 1.4823; (3′) 6.2 g, bp 72–73° (0.45 mm), $n^{19}D$ 1.4831. Glpc analysis[10a] of fractions 2′ and 3′ showed one major component; the ir spectrum showed no hydroxyl absorption but had significant absorptions at 5.85 (acetate), 5.97 (strained double bond), 7.27–7.35 (doublet, *gem*-dimethyl), and 8.05–8.15 μ (acetate). In the nmr the acetate

(9) Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined by a Varian A-60 spectrometer with carbon tetrachloride used as solvent; integrated area ratios agree well with the structures presented unless otherwise stated. All important distillations were performed using a Nester/Faust Annular Teflon spinning-band column. Analyses were done either by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or by Galbraith Laboratories, Inc., Knoxville, Tenn.

(10) An F & M Model 770 automatic preparative gas chromatograph was used throughout. For preparative glpc, sections of 8 ft × 0.75 in. stainless steel tubing were used that could be coupled to provide a maximum column length of 48 ft. Stainless steel tubing, 4–6 ft × 0.25 in., was used for analytical glpc. The solid support in all glpc columns, unless otherwise stated, was 60 mesh nonacid-washed Chromosorb W. The liquid phases used in the analytical and preparative columns together with the column temperature were as follows: (a) 20% Carbowax 20M at 185°; (b) diethylene glycol adipate (DEGA) at 180°; (c) same as (a) at 200°; (d) 20% Versamid 900 at 185°; (e) same as (d) at 180°; (f) 15% diethylene glycol sebacate (DEGS)–5% Bentone 34 at 180°; (g) 15% DEGA–5% Bentone at 180°; (h) same as (f) at 185°; (i) 8-ft 20% DEGA plus 8-ft 20% Versamid at 200°; (j) same as (b) at 175°; (k) same as (f) at 165°; (l) 20% polyphenyl ether (5 ring) at 170°.

1b showed peaks at τ 4.88 (t, >C=CH—), 5.42 (d, $-CH_2OAc$), 7.0 (br, s), 8.03 ($-O_2CCH_3$), and 9.0 (br, s, $>C(CH_3)_2$).

Repetition of the above experiment with camphene that contained *ca.* 15% tricyclene gave a product acetate (43% yield) that had $n^{19}D$ 1.4835 and whose ir spectrum was identical with that of the crude acetate previously obtained.

B. At Atmospheric Pressure.—A mixture of 62 g (0.45 mol) of pure camphene (*ca.* 95%), 6.1 g (0.20 mol) of paraformaldehyde, and 200 ml of glacial acetic acid was heated with stirring at 110–120° (gentle reflux) for 2 days. Conventional work-up of the mixture gave 43 g of a distilled product: bp 73–93° (0.50 mm), $n^{25}D$ 1.4798. This corresponded to a 94% yield of the acetate **1b**. Glpc analysis[10b] showed that it contained *ca.* 80% of the desired acetate **1b**.

Repetition of the preceding experiment at 116–125° for 16 hr with camphene that contained 20–25% tricyclene gave an 84% yield of a product, bp 90–94° (0.50 mm) and $n^{25}D$ 1.4865, that contained *ca.* 85% of the acetate **1b** (glpc analysis[10b]).

8-Hydroxymethylcamphene (1a).—To 1.20 g (0.0316 mol, 100% excess) of lithium aluminum hydride in 150 ml of anhydrous ether there was added slowly 5.90 g (0.0284 mol) of the acetate **1b**. This mixture was refluxed for 24 hr and, after a conventional work-up, afforded 4.5 g (96%) of distilled alcohol **1a** that had bp 68–72° (1.40 mm). After redistillation the alcohol **1a** of *ca.* 90% purity (glpc analysis[10a]) was obtained: bp 63° (0.15 mm), $n^{20}D$ 1.5018 [lit.[6] bp 109° (5.0 mm), $n^{25}D$ 1.5015]. Purification of this alcohol *via* preparative glpc[10o] followed by a final redistillation gave the alcohol **1a** of 98% purity (glpc analysis[10d]), $n^{20}D$ 1.5028. The ir spectrum of the alcohol **1a** had characteristic absorptions at 3.0 (OH), 5.95 (>C=C<), 7.23–7.34 [$(CH_3)_2C<$], and 9.80 μ (primary OH).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92; mol wt, 166.25. Found: C, 79.46, 79.60; H, 10.82, 10.97; mol wt, 163 (chloroform).

Methanolysis of the acetate **1b** catalyzed by dibutyltin oxide gave the alcohol **1a**, $n^{20}D$ 1.5025, in almost quantitative yield. The alcohol **1a** was also easily obtained, *ca.* 95% yield, by alkaline hydrolysis of the acetate **1b**.

Several derivatives of the alcohol **1a** were prepared by conventional procedures: the *p*-nitrobenzoate, mp 102–103° (from ethanol–water); the hydrogen phthalate, mp 124–125.2° from hexane (lit.[4,6,11] mp 124–125, 127–127.5, and 127°); the 3,5-dinitrobenzoate, mp 81.5–82° (from methanol) (lit. mp[11] 89°); and the trimethylsilylate, bp 71–73° (0.15 mm) and $n^{24}D$ 1.4680. Glpc analysis of the latter derivative[10e] showed only one component; the ir spectrum had significant absorptions at 5.98 (C=C), 7.23–7.32 [$(CH_3)_2C$], 8.0 (Si–CH_3), 9.0–9.4 (Si–O–CH_2–), 11.1–12.1 and 13.2–13.5 μ (Si–C).

Anal. ***p*-Nitrobenzoate.** Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.57, 68.64; H, 6.75, 6.75; N, 4.38, 4.46. **Hydrogen phthalate.** Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.49; H, 6.94. **3,5-Dinitrobenzoate.** Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.06; H, 5.77; N, 7.93. **Trimethylsilylate.** Calcd for $C_{14}H_{26}OSi$: C, 70.42; H, 11.01; Si, 11.78. Found: C, 70.67; H, 11.08; Si, 11.54.

The Phosphoric Acid Catalyzed Reaction of Camphene with Formaldehyde.—To a stirred mixture of 68.3 g (0.50 mol) of camphene, 9.00 g (0.30 mol) of paraformaldehyde, and 89 ml of glacial acetic acid at room temperature there was added dropwise a solution of 25 g of 85% phosphoric acid in 70 ml of acetic acid over a 30-min period. After this addition, the mixture was stirred at 23–29° for *ca.* 24 hr. A conventional work-up of the reaction mixture gave, upon distillation, 20.6 g of camphene and two principal product fractions: (1) 4.22 g, bp 69–77° (2.0 mm), $n^{25}D$ 1.4765; (2) 40.9 g, bp 77–98° (2.0 mm), $n^{25}D$ 1.4810. Glpc analysis[10f] showed that fraction 1 comprised mainly a mixture of low-boiling components; 79% of fraction 2 was the acetate **1b**, and most of the remainder was the alcohol **1a**. Fraction 2 corresponded to a 66% yield of 1:1 camphene–formaldehyde reaction products.

The Stannic Chloride Catalyzed Reaction of Camphene with Paraformaldehyde.—Fuming stannic chloride (0.30 ml) was added, under nitrogen, to a mixture of 65 g (0.48 mol) of pure camphene (*ca.* 95%) and 8.1 g (0.27 mol) of paraformaldehyde in 250 ml of dry methylene chloride. The mixture was stirred for 2 days at 25–27° and then 10 ml of dilute sodium hydroxide added. A conventional work-up of this mixture gave, after sublimation of unreacted camphene, 39 g of a main product fraction, bp 71–79° (0.35 mm) and $n^{25}D$ 1.4954, that corresponded to a 49% yield of a 1:1 reaction product. Glpc analysis[10g] of this crude product indicated that it contained *ca.* 65–70% of one major component, the alcohol **2a**. The pure alcohol **2a** (99% by glpc analysis[10h]) was obtained *via* preparative glpc:[10i] bp 81–82° (0.75 mm), $n^{25}D$ 1.4899. Its ir spectrum showed significant absorptions at 3.0 (OH), 3.45 (C–H), 7.2, 7.3 [$(CH_3)_2C$], and 9.47–9.62 μ (primary OH). In the near-ir the alcohol **2a** showed absorption at 1.672 μ, attributable to tertiary cyclopropanyl hydrogens. The nmr spectrum was reported earlier.[1a]

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.48; H, 10.82.

Repetition of the reaction described above on a larger scale (268 g of camphene and 26.4 g of paraformaldehyde) made it possible to isolate and characterize some of the accessory products of the reaction. As the first distillation of the crude reaction mixture was begun a volatile sublimate collected in the water-cooled condenser. This sublimate was resublimed at 0.2 mm, chromatographed over neutral alumina (petroleum ether (bp 30–60°) eluent), and finally sublimed at 25°(0.1 mm) to give a white, waxy solid, mp 129–130°. Spectral data indicated that it was the ether 10,10-dimethyltricyclo[4.3.$1^{1,7}$.$0^{1,5}$]-4-oxadecane (**3**). In the infrared it showed significant absorptions at 3.40, 3.50, 7.2, 7.3, 9.34, 10.19, and 11.64 μ; the nmr spectrum showed signals at τ 5.92–6.50 (m), 8.98 (s), and 9.15 (s).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92; mol wt, 166. Found: C, 79.56; H, 10.90; mol wt, 168–170 (benzene).

After removal of the ether **3**, fractional distillation of the crude reaction mixture gave four principal fractions: (1) 2.4 g, bp 61–72° (0.35 mm), $n^{25}D$ 1.4870; (2) 23.0 g, bp 78–88° (0.30 mm), $n^{25}D$ 1.4892; (3) 29.0 g, bp 88.5–90.5° (8.30 mm), $n^{25}D$ 1.4905; (4) 48.1 g, bp 140–175° (0.30 mm), $n^{25}D$ 1.5078. Redistillation of the combined fractions 2 and 3 gave the alcohol **2a** which contained a minor impurity (glpc analysis[10j]). The impurity was isolated *via* column chromatography over neutral alumina (ether–benzene as eluent) and proved to be identical with the major product formed in the boron trifluoride etherate catalyzed camphene–formaldehyde reaction (*vide infra*) and shown to be the *m*-dioxane derivative spiro[2,2-dimethylnorbornane-3,1′-(2′,4′-dioxacyclohexane)] (**4**). Finally, after several redistillations of fraction 4 there was isolated the unsymmetrical ether derived from alcohols **1a** and **2a**: bp 141° (0.30 mm); $n^{25}D$ 1.5068; ir spectrum, λ_{max} 6.0, 7.23, 7.32, 9.0–9.3, 11.25–11.4, and 12.0 μ; nmr signals at τ 5.0 (t, >C=C*H*–CH_2–), 6.21 (d, >C=CHC*H*$_2$–), 7.0 (s), 7.07 (–OC*H*$_2$–), 8.98 [d, (C*H*$_3$)$_2$C, camphene], and 9.17 [s, (C*H*$_3$)$_2$C–, tricyclo].

Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90; mol wt, 314.49. Found: C, 84.02, 84.13; H, 11.02, 11.03; mol wt, 320, 316 (benzene).

Reaction of Camphene with Paraformaldehyde Catalyzed by Boron Trifluoride Complexes. I. With Boron Trifluoride Etherate.—To a mixture of 105 g (0.773 mol) of camphene, 11.6 g (0.386 mol) of paraformaldehyde, and 300 ml of dry methylene chloride there was slowly added, with stirring under nitrogen, 1.5 ml of boron trifluoride etherate in 60 ml of methylene chloride. After being stirred for 2 hr at room temperature, the reaction mixture was worked up in a conventional manner. Unreacted camphene (54.5 g) was recovered and the residue distilled to give four fractions: (1) 14.7 g, bp 80–86° (0.40 mm), $n^{16}D$ 1.4940; (2) 2.6 g, bp 91–96° (0.40 mm), $n^{25}D$ 1.4938; (3) 2.4 g, bp 120–142° (0.40 mm), $n^{25}D$ 1.5050; (4) 4.1 g, bp 142–150° (0.40 mm), $n^{25}D$ 1.5068. Glpc analysis[10g] indicated that fractions 1 and 2 comprised a 45% yield of one major product. Fraction 2 (purity *ca.* 85%) was chromatographed over alumina. The material obtained with ether as eluent, bp 58–58.5° (0.15 mm), crystallized on standing. Sublimation at 25° (0.10 mm) gave a white solid, mp 44–44.5°, whose properties were in accord with the *m*-dioxane **4**: ir spectrum, λ_{max} 8.64, 9.01–9.11, 9.65–9.74, 10.00, and 11.8 μ; nmr spectrum τ 5.27 (quad, O–C*H*$_2$–O), 6.2–6.7 (m, –CH_2C*H*$_2$–O), 7.23 (bs, probably tertiary H), 9.07 and 9.16 [sh s, (C*H*$_3$)$_2$C].

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.36, 73.57; H, 10.28, 10.17.

II. With Boron Trifluoride Dihydrate.—To a stirred mixture of 66 g (0.485 mol) of camphene, 7.29 g (0.243 mol) of paraformaldehyde in 100 ml of methylene chloride, and 100 ml of acetic anhydride there was added, under nitrogen, a solution of 0.45 ml of boron trifluoride dihydrate in 40 ml of the mixed solvent over

(11) S. Watanabe, *Bull. Chem. Soc. Jap.*, **38** (8), 1231 (1965); *Chem. Abstr.*, **63**, 14909 (1965).

an 11-min period. Stirring was continued for another 76 min, during which time the reaction temperature rose to 54°. Dilute sodium hydroxide (20 ml) was added to the cooled mixture which was then worked up in a conventional way. Upon distillation there was obtained 9.2 g of camphene and three product fractions: (1) 10.1 g, bp 70–73° (0.45 mm), n^{28}D 1.4650; (2) 18.6 g, bp 73–79° (0.45 mm), n^{28}D 1.4678; (3) 20.3 g, bp 80–148° (0.45 mm), n^{25}D 1.5048. Fractions 1 and 2 represented at 57% yield of impure 1:1 reaction product. From two redistillations of fractions 1 and 2 there was obtained a center cut, bp 63° (0.3 mm), n^{25}D 1.4698, of the tricyclo acetate **2b**, purity >96% *via* glpc analysis:[10k] ir spectrum, λ_{max} 3.46, 5.73, 7.40, 8.14, and 9.66 μ; nmr spectrum, τ 6.07 (t, $-CH_2O-$), 8.06 (s, O_2C-CH_3), and 9.12 (s, $-CH_3$).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol wt, 208.29. Found: C, 74.91, 74.87; H, 9.68, 9.73; mol wt, 202 (chloroform).

Rearrangement of the Acetate 2b to the Acetate 1b.—A solution of 1.30 g (6.24 mmol) of the tricyclo acetate **2b** in 50 ml of glacial acetic acid was heated at 115–117° for *ca.* 4 days. A conventional work-up gave, after distillation, a 52% recovery of a monoacetate fraction, bp 97–98° (5.8–6.0 mm) and n^{25}D 1.4759, that contained the two acetates **1b** and **2b**. Glpc analysis[10l] indicated that the two acetates were present in about a 1:1 ratio. Addition of a sample of pure acetate **1b** enhanced the glpc peak representing the allylic acetate. Similarly, the glpc peak assigned to the trieyclo acetate was increased by the addition of pure tricyclo acetate.

8-Hydroxymethylcamphane (6).—Catalytic hydrogenation, in a Parr apparatus, of 40.9 g (0.246 mol) of the alcohol **1a** in 250 ml of absolute ethanol over 1.15 g of platnium black under 34–39 psi of hydrogen for 44 hr at room temperature gave, after distillation through a Vigreux column, 39 g (95%) of the saturated alcohol **6**: bp 107–112° (4.7 mm), n^{20}D 1.4895–1.4897. Partial resolution of the product into *endo* and *exo* isomers could be achieved by glpc analysis.[10l] Redistillation of the alcohol gave an analytical sample of **6**: bp 86–87° (0.43 mm), n^{21}D 1.4888 [lit.[6] bp 104–105° (5 mm), n^{26}D 1.4874].

Anal. Calcd for $C_{11}H_{20}O$: 78.51; H, 11.98. Found: C, 78.50; H, 11.89.

Methacrylates of the Alcohols 1a and 2a. I. 8-Hydroxymethylcamphene Methacrylate (8).—In an adaptation of the method of Burtle and Turek[12] a mixture of 25 g (0.15 mol) of the alcohol **1a**, 0.3 g of hydroquinone, 0.1 g of copper metal, 0.1 g of cupric chloride, and 17.2 g (0.20 mol) of methacrylic acid in 300 ml of benzene was distilled cyclically, in the presence of 0.20 g of *p*-toluenesulfonic acid, for *ca.* 7 hr; about 2.4 ml (89%) of water was collected. Work-up of the esterification gave, after distillation, 28 g (80%) of impure ester **8**: bp 98–113° (0.45 mm), n^{25}D 1.4881. Two redistillations gave a sample of the methacrylate **8** of purity >91% (glpc analysis[10g]): bp 79–80° (0.25 mm); n^{25}D 1.4908; ir spectrum, λ_{max} 5.89 (C=O), 6.01 (internal C=C), 6.15 (C=CH_2), 7.37, 7.4 [doublet, $(CH_3)_2C$], and 7.6–7.7 μ (C–O–); nmr spectrum, τ 3.97 [m, $(CH_3)C=CH_t-$], 4.54 (m, $CH_3C=CH_c$), 4.87 (t, $-C=CHCH_2$), 5.43 [d, $>C=C-(CH_2O)-$], 8.10 (t, $CH_3C=CH_2$), and 8.96 [d, $(CH_3)_2C$].

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.91, 77.03; H, 9.34, 9.35.

(12) J. G. Burtle and W. N. Turek, *J. Org. Chem.*, **19**, 1507 (1954).

II. 8-Hydroxymethylcamphane Methacrylate (7).—Transesterfication of 25.0 g (0.149 mol) of the alcohol **6** with 44.7 g (0.447 mol) of methyl methacrylate in the presence of 0.7 g of hydroquinone and 0.11 g of concentrated sulfuric acid was carried out at reflux temperature for 28 hr with slow removal of distillate (vapor temperature 67–80°). Work-up of the mixture gave, upon distillation, 21.6 g of excess methyl merthacrylate and two product fractions: (1) 3.71 g, bp 78–88° (0.1 mm), n^{21}D 1.4828; (2) 27.4 g, bp 88–92° (0.1 mm), n^{21}D 1.4822. Redistillation of fraction 2 gave the pure methacrylate **7** (glpc analysis showed it to be a mixture of *endo* and *exo* isomers): bp 95–96° (0.3 mm), n^{21}D 1.4827.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.42; H, 10.31.

Polymerization of the Methacrylate 7. I. Homopolymerization.—Polymerization of 4.12 g (17.5 mmol) of the methacrylate **7**, initiated with 0.02 g of azobisisobutyronitrile, was carried out at 40° for 2 days. The initially formed clear, hard, glasslike polymer was dissolved in benzene, filtered, and precipitated by dropwise addition to stirred methanol. The dried polymer (4.09 g) was repeatedly ground and dried at room temperature *in vacuo* to constant weight (*ca.* 95% yield). The polymer showed mp 207–215° and an intrinsic viscosity in benzene at 30° of 6.91 dl/g of polymer.

Anal. Calcd for $(C_{15}H_{24}O_2)_n$: C, 76.22; H, 10.24. Found: C, 75.94, 76.07; H, 10.14, 10.00.

Polymerization of the monomer **7** by the reflux emulsion technique[13] occurred smoothly to give the homopolymer in *ca.* 89% yield, mp 190–210°.

II. Copolymerization with Styrene.—Bulk copolymerization of 2.42 g (10.2 mmol) of the monomer **7** and 1.03 g (9.90 mmol) of styrene was effected at 40° over a period of 45 hr when initiated with 0.016 g of azobisisobutyronitrile. The crude copolymer was a soft, clear, rather rubbery material. The crude copolymer was dissolved in benzene filtered and precipitated with methanol. After successive pulverization and drying *in vacuo* at room temperature to constant weight, the copolymer (2.5 g) was obtained as a white powder: mp 196–205° and an intrinsic viscosity in benzene at 30° of 3.50 dl/g of polymer.

Anal. Found: C, 80.96, 81.19; H, 9.64, 9.78.

Registry No.—Camphene, 79-92-5; **1a**, 2226-05-3; *p*-nitrobenzoate of **1a**, 16159-26-5; hydrogen phthalate of **1a**, 2226-06-4; 3,5-dinitrobenzoate of **1a**, 2226-07-5; trimethylsilylate of **1a**, 16159-29-8; **1b**, 2226-03-1; **2a**, 16162-37-1; **2b**, 16162-38-2; **3**, 16162-39-3; **4**, 16203-58-0; **5**, 16 203-59-1;*exo* **6**, 16503-26-7; *endo* **6**, 16423-26-0; *exo* **7**, 16423-27-1; *endo* **7**, 16423-28-2; **8**, 16162-40-6.

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(13) Special Products Department Pamphlet, "Emulsion Polymerization of Acrylic Monomers," Rohm and Haas Co., Philadelphia, Pa., 1965, p 3.

Monocyclic Terpene Alcohols. VIII. *p*-Mentha-2,4(8)-dien-9-ol and *p*-Mentha-2,4(8)-dien-10-ol[1,2]

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Dehydration of ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) to afford dienic esters was studied under a variety of conditions. It was found that ethyl *p*-mentha-2,4(8)-dien-9-oate (V) was formed predominantly by phosphorus oxychloride–pyridine treatment of I, whereas pyrolysis of the acetate of I yielded ethyl *p*-mentha-2,4(8)-dien-10-oate (IV) and V in a 1:1 ratio. The same ratio was reached by thermal isomerization of V. *p*-Mentha-2,4(8)-dien-9-ol and *p*-mentha-2,4(8)-dien-10-ol were obtained by lithium aluminum hydride reduction of the corresponding esters.

In connection with our studies related to the synthesis of monocyclic terpene alcohols, the dehydration of the easily available[3] ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) as a potential source of dienic intermediates was investigated.

Treatment of this hydroxy ester with acidic dehydrating agents afforded complex mixtures containing six main components (glpc analysis), whose relative ratio was dependent on the conditions used. These products were isolated by preparative glpc and were submitted to spectral analyses (nmr, uv, and ir) which pointed to structures II–VII (Scheme I).

Structures II and III were confirmed by comparison with authentic specimens synthesized by an independent route.[4]

The stereochemical problem posed by isomers IV and V was settled on the basis of the well-known deshielding effect of an ethoxycarbonyl group,[5] structure V being assigned to that isomer in which the C_3-vinyl proton absorbed at lower field (IV, τ 3.55; V, τ 3.0).

Structure VI was based on spectral and analytical data.[6] Ir bands characteristic of the carbonyl absorption of α,β-unsaturated γ-lactone[7] appeared at 5.67 and 5.92 μ, uv absorption was at λ_{max} 218 mμ (ϵ 12,700), and nmr absorption occurred at τ 5.45, 8.25, and 8.98. While our work was in progress, an optically active form of lactone VI was isolated,[8,9] and the structure and stereochemistry of the four diastereomeric (asymmetric centers C_1 and C_8) keto acids, resulting from its hydrolysis, were elucidated.[10]

The hydrolysis of our racemic lactone afforded two crystalline derivatives, mp 110–112° and 123–124°. The spectral features of the former were consistent with those expected for keto acid XI. Ir absorption was at 3–4.25 and 5.9 μ; nmr absorption occurred at τ 0.9, 8.8, 8.93, and 7.2–8.7 (broad). The poor resolution of the C_1-methyl protons and the broad bands observed in the cyclohexane protons region substantiate the *trans*-*p*-menthane configuration assigned.[11,12]

Properties of the other crystalline compound pointed to the pseudo-acid (lactol) structure XII. Ir absorption was at 2.95 and 5.73 μ; nmr absorption occurred at τ 4.3, 8.8, and 7.2–8.6 (multiplet). In this case, the clearer splitting in the C_1-methyl group and the more acute cyclohexane ring protons envelope observed are consistent with a *cis*-*p*-menthane configuration.[11–13]

In view of the particular aim of our work, no serious attempt was made to isolate the other possible diastereomeric keto acids from the hydrolysis mixture or to elucidate the relative configuration at the C_8 center of our crystalline derivatives.

When lactone VI was reduced with lithium aluminum hydride, a liquid product was obtained with the features expected for diol X. This product afforded a crystalline bis-3,5-dinitrobenzoate derivative, which seemed to be a mixture of epimers because of the C_1-methyl protons' nmr absorption at τ 8.63 and 8.9. An optically active form of diol X has been recently prepared by lithium aluminum hydride reduction of menthofuran photoperoxide.[14]

Structure VII, assigned to the last product present in small amounts in the mixture after treatment of hydroxy ester I with acidic dehydrating agents, was substantiated by spectral data: uv, λ_{max} 219 mμ (ϵ 8200); ir, 5.68 and 5.93 μ; nmr, τ 8.24 and 5.14–5.4.

For preparative purposes, the dehydration of hydroxy ester I with *p*-toluenesulfonic acid in boiling benzene

(1) Parts V–VII of this series were presented at the XIII Meeting of the Real Sociedad Española de Física y Química, Pamplona-San Sebastián, June 1967; *An. Real Soc. Espan. Fis. Quim.*, in press.

(2) Supported by Grant FG-Sp-135 from the U. S. Department of Agriculture.

(3) F. Camps, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3510 (1966).

(4) F. Camps and J. Pascual, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **64**, 167 (1968).

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., Oxford, 1959, p 121.

(6) Project UR-E-25-(50)-36, Grant FG-Sp-135, U. S. Department of Agriculture, Report 6, Feb 1966–Jan 1967, p 8.

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(8) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenk, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).

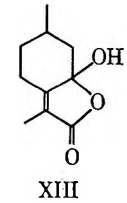
(9) J. A. Hirsch and R. H. Eastman, *J. Org. Chem.*, **32**, 2915 (1967).

(10) C. S. Foote, M. T. Wuesthoff, and I. G. Burstain, *Tetrahedron*, **23**, 2601 (1967).

(11) J. Albaigés, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3507 (1966).

(12) H. Booth, *Tetrahedron*, **22**, 615 (1966).

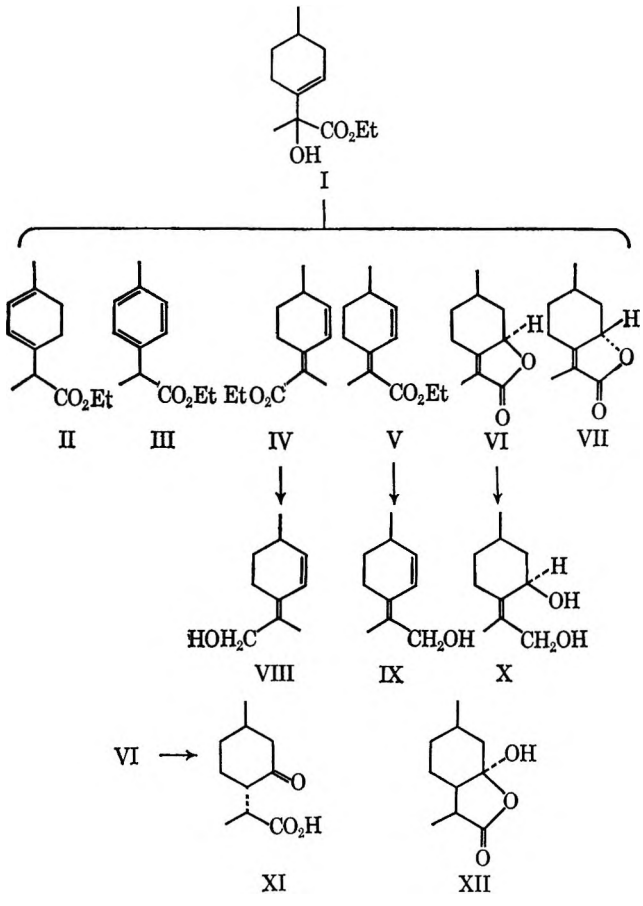
(13) Foote and coworkers[10] isolated two crystalline acids, mp 143–144 and 97–98°, assumed to be identical with the keto acids, mp 146–147 and 97–98°, previously obtained by R. B. Woodward and R. H. Eastman [*J. Amer. Chem. Soc.*, **72**, 399 (1950)] by reduction of the crystalline pseudo-acid XIII with sodium amalgam. The former with a *cis*-*p*-menthane configuration, appears to be mainly in the lactol form, whereas the latter exhibits the properties of a true keto acid and has a *trans*-*p*-menthane configuration. In both cases the configuration at C_8 center was elucidated. It is worth pointing out also that K. J. Crowley [*J. Chem. Soc.*, 4254 (1964)] isolated a keto acid, mp 151°, by hydrolysis of a liquid stereoisomer of XIII but made no structural assignment to it.



XIII

(14) K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **50**, 153 (1967).

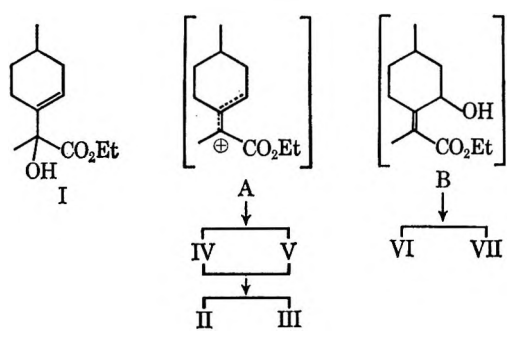
SCHEME I



was studied more closely. The results obtained showed that the amount of the esters IV and V in the mixture reached a maximum (about 50% in a 1:1 ratio) and then decreased steadily, ester II and lactone VI being the major components (about 75%) after prolonged treatment.

In a separate experiment, starting from a 1:1 mixture of esters IV and V, it was found that compounds II and III were formed directly from these esters, whereas lactones VI and VII should arise from hydroxy ester I, through a possible intermediate hydroxy ester B[15,16] (Scheme II).

SCHEME II



To improve our results, other methods of dehydration were investigated. Treatment of hydroxy ester I with phosphorus oxychloride and pyridine afforded ester V almost exclusively. Reduction of V with lithium aluminum hydride yielded *p*-mentha-2,4(8)-dien-9-ol (IX), that was purified *via* the 3,5-dinitrobenzoate derivative, mp 82.5–3.5°, followed by hydrolysis on alkaline aluminum oxide.[17]

From the aqueous mother liquors of this phosphorus oxychloride–pyridine treatment a crystalline by-product, mp 118–120°, was isolated with the properties expected for a pyridinium salt and the molecular formula $C_{17}H_{26}NO_3Cl$, consistent with the addition of pyridine hydrochloride to hydroxy ester I. When this product was refluxed in dry pyridine, a liquid mixture was formed in which the presence of esters II, IV, V, and lactone VI was detected by glpc analysis.

Preparation of ester IV could be accomplished by slow pyrolysis of the acetate of hydroxy ester I at 500° (0.9 mm) which gave an 80–85% 1:1 mixture of esters IV and V. Careful distillation of this mixture afforded ester IV which was submitted to the same treatment described above to yield *p*-mentha-2,4(8)-dien-10-ol (VIII) purified also through its 3,5-dinitrobenzoate derivative, mp 71–72.5°.

To increase the yield of ester IV several methods of isomerization of ester V were attempted and although some promising results were obtained by photochemical or iodine–benzoyl peroxide isomerizations,[18] it was found that the best results were reached by thermal treatment. Thus, submitting fractions rich in isomer V to the same conditions described above for the pyrolysis of the acetate of I, a 1:1 ratio of esters IV and V was obtained; when the temperature was lower, the isomer V was still predominant in the mixture.

The stereospecifity observed in the phosphorus oxychloride treatment is not clear at this stage, but could be explained by some kind of interaction (polar, proton bonding, π complex) between the double bond and the ethoxycarbonyl group in the intermediate state of the dehydration, leading to the predominant formation of V by a kinetically controlled process. This interaction would be absent in the presence of acid reagents that gave the 1:1 thermodynamic ratio of IV:V. However the elucidation of this point would deserve further work before drawing definitive conclusions.

Experimental Section

Melting points were taken on a Koffler hot-stage apparatus and are corrected. Infrared spectra were measured on Perkin-Elmer Infracord 137 and Infracord 137 G spectrophotometers. Ultraviolet spectra were run on a Perkin-Elmer 137 apparatus. The nmr spectra were recorded on a Perkin-Elmer R-10 at 35° operating at 60 Mc/sec with TMS as an internal reference. Bands due to hydroxyl protons in the nmr spectra have been routinely identified by their diamagnetic shift with increasing dilution. The glpc analyses and preparative separations were carried out on an Aerograph A-705 with flame ionization detector on different columns. Fractional distillation was achieved with a Büchi spinning-band column, Dr. H. Abegg system.

Treatment of Ethyl 8-Hydroxy-*p*-menth-3-en-9-oate (I) with *p*-Toluenesulfonic Acid.—Ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (1 g) in dry benzene (10 ml) was refluxed under nitrogen in presence of *p*-toluenesulfonic acid (0.2 g). The course of the reaction was monitored by glpc using a 20 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 175°. Analysis of aliquot parts of this mixture revealed the presence of six components besides the starting product, which were isolated by preparative glpc under the conditions above mentioned and identified as com-

(15) By an alternative explanation of formation of lactone VI, see ref 8.

(16) Two optically active isomers of postulate intermediate B (as the acid) have been described, although no structural assignments were made: R. Robinson and G. I. Fray, *Tetrahedron*, **9**, 295 (1960).

(17) J. Castells and G. A. Fletcher, *J. Chem. Soc.*, 3245 (1956).

(18) R. Grewe, E. Nolte, and R. H. Rotzoll, *Chem. Ber.*, **89**, 600 (1956).

pounds II–VII by spectral means. (The spectral data are given in the sections dealing with the preparation of the corresponding products using the most convenient method found.) The relative amounts of these products changed with the time of refluxing. Thus, after 4 hr the following relative amounts were found: II (14), III (2), I (14), IV (26), V (24), VI (14), VII (6). By increasing the reaction time, the relative amounts of esters IV and V diminished whereas those of esters II and III and lactones VI and VII increased. After 24 hr, the following ratios were determined: 36, 9, 3, 3.5, 2.5, 37, and 9.

Lactone VI.—Ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (15 g) treated with *p*-toluenesulfonic acid (3 g) in boiling dry benzene (150 ml) for 30 hr under a nitrogen atmosphere afforded, after the usual work-up, a yellowish oil (12.7 g) having a relative ratio similar with that observed above. Fractional distillation in a spinning-band column at reduced pressure yielded already known[4] ethyl *p*-mentha-1,3-dien-9-oate (II) (3 g), bp 95–97° (6 mm), among other fractions containing mixtures of the above mentioned products. The residue of this distillation (6 g) was fractionated at higher vacuum to give lactone VI (3.5 g): bp 87–89° (0.25 mm); $n^{21.5}$D 1.5002; λ_{max}^{EtOH} 218 mμ (ε 12,700); $\lambda_{max}^{CCl_4}$ 5.67, 5.92, 9.13, 9.35, and 9.70 μ; τ_{CCl_4} 5.45 (broad band, half-band width = 20 cps, 1 H), 8.25 (triplet, J = 1 cps, 3 H), 8.98 (doublet, J = 6 cps, 3 H), 7–9.1 (broad absorption, 7 H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.84.

From the higher boiling fractions of this distillation, a small amount of product could be isolated by preparative glpc with the spectral features expected for VII: λ_{max}^{EtOH} 219 mμ (ε 8200); $\lambda_{max}^{CCl_4}$ 5.68, 5.93, 8.05, 9.18, and 9.70 μ; τ_{CCl_4} 5.1–5.5 (broad band, 1 H), 8.24 (triplet, J = 1 cps, 3 H), 8.84 (doublet, J = 7 cps, 3 H), 7.3–9 (broad absorption, 7 H).

Ethyl *p*-Mentha-2,4(8)-dien-9-oate (V).—Phosphorus oxychloride (5 ml) was added dropwise under stirring to an ice-cooled solution of ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (5 g) in dry pyridine (50 ml) under nitrogen atmosphere. The mixture was kept overnight in a refrigerator. Then, it was hydrolyzed with cool 2 *N* sulfuric acid and extracted several times with ethyl ether. After the usual treatment, the joined organic fractions were evaporated at reduced pressure to yield a colorless oil (2.7 g). Glpc analysis of this oil, under the conditions mentioned above, revealed the presence of V (65–70%) and IV (10–15%) together with minor amounts of II (5–10%) and starting hydroxy ester I (8–10%). Fractional distillation of this oil (13.5 g) in a spinning-band column gave pure ester V (4 g): bp 124° (8 mm), 69° (0.2 mm); n^{25}D 1.5068; λ_{max}^{EtOH} 267.5 mμ (ε 13,500); λ_{max}^{film} 5.86 6.2, 6.35, 8.1–8.3, 8.65, 8.95, 9.1–9.2, 12.2, 12.55, and 12.8 μ; τ_{CCl_4} 2.98 (double doublet, J = 10 cps, J' = 2 cps, 1 H), 4.25 (broad bands, doublet, J = 10 cps, 1 H), 5.85 (quartet, J = 7 cps, 2 H), 8.1 (singlet, 3 H), 8.7 (triplet, J = 7 cps, 3 H), 8.95 (doublet, J = 7 cps, 3 H), 7.2–8.3 (broad band, 5 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.40.

The mother liquors of the dehydration (from 5 g of hydroxy ester I) were extracted with chloroform to give after the usual treatment and evaporation of the organic solvent a thick brown oil (3.5 g), which crystallized by addition of acetone. Recrystallization from methylene chloride–acetone gave bright flakes, mp 118–120°, which turned red upon heating. This product gave a positive halide test (Beilstein) and exhibited the spectral features consistent with a pyridinium salt: λ_{max}^{KBr} 3, 5.75, 6.15, 8, 8.7, 9.82, 12.7, 14, and 14.55 μ; τ_{CCl_4} 0.52 (split doublet, J = 6 cps, 2 H), 1.17–1.57 (multiplet, 3 H), 3.96 (broad band, 1 H), 5.62 (quartet, J = 6 cps, 2 H), 6.92 (broad singlet, 1 H), 7.60 (singlet, 1 H), 8.67 (triplet, J = 6 cps, 3 H), 8.97 (doublet, J = 5 cps, 3 H), 7.4–8.5 (broad absorption).

Anal. Calcd for $C_{17}H_{26}NO_3Cl$: C, 62.12; H, 7.99; N, 4.27; Cl, 10.79. Found: C, 62.19; 62.05; H, 7.93; 7.95; N, 4.33; Cl, 11.27.

When this product (0.5 g) was heated in dry pyridine (5 ml), a liquid (0.2 g) was recovered after the usual treatment, which after glpc analysis (peak enhancement) revealed the presence of compounds II (16%), V (41%), IV (28%), and VI (14%).

Ethyl *p*-Mentha-2,4(8)-dien-10-oate (IV).—A mixture of hydroxy ester I (10.5 g) and melted sodium acetate (10.5 g) in acetic anhydride (105 ml) was refluxed 90 hr under nitrogen atmosphere. After evaporation of the solvent at reduced pressure, the residue was extracted several times with ethyl ether. The joined organic fractions afforded after the usual treatment a brown oil (2 g) which exhibited a single band in the glpc analysis and the features expected for the acetate of I in the nmr spectrum: τ_{CCl_4} 4.2 (broad band, 1 H), 5.9 (quartet, J = 7 cps, 2 H), 8 (singlet, 3 H), 8.4 (singlet, 3 H), 8.8 (triplet, J = 7 cps, 3 H), 9.05 (doublet, J = 6 cps, 3 H), 7.8–8.5 (broad absorption, 7 H). Slow distillation of this crude acetate at 0.9 mm through a 58 × 1.5 cm quartz tube, packed with glass wool, heated at 500°, collecting the exit gases in a cool trap, afforded a yellowish oil (6.2 g), glpc analysis of which revealed the presence of three components: II (17%), IV (42%), and V (41%). Careful distillation of the pyrolysate (21.3 g) in a spinning-band column at reduced pressure afforded pure ester IV: bp 112–113° (5 mm); n^{23}D 1.5032; λ_{max}^{EtOH} 269.5 mμ (ε 14,900); λ_{max}^{film} 5.86, 6.2, 6.33, 8.1, 8.3, 8.65, 8.95, 9.15, 11.6, 12.25, 12.9, and 13.35; τ_{CCl_4} 3.55 (doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.06 broad bands, (doublet, J = 10 cps, 1 H), 5.82 (quartet, J = 7 cps, 2 H), 8.05 (singlet, 3 H), 8.7 (triplet, J = 7 cps, 3 H), 8.92 (doublet, J = 7 cps, 3 H), 7–8.3 (broad band, 5 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.39. Found: C, 74.07; H, 9.56.

Thermal Rearrangement of Esters IV and V.—A mixture of esters IV and V (5.4 g) in a 38:62 ratio was distilled under the same conditions described in the preceding section for the pyrolysis of the acetate of I. The condensed pyrolysate (4.9 g) was analysed by glpc which showed a 1:1 ratio of both esters. No other products were detected. This ratio remained unchanged by further distillation under the same conditions.

Treatment of Esters IV and V with *p*-Toluenesulfonic Acid.—A 1:1 mixture of esters IV and V (2 g) and *p*-toluenesulfonic acid (0.2 g) in dry benzene (20 ml) was refluxed under nitrogen atmosphere. Analysis of aliquot parts by glpc revealed its rapid transformation into esters II and III. After 6 hr, the following ratio was found: II (67%), III (18%), IV (6%), and V(9%). When the reaction was carried out in presence of some drops of water, the reaction was slower and the formation of a small amount of lactone VI was observed. Under these conditions after 36 hr, the following ratio was found: II (56%), III (13%), IV (7.5%), V (18%), and VI (5%).

***p*-Mentha-2,4(8)-dien-9-ol (IX).**—To a well-stirred solution of ester V (95% steric purity) (1.7 g) in dry ethyl ether (20 ml), lithium aluminum hydride (0.25 g) was added at −40° under nitrogen. Stirring was maintained for 10 hr during which the mixture was warmed slowly to room temperature. After the usual treatment, a colorless oil (1.3 g) was obtained which exhibited no carbonyl absorption in the spectrum ir. Dinitrobenzoylation by the conventional procedure yielded a crude dinitrobenzoate derivative (2.9 g) which, by repeated crystallization from ethanol–ethyl ether, gave yellow spheric aggregates: mp 83.5–84.5° (0.9 g); τ_{CDCl_3} 0.85 (multiplet, 3 H), 3.5 (double doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.3 (broad bands, doublet, J = 10 cps, 1 H), 4.98 (singlet, 2 H), 8.1 (singlet, 3 H), 8.96 (doublet, J = 7 cps, 3 H), 7.4–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.03; H, 5.50; N, 7.84.

Hydrolysis of this derivative (0.9 g) on alkaline aluminum oxide (40 g) under nitrogen using a 2:1 *n*-hexane–benzene elution mixture yielded *p*-mentha-2,4(8)-dien-9-ol (IX) (0.4 g): bp 76.5–77.5° (0.7 mm); n^{23}D 1.5301; λ_{max}^{EtOH} 243 mμ (ε 21,000); λ_{max}^{film} 3.05, 6.15 (weak), 10, 10.5, 12.35, 13.3, and 13.6 μ; τ_{CCl_4} 3.58 (double doublet, J = 10 cps, J = 1.5 cps, 1 H), 4.47 (broad bands doublet, J = 10 cps, 1 H), 5.9 (singlet, 2 H), 8.2 (singlet, 3 H), 8.98 (doublet, J = 6 cps, 3 H), 7.3–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.65; H, 10.32.

***p*-Mentha-2,4(8)-dien-10-ol (VIII).**—A solution of ester IV (95% steric purity) (2.3 g) in dry ethyl ether (25 ml) was reduced with lithium aluminum hydride (0.35 g) under the same conditions described in the precedent section. After the usual procedure, a colorless oil (1.8 g) was isolated which was submitted to dinitrobenzoylation to give a crude derivative (3.5 g) which by repeated crystallizations from ethanol–ethyl ether yielded pure dinitrobenzoate of VIII: mp 71–72.5°; τ_{CDCl_3} 0.8 (multiplet, 3 H), 3.6 (double doublet, J = 10 cps, J' = 1.5 cps 1 H), 4.23 (broad bands doublet, J = 10 cps, 1 H), 4.93 (singlet, 2 H), 8.08 (singlet, 3 H), 8.95 (doublet, J = 7 cps, 3 H), 7.2–8.7 (broad absorption, 5 H).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.71; H, 5.08; N, 7.91.

Hydrolysis of this 3,5-dinitrobenzoate (1.2 g) on alkaline aluminum oxide (30 g) under the same conditions described above

afforded *p*-mentha-2,4(8)-dien-10-ol (VIII) (0.5 g): bp 77.5–79° (0.6 mm); $n^{23}D$ 1.5312; λ_{max}^{EtOH} 245 mμ (ε 28,500); λ_{max}^{film} 3.05, 6.15 (weak), 6.25 (weak), 8.8, 10, 10.5, 12.35, 13.35, and 13.65 μ; τ_{CCl_4} 3.63 (double doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.36 (broad bands, doublet, J = 10 cps, 1 H), 5.9 (singlet, 2 H), 6.2 (broad singlet, 1 H), 8.2 (singlet, 3 H), 8.98 (doublet, J = 7 cps, 3 H), 7.2–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.14; H, 10.59.

p-Menth-4(8)-ene-3,9-diol (X).—Lithium aluminum hydride (0.5 g) was added to a well-stirred solution of lactone VI (2 g) in ethyl ether (20 ml) at 0° under nitrogen. Stirring was maintained for 10 hr while the mixture was warmed slowly to room temperature. After the usual work-up procedure, a colorless, thick oil (1.8 g) was obtained which failed to crystallize from *n*-hexane after standing several days in the refrigerator. Features of the nmr spectrum of this compound pointed to structure of diol X: τ_{CCl_4} 5.3–6 (broad band), 8.25 (singlet), and 8.95 (doublet). Dinitrobenzoylation by the conventional procedure gave a thick brown oil (4.3 g) which upon repeated crystallization with acetone afforded a bis-3,5-dinitrobenzoate (0.3 g): mp 133–134.5°; τ_{CDCl_3} 0.95 (multiplet), 3.55 (broad band), 4.5 (doublet, J = 12 cps), 4.85 (doublet, J = 12 cps), 7.2–7.9 (broad band), 8.03 (singlet), 8.63 (doublet, J = 4 cps), 8.9 (doublet, J = 4 cps).

Anal. Calcd for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.44; H, 3.92; N, 9.79.

Keto Acid XI and Lactol XII.—A solution of lactone VI (3.6 g) in 25% methanolic potassium hydroxide (36 ml) was refluxed 2 hr under nitrogen atmosphere. The solution was diluted with water and extracted with ethyl ether. The aqueous layer was acidified with 6 *N* hydrochloric acid and extracted with ethyl ether to give after the usual treatment a yellow oil (3.4 g) which crystallized upon cooling. Methylation of this product with diazomethane ethyl ether solution and glpc analysis on a 20 ft × 0.375 in. 20% XF-1150 on Chromosorb W column at 190° revealed the presence of three main components in a 26:62:12 ratio. Recrystallization with benzene–hexane afforded a mixture of crystals, mp 85–105° (0.5 g), which, after three new recrystallizations, gave pure lactol XII (0.1 g): mp 123–124; λ_{max}^{KBr} 2.95, 5.73, 9.3, 10.5, 10.65, 12.05, 12.4, and 13.65 μ; τ_{CCl_4} 4.3 (broad singlet, 1 H), 8.8 (doublet, J = 6 cps, 3 H), 9.05 (doublet, J = 6 cps, 3 H), 7.2–8.6 (multiplet, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.13; H, 9.01.

From the first mother liquors a new crop of crystals (0.6 g), mp 75–95°, was obtained, which by repeated crystallization from benzene–hexane afforded keto acid XI: mp 110–112°; λ_{max}^{KBr} 3–4.25 (broad), 5.9, 7.78, 7.85, 8.03, 8.15, 8.4, and 10.65 μ; τ_{CCl_4} 0.9 (broad absorption, 1 H), 8.8 (doublet, J = 7 cps, 3 H), 8.93 (doublet, J = 4 cps, 3 H); $\tau_{CCl_4-C_6H_6}$ 8.85 (doublet, J = 7 cps), 9.05 (doublet, J = 4 cps), 7.2–8.7 (broad absorption, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.15; H, 8.47.

Glpc analysis of the methylated keto acid under the conditions described above gave a single band identified by peak enhancement as the major component (62%) of the original oil. On the other hand, application of the same method to lactol XII gave puzzling results not consistent with the spectral data. Under the conditions described, the methylated lactol exhibited two bands in a similar ratio which corresponded to the two major products of the starting mixture (26 and 62%).

Registry No.—IV, 16434-34-7; V, 16434-35-8; VI, 16434-36-9; VII, 16434-37-0; VIII, 16434-38-1; dinitrobenzoate of VIII, 16434-39-2; IX, 16452-31-6; dinitrobenzoate of IX, 16434-40-5; X, 16434-41-6; XI, 16434-42-7; XII, 16434-43-8; $C_{16}H_{26}NO_3Cl$, 16450-58-1.

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The Synthesis of 2- and 4-Fluoroestradiol[1]

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The 2- and 4-fluoro isomers of estradiol, which were of interest in the National Institutes of Health cancer program, have been synthesized by an unambiguous route *via* a Schiemann type of reaction from the respective amino precursors; the preparation of these as well as the consecutive steps is described below. A remarkably easy formation of a steroid nitrite ester and its decomposition to the corresponding ketone at low temperatures (15–25°) is reported. A striking difference in the intensities of the ultraviolet spectra enables a facile differentiation of the 2- from the 4-substituted series.

The synthesis of the 2- and 4-fluoroestradiol (2- and 4-fluoro-1,3,5(10)-estratriene-3,17β-diol, VIIa and b) was undertaken for the cancer program of the Cancer Chemotherapy National Service Center of the National Institutes of Health.[1,2] The 4-fluoro isomer had been prepared earlier by Neeman and Osawa[3] *via* a lengthy route starting with 19-nortestosterone. This route, however, was inapplicable to the preparation of the 2 isomer and for the 4 isomer the present route appears also to be the preferred one. Our initial attempts to introduce the fluorine by an unpublished procedure[4] requiring ultraviolet irradiation of the pertinent diazotized aminoestradiol 3-methyl ethers in a mixture of anhydrous hydrogen fluoride and dioxane in the presence of a copper powder catalyst were unsuccessful. The melting points reported in this procedure, which were the only physical data given, differed markedly (30–50°) from those found in this laboratory. On the other hand, our physical data for the 4 isomer agree fully with those reported by Neeman and Osawa.

We adopted the Schiemann reaction for the introduction of the fluorine into the aromatic ring., *i.e.*, thermal decomposition of the solid estrone 2- and 4-diazonium fluoroborate salts. For reasons explained below estrone was used as a starting material rather than estradiol and was nitrated with 1 equiv of nitric

(1) Supported by Contract No. PH-43-62-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

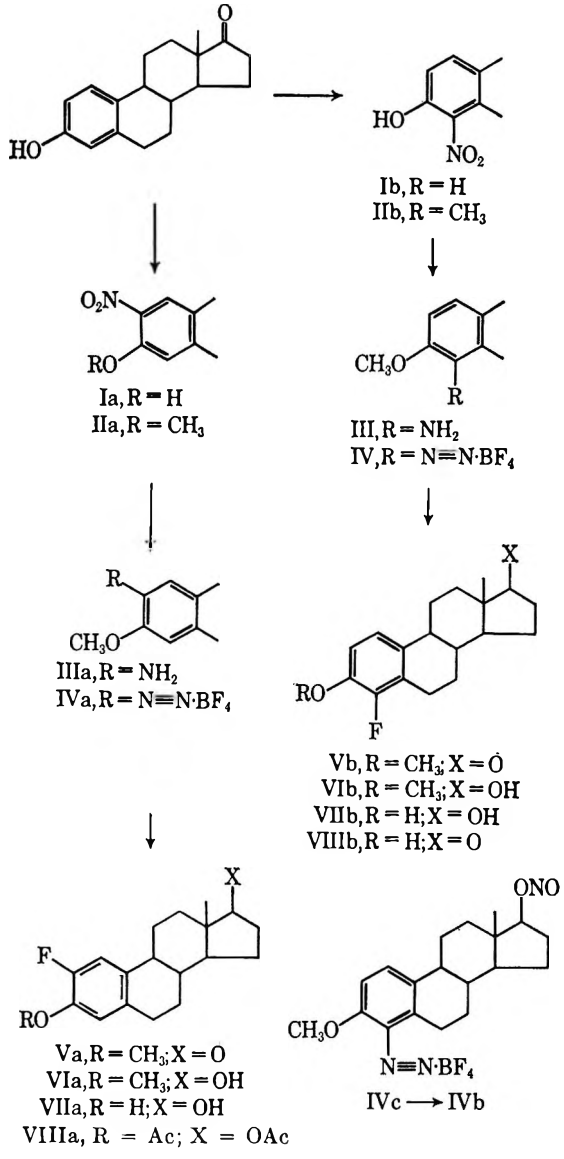
(2) Both 2- and 4-fluoroestradiol were found active in anti-implantation and estrogen tests (30 and 140% of estradiol, respectively) in the laboratories of Dr. J. R. Brooks and Dr. D. J. Patanelli of the Merck Institute for Therapeutic Research, Rahway, N. J. The uterotropic results were confirmed in the laboratories of the National Institutes of Health, Bethesda, Md., while at higher doses (*i.e.*, ten times) both epimers exhibited androgenic activities. With respect to cancer, no information has as yet been received by us from the National Institutes of Health.

(3) N. Neeman and Y. Osawa, *Tetrahedron Lett.*, **28**, 1987 (1963).

(4) This procedure was made available to us through the Cancer Chemotherapy National Service Center, Bethesda, Md. A mixture from this source was purified by thin layer chromatography and tested biologically by E. Hecker and G. Farthofer-Boeckh, *Biochem. Z.*, **338**, 1628 (1963).

acid, essentially as described by Werbin and Holoway.[5] The two isomers (Ia and b) were easily separated owing to the greater solubility of the 2-nitro isomer and obtained in about equal yield, 40% of the 4- and 37% of the 2-nitro isomer, which with dimethyl sulfate and dilute alkali[6] gave the methyl ethers (IIa and b) in 91 and 76% yield, respectively. Nuclear magnetic resonance spectra for these isomers showed two singlets at τ 2.17 and 3.18 in one case (IIa) and a pair of doublets at τ 2.55, 2.70 and 3.05, 3.20 (J = 9 cps) in the other (IIb), consistent with substitution of the 2 and the 4 positions, respectively. These assignments agree with those of Werbin and Holoway, which were arrived at by means of ultraviolet and infrared spectroscopy, as opposed to assignments by Niederl and Vogel[7] as well as Hillmann-Elies and coworkers.[8] Hydrogenation of the nitro isomers over Raney nickel gave good yields, 79% in each instance, of the two amino derivatives (IIIa and b) having physical properties similar to those reported by Kraychy, who prepared the same amines by another method.[6,9] They were diazotized in aqueous fluoroboric acid to yield the corresponding 2- or 4-diazonium fluoroborate (IVa and b) as solid yellow salts in 75 and 86% yield, respectively. Thermal decomposition of these salts at 130–135° under vacuum and in the presence of copper powder, serving both as catalyst and heat transfer agent, permitted isolation of the respective fluoro derivatives (Va and b) as sublimates, yielding 35% in both cases after chromatography. Reduction with sodium borohydride in tetrahydrofuran gave the respective 17β-carbinols (VIa and b) in nearly quantitative yields. Cleavage of the methyl ethers with pyridine hydrochloride yielded the desired 2- and the 4-fluoroestradiol (VIIa and b) in yields of 35 and 39%, respectively.[10] The 2 isomer was contaminated with a little estradiol, apparently formed during one of the latter steps, requiring separation *via* the diacetate (VIIIa). The previous assignment of structures to the nitro derivatives was confirmed by the proton magnetic resonance spectra of the fluoroestradiols. The appearance in the aromatic region of one spectrum (VIIa) of two doublets at τ 2.91, 3.13 and 3.24, 3.40 (J = 13 and 9.5 cps) indicated that the fluorine was located on carbon 2, since the pattern is characteristic for *ortho* and *meta* proton–fluorine coupling. The location of the fluorine at carbon 4 of the other isomer (VIIb) was arrived at by inference, the spectrum showing an aromatic multiplet centered at approximately τ 3.15. All other physical data were in accord with these structural assignments for the final products as well as the intermediates.

When initially estradiol was employed as the starting material, in a reaction sequence equivalent to the route described above, the diazotization reaction on the 4-aminoestradiol 3-methyl ether gave no solid fluoroborate salt but dark oils only. However, when a 1 mol excess of sodium nitrite was used, a yellow solid was rapidly formed. It was identified as the 17β-nitrite ester of the diazonium fluoroborate salt of estradiol methyl ether (IVc), the mode of formation and its behavior substantiating the structure. The product was very unstable and decomposed to the corresponding 17-ketone (IVb) on standing over several days at 20–



25° or at an accelerated rate at elevated temperatures. If left in the original reaction mixture, the product decomposed much faster; after stirring at 15–25° for 1 hr, the ketone was isolated directly, in yields of 60–85%. Heating under vacuum to 130° in the presence of copper powder gave the 4-fluoroestrone methyl ether (Vb), identical with the product obtained *via* the above-described route from estrone. The general utility of these reactions for preparative use are presently being looked into, particularly with a view toward a convenient way of preparing steroid nitrites and/or a mild method for oxidizing secondary alcohols, etc. Previously Coe and Doumani[11] prepared the *t*-butyl nitrite in the presence of aqueous sulfuric acid and decomposed it photochemically to acetone and nitro-

(5) H. Werbin and C. Holoway, *J. Biol. Chem.*, **223**, 651 (1956).

(6) S. Kraychy, *J. Amer. Chem. Soc.*, **81**, 1702 (1959); methanol was replaced with tetrahydrofuran as solvent.

(7) J. B. Niederl and H. J. Vogel, *ibid.*, **71**, 3566 (1949).

(8) E. A. Hillmann-Elies, G. Hillmann, and U. Schiedt, *Z. Naturforsch., B*, **8b**, 436 (1953).

(9) S. Kraychy and T. F. Gallagher, *J. Amer. Chem. Soc.*, **79**, 754 (1957); *J. Biol. Chem.*, **229**, 519 (1957).

(10) Reversal of the order of these two last steps gave a lesser over-all yield (20%); a small amount of 4-fluoroestrone (VIIIb) was thus prepared.

(11) C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.*, **70**, 1516 (1948).

somethane. Barton and coworkers[12,13] prepared steroid nitrites with nitrosyl chloride in pyridine and subjected them to photolysis, causing rearrangements to the corresponding hydroxamic acids. They also briefly mentioned pyrolysis at high temperatures (160–300°?) of two steroid nitrites to a mixture of the corresponding ketones and alcohols; few experimental details and no yields were given.[14] In our case the ease of both the nitrite ester and the ketone formation was quite remarkable, the latter taking place at room temperature with or without isolation of the ester.[15] It is not yet clear if this facility is due to the particular conditions in the reaction mixture, such as an influence of the fluoroboric acid on the rate of decomposition, or due to some long-range effects from the diazonium fluoroborate group (over eight carbon atoms) or intermolecular phenomena, in either case interesting aspects.

It is noteworthy that in these series the ultraviolet absorption intensities of the 2-substituted steroids are considerably higher, mostly about two to four times, than those of the 4 isomers. This is true for all members of the two series, regardless of the electronic nature of the substituents, *i.e.*, whether they are electron-withdrawing or -donating groups. There are also minor variations in the wavelengths and some additional bands in the 2-substituted series, while in base the differences are largely eliminated. Table I illustrates

TABLE I
ULTRAVIOLET ABSORPTION INTENSITIES OF 2- AND 4-SUBSTITUTED ESTRONES AND ESTRADIOLS (IN METHANOL)

	4 substituted[a]	2 substituted[b]
I (NO_2)	ϵ_{275} 1700 (ϵ_{217} 11,000)	ϵ_{284} 6800 (ϵ_{216} 17,200)
I in base	ϵ_{288} 4480 (ϵ_{240} 15,400)	ϵ_{287} 5100 (ϵ_{233} 18,700)
II (NO_2)	ϵ_{275} 1525	ϵ_{275} 4400 (ϵ_{339} 3,070)
III (NH_2)	ϵ_{287} 2770	ϵ_{296} 4380 (ϵ_{237} 6,800)
V (F)	ϵ_{274} 1410	ϵ_{277} 2470
VI (F)	ϵ_{273} 1240	ϵ_{277} 2780
VII (F)	ϵ_{277} 1280	ϵ_{280} 2810
VII in base	ϵ_{290} 2300 (ϵ_{238} 9,700)	ϵ_{296} 3720 (ϵ_{237} 9,050)
VIII (F)	ϵ_{277} 1420 (ϵ_{217} 8,150)	

[a] b series. [b] a series.

this phenomenon and could serve to identify and distinguish between 2- and 4-substituted isomers of 1,3,5(10)-estratrienes.[16]

Experimental Section

Melting points were taken on a calibrated Thomas–Hoover Unimelt apparatus. Ultraviolet spectra were run on a Cary 11 spectrophotometer, infrared spectra on a Perkin-Elmer 421 grating spectrophotometer, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer. Chemical shifts are reported in τ values relative to tetramethylsilane. Optical rotations were measured on a Zeiss precision polarimeter.

2-Nitroestrone (Ia) and 4-nitroestrone (Ib) were prepared essentially as described by Werbin and Holoway.[5] Nitration of estrone in acetic acid with 1 mol of concentrated nitric acid gave about equal amounts of each isomer, 37 and 40%, respectively. During the work-up the 4 isomer separated directly in nearly pure form whereas the more soluble 2 isomer was obtained from the mother liquors. Chromatography on alumina (Merck) with chloroform gave the pure 4 isomer (Ib), mp 274–280° (lit.[5,7] 270–280°, 258°), λ_{max}^{MeOH} 275 mμ (ϵ 1700) [lit.[5] 278 mμ (ϵ 1720)], and the pure 2 isomer (Ia), mp 179–183° (lit.[5,8] 183–184°, 155°), λ_{max}^{MeOH} 284 (ϵ 6800) and 216 mμ (ϵ 17,200) [lit.[5] 293 mμ (ϵ 8220)]. The infrared spectra were as expected for both isomers. Nuclear magnetic resonance data on the methylated derivatives below supported the structural assignments of Werbin and Holoway[5] and disagreed with those of Niederl and Vogel[7] and of Hillmann-Elies and coworkers.[8]

2- and 4-Nitroestrone Methyl Ether (IIa and b).—Methylation with dimethyl sulfate and dilute alkali in tetrahydrofuran in the usual manner[6] gave the 2- and 4-nitroestrone methyl ethers in 91 and 76% yields, respectively. The 2 isomer (IIa) showed mp 163–166° (lit.[6] 147°; 157–159°), λ_{max}^{MeOH} 275 (ϵ 4400) and 339 mμ (ϵ 3070) [lit.[6] 272.5 (ϵ 4510) and 336 mμ (ϵ 3130)]; the 4 isomer (IIb) showed mp 253–256° (lit.[6] 261–261.5°), λ_{max}^{MeOH} 275 mμ (ϵ 1525) [lit.[6] 275.5 mμ (ϵ 1570)]. The infrared spectra were as expected for both epimers.

The nuclear magnetic resonance spectra (in deuteriochloroform) of the two isomers showed in addition to the common features of peaks at τ 9.08 (18-CH_3) and 6.07 or 6.13 (CH_3O–) also two singlets at τ 2.17 and 3.18 in one case (IIa) and a pair of doublets at τ 2.55, 2.70 and 3.05, 3.20 in the other (IIb) (J = 9 cps), consistent with substitution of the 2 position and the 4 position, respectively.

2-Aminoestrone Methyl Ether (IIIa).—2-Nitroestrone methyl ether (IIa, 20 g) was hydrogenated in 2.4 l. of absolute ethanol over 9 g of Raney nickel (W-2) catalyst at 25° and an initial pressure of 40 psi, until the theoretical amount of hydrogen was absorbed. The catalyst was removed, the filtrate concentrated to dryness under vacuum and the residue recrystallized from methanol to yield 15 g (79%) of 2-aminoestrone methyl ether (IIIa), mp 170–173° (lit.[6] 172–174°). The product showed a single spot on a thin layer chromatogram (alumina–benzene), λ_{max}^{MeOH} 237 (ϵ 6800) and 296 mμ (ϵ 4380) [lit.[6] 239 (ϵ 6980) and 295.5 mμ (ϵ 4480)]. The infrared spectrum was consistent with the structure IIIa exhibiting bands at 3450, 3370 (N–H), 1725 (17-C=O), 1610, 1585, 1580 (Ph), 1260, 1280 cm^{-1} (OCH_3).

Estrone Methyl Ether 2-Diazonium Fluoroborate (IVa).—A suspension of 25 g of 2-aminoestrone methyl ether (IIIa) in a mixture of 100 ml of tetrahydrofuran, 20 ml of dioxane, and 125 ml of 48% aqueous fluoroboric acid was chilled to 0° to −5°. A solution of 12.5 g of sodium nitrite in 40 ml of cold water was added dropwise over 5 min to the vigorously stirred mixture while maintaining the above temperature. Stirring the slurry at 0 to 10° for 1 hr gave a reddish colored solution from which, upon dilution with 1.3 l. of cold water, the yellow diazonium fluoroborate salt precipitated. This was stirred for 1 hr at 0°, filtered off and washed with cold water, sucked as dry as possible, washed with ether, and dried under vacuum to yield 25 g (75%) of estrone methyl ether 2-diazonium fluoroborate (IVa), mp 160–165° dec. The infrared spectrum was consistent with the assigned structure IVa, exhibiting bands at 2230 (N≡N), 1735 (17-C=O), 1600, 1550, 1490 (Ph), 1280 (OCH_3), and 1050–1080 (br) cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{23}O_2N_2BF_4$ (398.20): C, 57.40; H, 5.81; N, 7.03; F, 19.08. Found: C, 57.00; H, 5.70; N, 6.90; F, 18.60.[17]

2-Fluoroestrone Methyl Ether (Va).—A mixture of 17 g of estrone methyl ether 2-diazonium fluoroborate (IVa) and 17 g of copper powder (Martin Marietta Corp.) was spread in a thin layer in a sublimation apparatus (diameter of the pot, 13 cm). The diazonium salt was decomposed under vacuum (0.2 mm) by increasing the oil-bath temperature slowly to 130–135° over a

(12) C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, and D. H. R. Barton, *Tetrahedron*, **21**, 743 (1965); see also *J. Amer. Chem. Soc.*, **83**, 1771 (1961).

(13) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **83**, 4076 (1961).

(14) After our article was first submitted a report by D. H. R. Barton, G. C. Ramsay, and D. Wege appeared in *J. Chem. Soc.*, 1915 (1967), describing the use of primary nitrites, prepared according to the method of Coe and Doumani,[11] in photolysis and pyrolysis reactions at 300 ± 10°. One steroidal nitrite was also converted at 132° in solution to the corresponding ketone and alcohol; no yields were given.

(15) This work was actually done in early 1965 and reported in the "Quarterly Progress Reports to the Cancer Chemotherapy National Service Center," Merck Sharp & Dohme Research Laboratories, Rahway, N. J., No. 30, 1965, p 11, and No. 31, 1965, p 12.

(16) This information was used advantageously in a forthcoming publication (*J. Org. Chem.*, in press) from this laboratory on the synthesis of 2- and 4-bromoestradiol suggesting that a previous preparation in the literature was impure or possibly not the desired isomers.

(17) The elemental analyses of this and the two following diazonium fluoroborates (IVb and c) are as good as can reasonably be expected for a direct precipitate that was not at all purified.

period of 1 hr, kept at this temperature for 2 hr, and finally increased to 170° for 3 hr. During this period some white solid and a red by-product sublimed onto the sides of the still. After cooling, the solids were dissolved in chloroform and filtered, and the filtrate was concentrated to dryness to yield 16 g of a dark amorphous solid. This material was stirred for 10 min in 125 ml of benzene and filtered to remove some tarry material; the filtrate was concentrated to dryness to yield 10 g of dark product. Chromatography on 300 g of acid-washed alumina (Merck) and elution with benzene yielded 4.5 g (35%) of 2-fluoroestrone methyl ether (Va), mp 125–128°, $[\alpha]^{25}D$ +69° (*c* 1, chloroform). Thin layer chromatography (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 2470). The infrared spectrum was consistent with the structure Va showing bands at 1735 (17-C=O), 1610–1620, 1590–1510 (Ph), and 1270 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{23}O_2F$ (302.39): C, 75.50; H, 7.65; F, 6.28. Found: C, 75.25; H, 7.70; F, 5.96.

2-Fluoroestradiol 3-Methyl Ether (VIa).—A solution of 11 g of 2-fluoroestrone methyl ether (Va) in 240 ml of tetrahydrofuran was chilled to 0–5° and treated with a solution of 4 g of sodium borohydride in 50 ml of cold methanol at 0–5° for 30 min. The solution was acidified by the cautious addition of 40 ml of cold 4 *N* hydrochloric acid, during which time the product precipitated. Most of the organic solvents were removed under vacuum on a water bath, 500 ml of water was added, and the mixture was stirred at 0–5° for 1 hr. The white 2-fluoroestradiol 3-methyl ether (VIa) was washed to neutrality with water and recrystallized from methanol to yield 10 g (90%), mp 84–86°, $[\alpha]^{25}D$ +61° (*c* 1, chloroform). A thin layer chromatogram (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 2780). The infrared spectrum was consistent with the structure VIa, with bands at 3000–3650 (OH), 1580–1620, 1500 (Ph), and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{25}O_2F$ (304.40): C, 75.01; H, 8.16; F, 6.24. Found: C, 74.80; H, 7.90; F, 5.93.

2-Fluoroestradiol (VIIa).—2-Fluoroestradiol 3-methyl ether (VIa, 10g) was mixed thoroughly with 100 g of pyridine hydrochloride in a glass vial and heated in a steel bomb to 180° for 4 hr. After cooling, the residue was treated with 0.1 *N* hydrochloric acid and extracted with ether, and the combined extracts were washed with 0.1 *N* hydrochloric acid and water. The ether layer was extracted four times with 250-ml portions of 1 *N* potassium hydroxide, the combined alkaline extracts were washed with ether and acidified with concentrated hydrochloric acid, and the organic material was extracted with chloroform. The combined extracts were washed to neutrality with water and concentrated to dryness under vacuum yielding 8 g of crude 2-fluoroestradiol. Recrystallization from methanol and treatment with charcoal gave 6.0 g of crystalline product, mp 170–173°. Phase solubility analysis and thin layer chromatograms on both alumina or silica gel (chloroform) showed a single component; however, two spots were visible on cellulose (ethylene glycol–benzene). The close physical similarities of the two components required their separation as the diacetates. Thus, 3.5 g of this material was treated with 14 ml of pyridine and 14 ml of acetic anhydride at 25° overnight. Addition of 500 ml of cold water, stirring for 2 hr, and washing with water yielded 4 g of diacetate, mp 95–105°. (A thin layer chromatogram showed the impurity to be the more polar estradiol diacetate.) This material was chromatographed on 120 g of silica gel (Baker); elution with benzene yielded 2.6 g (58%) of pure 2-fluoroestradiol 3,17-diacetate (VIIIa), mp 118–120°. A thin layer chromatogram (silica gel–benzene) now showed a single spot. The infrared spectrum (in Nujol) was consistent with the diacetate structure, as was a hydrolytic acetyl determination. The diacetate was hydrolyzed in 25 ml of methanol and 8 ml of water with a solution of 1.25 g of potassium hydroxide in 15 ml of methanol by stirring at 25° under nitrogen. The steroid dissolved within 5 min while the reaction mixture was stirred for 8 hr to ensure complete hydrolysis, then was neutralized with acetic acid and concentrated under vacuum on a water bath to remove most of the organic solvent. Water (50 ml) was added, the mixture was stirred at 0–5° for 1 hr, and the solids were washed with water to give 2.1 g of product. Sublimation at 180° (50 μ) gave 1.9 g (35%) of pure 2-fluoroestradiol (VIIa), mp 173–175°, $[\alpha]^{25}D$ +76° (*c* 1, methanol). A thin layer chromatogram (cellulose–ethylene glycol–benzene) showed a single spot; uv, λ_{max}^{MeOH} 280 mμ (ε 2810), in base 296 mμ (ε 3720) and 237 (9050). The infrared spectrum (in Nujol) exhibited bands at 3100, 3350–3400, 3550–3600 (OH), 1610, 1590, 1500 cm^{-1} (Ph). The nuclear magnetic resonance spectrum (in deuterioacetone) was consistent with the assigned structure VIIa, with peaks at τ 9.22 (18-CH_3), 6.30 (17-OH), and two doublets at 2.91, 3.13 and 3.24, 3.40 (J = 13 and 9.5 cps). The latter pattern is characteristic for *ortho* and *meta* proton–fluorine coupling respectively, indicating that the fluorine was located on carbon 2.

Anal. Calcd for $C_{18}H_{23}O_2F$ (290.38): C, 74.45; H, 7.98; F, 6.54. Found: C, 74.42; H, 8.08; F, 6.32.

4-Aminoestrone Methyl Ether (IIb).—4-Nitroestrone methyl ether (IIb, 20 g) was hydrogenated as described for the 2 isomer (IIIa) and the residue recrystallized from methanol, yielding 15 g (79%) of 4-aminoestrone methyl ether (IIIb), mp 173–175° (lit.[6] 188–191°). Thin layer chromatography (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 287 mμ (ε 2770) [lit.[6] 287.5 mμ (ε 2820)]. The infrared spectrum was consistent with the structure IIIb, with bands at 3400, 3450 (N–H), 1730 (17-C=O), 1600 (NH_2), and 1560, 1480 cm^{-1} (Ph).

Estrone Methyl Ether 4-Diazonium Fluoroborate (IVb).—A suspension of 20 g of 4-aminoestrone methyl ether (IIIb) in a mixture of 40 ml of dioxane and 80 ml of 48% aqueous fluoroboric acid was diazotized as described for the 2 isomer (IVa), yielding 23 g (86%) of estrone methyl ether 4-diazonium fluoroborate (IVb), mp 160–165° dec. The infrared spectrum was consistent with the structure IVb, with bands at 2230 (N≡N), 1735 (17-C=O), 1600, 1550, 1490 (Ph), 1280 (OCH_3) and 1050–1080 (br) cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{23}O_2N_2BF_4$ (398.20): C, 57.40; H, 5.81; N, 7.03; F, 19.08. Found: C, 57.33; H, 5.81; N, 7.02; F, 18.50.[17]

4-Fluoroestrone Methyl Ether (Vb).—A mixture of 17 g of estrone methyl ether 4-diazonium fluoroborate (IVb) and 17 g of copper powder was treated in the same manner as the 2 isomer (Va), to yield 4.5 g (35%) of pure 4-fluoroestrone methyl ether (Vb), mp 160–163°, $[\alpha]^{25}D$ +132° (*c* 1, chloroform). Thin layer chromatography (alumina–benzene) showed a single spot, uv, λ_{max}^{MeOH} 274 mμ (ε 1410). The infrared spectrum was consistent with the structure Vb, with bands at 1730 (17-C=O), 1600–1620, 1590 (Ph), and 1280 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{23}O_2F$ (302.39): C, 75.50; H, 7.65; F, 6.28. Found: C, 75.45; H, 7.87; F, 5.95.

4-Fluoroestradiol 3-Methyl Ether (VIb).—To a solution of 8 g of 4-fluoroestrone methyl ether (Vb) in 160 ml of tetrahydrofuran chilled to 0–5° was added 4 g of sodium borohydride dissolved in 50 ml of cold methanol, as described for the 2-fluoro isomer (VIa). The 4-fluoroestradiol 3-methyl ether (VIb) was recrystallized from methanol to yield 7.2 g (90%), mp 135–138°, $[\alpha]^{25}D$ +75° (*c* 1, chloroform). A thin layer chromatogram (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 273 mμ (ε 1240). The infrared spectrum was consistent with the structure VIb, with bands at 3600, 3450 (OH), 1600–1620, 1500 (Ph), and 1290 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{23}O_2F$ (304.40): C, 75.01; H, 8.16; F, 6.24. Found: C, 74.83; H, 8.00; F, 5.95.

4-Fluoroestradiol (VIIb).—4-Fluoroestradiol 3-methyl ether (VIb, 8 g) was mixed with 80 g of pyridine hydrochloride and treated as described for the 2-fluoro isomer (VIIa), yielding 7 g of material. Recrystallization from methanol gave 3.0 g (39%) of pure 4-fluoroestradiol (VIIb), mp 189–191° (lit.[3] mp 190–191°), $[\alpha]^{25}D$ +70.8° (*c* 1, methanol). A thin layer chromatogram (alumina–chloroform) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 1280) [lit.[3] 274 mμ (ε 1210)], in base 290 mμ (ε 2300) and 238 (9700) [lit.[3] 292 mμ (ε 2340)]. The infrared spectrum (in Nujol) showed bands at 3200–3500 (OH), 1610, 1580, 1490 cm^{-1} (Ph). The nuclear magnetic resonance spectrum (in deuterioacetone) was consistent with the assigned structure VIIb, with peaks at τ 9.23 (18-CH_3), 6.30 (17-OH), and an aromatic multiplet extending from 2.97 to 3.40, centered at approximately 3.15.

Anal. Calcd for $C_{18}H_{23}O_8F$ (290.38): C, 74.45; H, 7.98; F, 6.54; C, 74.50; H, 7.91; F, 6.54.

Estradiol 3-Methyl Ether 4-Diazonium Fluoroborate 17β-Nitrite Ester (IVc).—To a solution of 5 g of 4-aminoestradiol 3-methyl ether in a chilled mixture of 8 ml of dioxane and 8 ml of 48% aqueous fluoroboric acid was added dropwise 2.5 g of sodium nitrite in 3 ml of cold water over 5 min while maintaining the temperature at 0–5°. The yellow precipitate which formed was filtered off after stirring for 10 min at 0–5°, washed with cold water, sucked as dry as possible, and washed with ether. The product, weighing 5 g (67%), was shown to be the estradiol 3-methyl ether 4-diazonium fluoroborate 17β-nitrite ester (IVc),

as also suggested by its mode of formation and behavior. The infrared spectrum (in Nujol) was consistent with this structure, showing bands at 1650 (-ONO_2 or ONO), 2280 (N≡N), 1610, 1580, 1500 (Ph), 1020–1090 cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{24}O_3N_3BF_4$ (429.22): C, 49.50; H, 5.22; N, 9.10; F, 16.45. Found: C, 50.54; H, 5.17; N, 9.47; F, 17.05.[17]

The product was very unstable and decomposed rapidly without melting at about 120°, giving off a brown gas, while standing at 20–25° for several days gave a pale yellow solid, identified as the estrone 3-methyl ether 4-diazonium fluoroborate (IVb). In experiments where the initial precipitate of the diazonium fluoroborate nitrite ester was left stirring in the original reaction mixture for 1 hr at 15–25°, good yields (60–85%) of the 17-ketone (IVb) were obtained directly.[18] This could be converted into the 4-fluoroestrone methyl ether (Vb), as described above in 33% yield.

4-Fluoroestrone (VIIIb).—4-Fluoroestrone methyl ether (Vb, 500 mg) was mixed thoroughly with 5 g of pyridine hydrochloride and treated as described for the 4-fluoroestradiol methyl ether (VIb), yielding 100 mg (21%) of 4-fluoroestrone (VIIIb), mp 223–225°, $[\alpha]^{25}D$ +144° (*c* 1, chloroform). A thin layer chromatogram (alumina–chloroform) showed a single spot; uv, λ_{max}^{MeOH} 277.5 mμ (ε 1420) and 217 (8150). The infrared spectrum (in Nujol) was consistent with the structure VIIIb, with bands at 3200–3500 (OH), 1610, 1580, 1490 (Ph), 1730 cm^{-1} (17-C=O).

Anal. Calcd for $C_{18}H_{21}O_2F$ (288.37): C, 75.00; H, 7.33; F, 6.59. Found: C, 74.90; H, 7.40; F, 6.50.

Registry No.—Ia, 5976-73-8; Ib, 5976-74-9; IIa, 16223-65-7; IIb, 14846-62-9; IIIa, 13010-22-5; IIIb, 13010-21-4; IVa, 16222-59-6; IVb, 15091-55-1; IVc, 16222-60-9; Va, 16205-28-0; Vb, 16205-29-1; VIa, 16205-30-4; VIb, 16205-31-5; VIIa, 16205-32-6; VIIb, 1881-37-4; VIIIa, 16205-34-8; VIIIb, 1881-36-3.

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(18) NOTE ADDED IN PROOF.—Subsequently this procedure was improved upon by filtering off the nitrite ester (IVc) and re-treating it with the original volumes of dioxane and aqueous fluoroboric acid at about 20°. After the evolution of gas had subsided, the estrone 3-methyl ether 4-diazonium fluoroborate (IVb) crystallized from the cooled (0°) reddish solution in 90% yield. This high yield indicates that this reaction proceeds by a mechanism quite different from the one suggested by Barton and coworkers[12-14] or authors cited by Barton, for the thermal decomposition of nitrite esters. Their mechanism requires the formation of equal amounts of ketone and the corresponding carbinol *via* an over-all disproportionation reaction, whereas we found no such alcohol. It is hoped that this subject can be expanded upon

$$2R_2CHO—N=O \longrightarrow R_2C=O + R_2CHOH + 2NO$$

in a planned forthcoming publication on low temperature decomposition of nitrite esters.

Synthesis of Optically Active 1-C-Phenylglycerols and Their Derivatives[1a]

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Addition of phenylmetallic reagents to 1,2-*O*-isopropylidene-D-glyceraldehyde leading to the formation of optically pure D-*erythro*- and D-*threo*-1-*C*-phenylglycerol was investigated. Oxidation of the newly formed hydroxyl group in the addition products by Moffatt's reagent gave the expected ketone, which was reduced by $LiAlD_4$ to yield a pair of optically active diastereomers, 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol-1-d_1 and 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol-1-d_1. The absolute configuration of the phenylglycerols and their derivatives was established by conversion into compounds of known configuration and supported by infrared and nuclear magnetic resonance (nmr) spectrometric studies. The complex nmr splitting patterns of the 1-*C*-phenylglycerols and their acyclic derivatives are interpretable by their resemblance to simple first-order splitting patterns.

Stereoselective addition of phenylmagnesium bromide to *aldehydro* and *keto* sugars and the determination of absolute configuration at the benzylic center was reported[2] recently. The steric difference between phenyllithium and phenylmagnesium bromide reagents was suggested as an explanation for the dramatic difference in diastereomeric product distribution, when these reagents added to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine.[3] Addition of phenylmagnesium bromide to 2,3-di-*O*-benzoyl-D-glyceraldehyde was reported to yield a single optically active product, whose absolute configuration was not firmly established, but which was identified as "dibenzoyl-α-D-phenylglycerol" by the authors.[4] In this Article, we shall describe the synthesis of optically active 1-*C*-phenylglycerols; their derivatives, including some with a deuterium atom attached to the benzylic carbon; and the assignment of absolute configuration to these compounds.

When phenyllithium or phenylmagnesium bromide was allowed to react with 2,3-*O*-isopropylidene-D-glyceraldehyde,[5] the same pair of diastereomers, 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol (1) and 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol (4), were obtained in good yield. Product analysis by glpc revealed that the phenyllithium addition gives almost the same diastereomeric distribution (62% *threo*, 38% *erythro*) as the phenylmagnesium bromide addition (58% *threo*, 42% *erythro*). The preponderant isomer in each case was the one predicted by Cram's rule of asymmetric induction.[6] Although the stereoselectivity of phenylmagnesium bromide reagent appears to be somewhat less than that observed for phenyllithium, no dramatic reversal of product distribution was noted in the course of this work, contrary to the reversal noted by Yoshimura, Ohgo, and Sato[3] for their work involving the addition of these two reagents to *N*-benzyl-2,3-*O*-

(1) (a) Presented at 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, Abstracts, p C2. (b) National Science Foundation Undergraduate Research Program Participant, Grant No. GY-817.

(2) T. D. Inch, R. V. Levy, and P. Rich, *Chem. Commun.*, 865 (1967).

(3) J. Yoshimura, Y. Ohgo, and T. Sato, *J. Amer. Chem. Soc.*, **86**, 3860 (1964).

(4) M. Tiffeneau, I. Neuberg-Rabinovitch, and H. Cahnmann, *Bull. Soc. Chim. Fr.*, [v] **2**, 1866 (1935).

(5) E. Baer and H. O. L. Fisher, *J. Biol. Chem.*, **128**, 463 (1939).

(6) (a) D. J. Cram and F. A. Abd. Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952); (b) D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963).

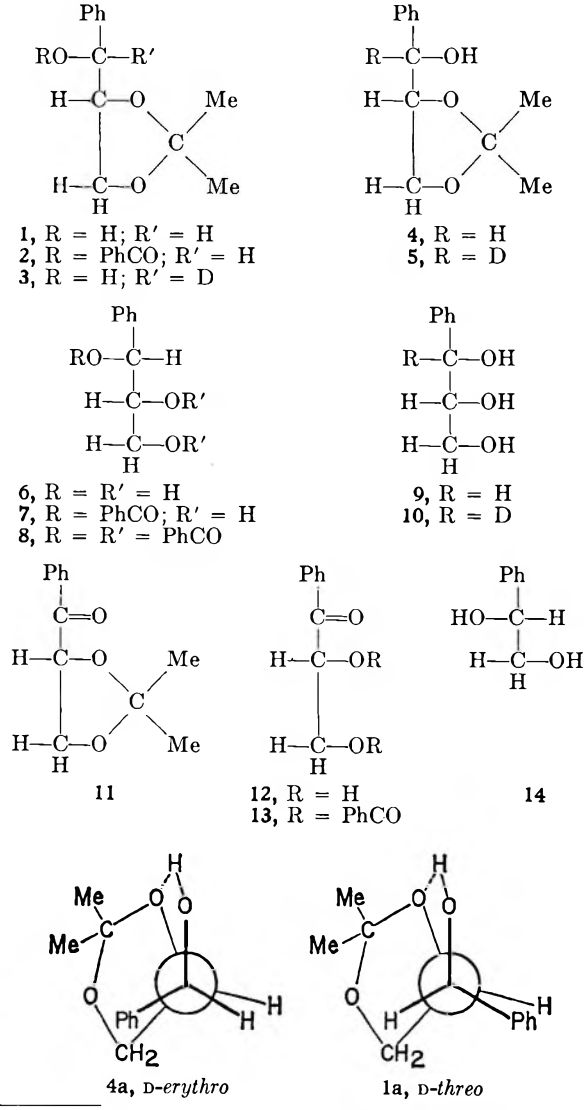
isopropylidene-D-glyceraldimine, which is a nitrogen analog of 2,3-*O*-isopropylidene-D-glyceraldehyde.

Assignment of structures to the two diastereomers was made by converting them into compounds of known configuration and supported by study of the intramolecular hydrogen bonding present in **1** and **4**. The absolute configuration of crystalline 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol (**1**, mp 74–75°) was firmly established by benzoylation to give a monobenzoate (**2**), which was hydrolyzed by dilute acid to give 1-*O*-benzoyl-D-*threo*-1-*C*-phenylglycerol (**7**). Lead tetraacetate cleavage of **7** followed by lithium aluminum hydride reduction of the cleavage product gave optically pure L-(−)-1-phenyl-1,2-ethanediol (**14**), $[\alpha]^{23}D$ −57.8°. This compound with rotation of $[\alpha]^{28}D$ −47.1° was prepared by Eliel and Delmonte[7] by hydride reduction of D-(−)-mandelic acid of 82% optical purity. Assuming that the optical purity reported by Eliel and Delmonte is correct, simple calculation indicates that the L-(−)-1-phenyl-1,2-ethanediol from the degradation study is optically pure, which, in turn, suggests that all the steps in the reaction sequence from 2,3-*O*-isopropylidene-D-glyceraldehyde to L-(−)-1-phenyl-1,2-ethanediol proceeded with complete retention of configuration. This degradation study firmly established the configuration of the benzylic carbon; hence, the configuration of **1** must be D-*threo*, since the other asymmetric carbon was of known configuration and no evidence of racemization was noted in the reaction sequence.

The structural assignment for the liquid 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol (**4**) was supported by dilute acid hydrolysis of the isopropylidene group to yield D-*erythro*-1-*C*-phenylglycerol (**9**) whose physical constants were identical with those reported for "α-D-phenylglycerol."[4] The diastereomeric relationship of **1** and **4** can be deduced from the fact that dicyclohexylcarbodiimide–dimethyl sulfoxide oxidation of **1** or a mixture of **1** and **4** yielded the same ketone (**11**). Also, lithium aluminum hydride reduction of the ketone (**11**) produced the diastereomers **1** and **4**, identical in all respects with the products obtained from the organometallic addition reactions. On the basis of acid hydrolysis, oxidation, and reduction studies described, it can be concluded that **4** must have the *erythro* configuration.

Additional support for the structural assignment of the *threo* configuration to **1** and the *erythro* configuration to **4** was obtained by an infrared spectrometric study of their intramolecular hydrogen bond strengths; in fact, tentative structural assignment was made on this basis. The Newman representation **1a** and **4a** of the diastereomers, drawn in the conformation most favorable for hydrogen bonding between the 1-hydroxyl hydrogen atom and the C-2 oxygen atom, clearly shows that in the D-*threo* isomer (**1a**) the phenyl group is aligned with a hydrogen, whereas in the D-*erythro* isomer (**4a**) the phenyl is aligned with C-3. Since repulsion between hydrogen and phenyl is less than between methylene and phenyl, the *threo* isomer provides the more favorable spatial arrangement for intramolecular hydrogen bonding. Infrared spectra of very dilute solutions of **1** and **4** in carbon tetrachloride provided $\Delta\nu$ values for the *threo* (35 cm^{-1}) and *erythro* (30 cm^{-1}) diastereomers. The frequency difference, $\Delta\nu$, is the distance (in cm^{-1}) between the free hydroxyl band and the bonded hydroxyl band. Kuhn[8] showed that a direct relationship exists between $\Delta\nu$ and the strength of the hydrogen bond; *e.g.*, he noted that a weaker hydrogen bond is formed in *meso*-butane-2,3-diol ($\Delta\nu$ = 39 cm^{-1}) than in *d*-butane-2,3-diol ($\Delta\nu$ = 45 cm^{-1}). Kuhn attributes the difference in hydrogen bond strength between these diastereomers to the fact that formation of an intramolecular hydrogen bond between the two hydroxyl groups requires a sterically unfavorable eclipsing of the two methyl groups in the *meso* isomer, whereas only hydrogen-methyl eclipsing is involved in the *d* isomer. By analogy, the crystalline diastereomer (**1**) having the larger $\Delta\nu$ value was assigned the D-*threo* configuration, since the molecule with this configuration would experience the least steric repulsion when it assumes the most favorable conformation for hydrogen bonding.

Ketone **11** was prepared by dicyclohexylcarbodiimide–dimethyl sulfoxide oxidation of either **1** or **4**. The ketone (**11**) provides a route for introducing a deuterium atom to the benzylic position of **1** and **4**. When **11** was reduced by lithium aluminum deuteride in anhydrous ether, 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenyglycerol-1-d_1 (**3**) and 2,3-*O*-isopropylidene-D-



(7) E. L. Eliel and D. Delmonte, *J. Org. Chem.*, **21**, 595 (1956).

(8) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

TABLE I
CHEMICAL SHIFTS AND COUPLING CONSTANTS 1-C-PHENYLGLYCEROLS AND DERIVATIVES

	Solvent	Chemical shifts, ppm				Coupling constants, Hz			
		H_1	H_2	H_3	$H_{3'}$	J_{12}	J_{23}	$J_{23'}$	$J_{33'}$
D-*threo*-1-*C*-Phenylglycerol (6)	D_2O	4.66	3.87	3.43	3.43	6.5	3.5	6.5	
D-*erythro*-1-*C*-Phenylglycerol (9)	D_2O	4.63	3.89	3.78	3.52	6.5	3.0	7.0	12
D-*erythro*-1-*C*-Phenylglycerol-1-d_1 (10)	D_2O		3.89	3.78	3.53		3.0	7.0	12
1,2,3-tri-*O*-Benzoyl-D-*threo*-1-*C*-phenylglycerol (8)	$DCCl_3$	6.53	6.05	4.67	4.33	7.0	4.0	5.5	12
(*R*)-α,β-Dihydroxypropiophenone (12)	$DCCl_3$		5.15	4.01	3.68		3.5	5.0	12
(*R*)-α,β-Dibenzoyloxypropiophenone (13)	$DCCl_3$		6.57	5.02	4.73		4.0	7.0	12

erythro-1-*C*-phenylglycerol-1-d_1 (**5**) were produced in the ratio of 67:33, respectively. The deuterated diastereomers have identical physical constants with their hydrogen counterparts. The nmr signals for the H_1 proton at δ 4.50 for the *threo* isomer and 4.85 for the *erythro* isomer were absent in the spectra of the deuterated isomers.

A benzene solution of the ketone (**11**) was reduced with lithium aluminum hydride to give the diastereomers **1** and **4** in the ratio of 60:40, respectively. Apparently, the product distribution is not altered drastically by the nature of the solvent. It is surprising to find that the synthesis of **1** and **4** either *via* the addition of phenyllithium or phenylmagnesium bromide to 2,3-*O*-isopropylidene-D-glyceraldehyde or *via* hydride reduction of ketone **11** favors the *threo* isomer. Cram and Allinger[9] demonstrated that the synthesis of 1,2-diphenyl-2-methyl-1-butanol *via* the addition of phenylmagnesium bromide to 2-methyl-2-phenylbutanal favored the formation of one diastereomer, whereas synthesis *via* hydride reduction of 1,2-diphenyl-2-methyl-1-butanone favored the other, which is in accordance with Cram's rule of asymmetric reduction.[6a]

Several model transition states have been proposed to help predict and correlate the addition to and the reduction of carbonyl compounds containing heteroatoms on the α position: the cyclic model,[6b] where the metal ion coordinates with the carbonyl oxygen and the heteroatom on the α position; the dipolar model,[10] where the substrate molecule assumes a conformation placing the carbonyl oxygen, and the heteroatom on the α position as far apart as possible; and the eclipsed model,[11] where the double bond of the carbonyl group eclipses the single bond of the α position giving the lowest energy transition state. After careful consideration of these model transition states, it was concluded that not one model can be chosen which could explain consistently the favored formation of **1** over **4** by both synthetic routes. Conceivably, the oxygen on C-3 may have an undetermined influence on these reactions. Since hydrogen bonding study seems to suggest that the predominating *threo* isomer (**1**) is more stable than the *erythro* isomer (**4**), perhaps, the stereoselectivity in this work is controlled by product stability, as proposed by Brown and Muzzio[12] for some acyclic ketones.

Magnetic nonequivalence resulting from molecular asymmetry was reviewed by Martin and Martin.[13] Some additional examples of nonequivalent methylene protons in nonrigid molecules were reported by Snyder.[14] The 1-*C*-phenylglycerols and their derivatives (Table I) having one or more asymmetric centers, gave complex splitting patterns. It was surprising to find, however, that the splitting pattern for all the acyclic 1-*C*-phenylglycerols and derivatives could be identified by their resemblance to first-order splitting. The values listed in Table I were obtained by the trial and error method suggested by Bible[15] and are found to match the spectra rather well; *e.g.*, see Figures 1 and 2. Correct assignment for proton resonance was aided by comparing the spectra of the phenylglycerols and the same isomers having a deuterium in place of a hydrogen at the benzylic carbon. The absence of the doublet in the δ 4.6 region (proton on C-1) and the deuterium quadrupole broadening of the multiplet at δ 3.8 (proton on C-2) in the spectra of the deuterated compound as compared to the spectra of its parent hydrogen compound permitted the assignment of the δ 4.6 region to the proton on C-1, δ 3.9 region to the proton on C-2, and δ 3.4–3.8 region to the geminal protons on C-3. It is interesting to note that the configurational difference at C-1 of the diastereomeric phenylglycerols is

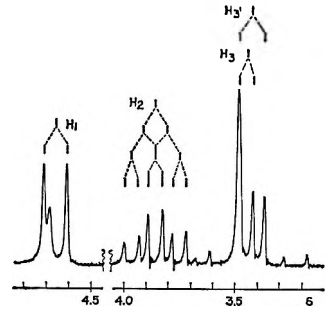


Figure 1.—A partial nmr spectrum (D_2O) at 60 MHz and the splitting pattern from first-order consideration of D-*threo*-1-*C*-phenylglycerol. The phenyl protons are not shown. Resonance peak at δ 4.7 is due to DOH.

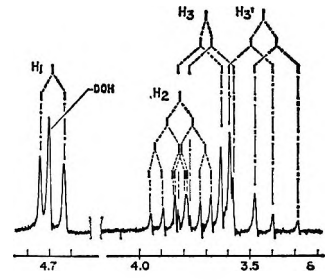


Figure 2.—A partial nmr spectrum (D_2O) at 60 MHz and the splitting pattern from first-order consideration of D-*erythro*-1-*C*-phenylglycerol. The phenyl protons are not shown.

(9) D. J. Cram and J. Allinger, *J. Amer. Chem. Soc.*, **76**, 4516 (1954).
(10) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).
(11) G. J. Karabetsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967).
(12) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).
(13) L. Martin and J. Martin, *Bull. Soc. Chim. Fr.*, 2117 (1966).
(14) E. I. Snyder, *J. Amer. Chem. Soc.*, **88**, 1155 (1966).
(15) R. H. Bible, "Interpretation of NMR Spectra—An Empirical Approach," Plenum Press, New York, N. Y., 1965.

manifested in the nmr spectra (Figures 1 and 2). The methylene region (δ ~3.4–3.8) is more complex for D-*erythro*- than for the D-*threo*-phenylglycerol. Apparently, the chemical shifts of the geminal protons of the D-*threo* isomer are very similar, thereby giving a simpler splitting pattern in comparison to the *erythro* isomer. The low intensity doublets, centered at δ 3.2 and 3.6 of the nmr spectrum for the *threo* isomer (Figure 1), could be the remnant of the outside lines for a more complex splitting pattern of the geminal protons.

Experimental Section[16]

The hydrogen bonding study was carried out in CCl_4 in a decimeter quartz cell using the Beckman IR-12 infrared spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 instrument. All rotations were obtained in a decimeter cell in a Rudolph 80 polarimeter.

Gas chromatographic analyses were carried out using an Aerograph Model 328, thermal-conductivity instrument employing a 10 ft × 0.25 in. o.d. copper column. Helium flow was kept between 80 and 100 cc/min, column temperature was 190°, and the injection port temperature was maintained at 270°. Samples were collected in a glass U tube.

All column chromatographic purifications were carried out with a 20-mm diameter column of silicic acid (100–200 mesh), prepared by pouring a benzene slurry of the silicic acid (80 g) into a 20-mm i.d. glass column and permitting the silicic acid to settle undisturbed for 1 hr. The sample (dissolved in the minimal quantity of benzene and/or chloroform, if necessary) was added carefully to the column and eluted with 120-ml portions of solvent, which were applied to the column in order of increasing elution capacity. The eluent was collected in 60-ml fractions. The eluting solvent systems and the order of addition were benzene, benzene–chloroform (3:1, v/v), benzene–chloroform (1:1 v/v), benzene–chloroform (1:3 v/v), chloroform, chloroform–ethyl acetate (3:1, v/v), chloroform–ethyl acetate (1:1 v/v), chloroform–ethyl acetate (1:3 v/v), ethyl acetate, ethyl acetate–acetone (3:1 v/v), ethyl acetate–acetone (1:1 v/v), ethyl acetate–acetone (1:3 v/v), and acetone. The solvent system, which is listed for a given chromatographic purification, is the eluting solvent passing through the column when the major portion of the desired compound was eluted from the column. The eluent fractions were examined for contents by thin layer chromatography (tlc), which were conducted on 1 × 3 in. glass plates covered with a layer of Adsorbosil-3[17] using the solvent systems specified. The components were detected by iodine vapor.

Condensation of 2,3-*O*-Isopropylidene-D-glyceraldehyde[5] with Phenyllithium.—Bromobenzene (30 ml, 0.29 mol) was added dropwise to an ether (300 ml) suspension of finely cut lithium ribbon (4.0 g, 0.57 g-atom) in a 500-ml flask, which was equipped with a condenser and drying tube. After all the bromobenzene was added, the suspension was stirred for 2 hr. 2,3-*O*-Isopropylidene-D-glyceraldehyde (17.0 g, 0.13 mol), dissolved in 30 ml of diethyl ether, was added slowly to the phenyllithium suspension with vigorous stirring. After stirring for 3 hr, the reaction mixture was poured into ice–water. The organic layer was washed twice with 100-ml portions of water and dried over anhydrous sodium sulfate. Solvent removal under reduced left 27 g of an amber syrup. Gas chromatography of the syrup showed two major components with slightly different retention times. The relative ratio of the peak areas is 38:62 in favor of the isomer with the longer retention time. After cooling overnight, long needles formed in the syrup, which were collected on a sintered glass funnel and washed with *n*-hexane (8.4 g, mp 70–73°). Gas chromatography of the mother liquor again indicated the presence of two major components with identical retention times as the original syrup, but the peak area ratio (65:35) is now in favor of the faster moving component. The change in peak area ratio suggests that the isomer with the longer retention time is the crystalline one.

A pure sample of the crystalline compound (**1**) was obtained by two recrystallizations from *n*-hexane: mp 74–75°; $[\alpha]^{23}D$ −30.0° (*c* 3.0, CH_3OH); infrared absorption (5 × $10^{-3}M$ CCl_4), ν_{OH} 3623 and $\nu_{OH\cdots O}$ 3588 cm^{-1}; nmr signals ($DCCl_3$) at δ 1.4 (-CH_3), 2.9 (-OH), 3.7 (H_3), 4.2 (H_2), 4.5 (H_1), 7.2 (ArH).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.74. Found: C, 69.30; H, 7.62.

A pure sample of the liquid isomer (**4**) was obtained by repeated injections of 25-μl portions of an acetone solution of the isomeric mixture to a column (0.25 in × 10 ft) of 10% QF-1[18] on ABS-70/80[19] at 190°: $[\alpha]^{23}D$ +4.5° (*c* 4.0, CH_3OH); infrared absorption (5 × 10^{-3} *M*, CCl_4), ν_{OH} 3626 and $\nu_{OH\cdots O}$ 3596 cm^{-1}; nmr signals ($DCCl_3$) at δ 1.14 (-CH_3), 2.6 (-OH), 3.9 (H_3), 4.2 (H_2), 4.9 (H_1), 7.3 (Ar-H).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.74. Found: C, 69.29; H, 7.74.

Condensation of 2,3-*O*-Isopropylidene-D-glyceraldehyde with Phenylmagnesium Bromide.—The Grignard reagent was prepared by reacting magnesium metal (4.8 g, 0.19 g-atom) with bromobenzene (24 ml, 0.23 mol) in 300 ml of anhydrous ether. To the Grignard reagent was added 17.0 g of 2,3-*O*-isopropylidene-D-glyceraldehyde in small portions. The same reaction time and procedure used for the phenyllithium reaction was followed. Gas chromatography showed two major components in a ratio of 58:42 in favor of the crystalline isomer.

Benzoylation of the Crystalline Isomer (1).—The monobenzoate (**2**) was formed by dropwise addition of 2.6 ml of benzoyl chloride to 4.0 g of **1** in pyridine (30 ml). After standing overnight the reaction mixture was poured into ice–water from which **2** crystallized to yield 5.9 g, 98%. Recrystallization from ethanol gave a pure sample (5.5 g, 91%): mp 71.5–72.5°; $[\alpha]^{23}D$ +11.7° (*c* 3.6, $HCCl_3$).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.17; H, 6.68.

Determination of the Configuration of the Crystalline Isomer (1).—The isopropylidene group was hydrolyzed from 1 g of **2** by refluxing for 20 min in ethanol (40 ml) containing 2 ml of 3 *N* HCl. After neutralizing the acid, 1-*O*-benzoyl-1-*C*-phenylglycerol (**7**) was isolated as a syrup, which was purified by Bio-sil A[20] column chromatography, eluting with chloroform–ethyl acetate (3:1); tlc showed one spot, R_f 0.38 (chloroform). A 10-ml benzene solution of compound **7** (0.5 g) was allowed to react for 10 min with lead tetraacetate (3.2 g). After the excess lead tetraacetate was destroyed by adding 1 ml of ethylene glycol to the reaction mixture, the inorganic salts were removed by filtration. The filtrate was diluted with 50-ml of diethyl ether, washed twice with 10% aqueous bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to a syrup. The syrup, dissolved in 5 ml of ether, was added to 0.2 g of $LiAlH_4$ suspended in 15 ml of anhydrous ether. After 3 hr, sufficient water was added carefully to the reaction mixture to destroy the excess hydride and cleave the complex, without forming a distinct aqueous layer. After removal of inorganic salts by filtration, the ethereal filtrate was concentrated *in vacuo* to a syrup. The crude syrup was chromatographed on a column of Bio-sil A (80 g), eluting with chloroform–ethyl acetate (1:3 v/v) to give chromatographically pure syrup (0.14 g, 56%) which slowly crystallized from a small volume of ether–pentane (1:3 v/v); tlc showed one spot, R_f 0.65 (ethyl acetate). Pure crystalline L-(−)-1-phenyl-1,2-ethanediol (**14**) was obtained by recrystallization from ether–pentane (1:3 v/v): mp 66–67°, $[\alpha]^{23}D$ −57.8° (*c* 3.2, ether) [lit. mp 67°, $[\alpha]^{20}D$ −47.1° (ether), from hydride reduction of D-(−)-mandelic acid of 82% optical purity[7]].

Oxidation of Compounds 1 and 4 to 4-(*R*)-Benzoyl-2,2-dimethyldioxolane (11).—Moffatt's reagent[21] was prepared by carefully adding dicyclohexylcarbodiimide (7.5 g), pyridine (1 ml), and trifluoroacetic acid (0.5 ml) to 30 ml of cold benzene–dimethyl sulfoxide (1:1 v/v). To the prepared reagent, a 10-ml benzene solution of compound **1** (0.55 g) was added and stored overnight at room temperature. After removal of the solid material by filtration, the filtrate was diluted by adding diethyl

(16) Elemental Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. All melting points are uncorrected.

(17) Silicic acid with 10% binder, 10–18 Å, Applied Science Laboratories, Inc., State College, Penn.

(18) A fluorosilicone polymer, Analabs, Inc., Hamden, Conn.

(19) Acid- and base-washed, silanized diatomaceous earth, 70/80 mesh, Analabs, Inc., Hamden, Conn.

(20) Chromatographic grade silicic acid, 100–200 mesh, Bio-Rad Laboratories, Richmond, Calif.

(21) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

ether (50 ml). The ethereal solution was washed twice with 10% aqueous oxalic acid, followed by a 10% aqueous sodium bicarbonate washing, then dried over sodium sulfate. Solvent removal *in vacuo* left a residual syrup (0.50 g), which crystallized on adding pentane and cooling. The crystals were removed by filtration and washed with a little cold pentane (0.26 g, 47%; mp 58–60°). Some difficulty was noted in removing the decomposition by-products from **11**.

Using this procedure, isomeric mixtures of compounds **1** and **4** were were oxidized to compound **11** in comparable yield.

A pure sample of compound **11** was obtained by three crystallizations from pentane: mp 61–62°; $[\alpha]^{23}D$ +15.3° (*c* 3.6, CH_3OH); nmr signals ($DCCl_3$) at δ 1.4 ($-CH_3$), 4.3 (H_3), 5.2 (H_2), 7.4 and 8.0 (Ar–H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.76; H, 6.91.

2,3-*O*-Isopropylidene-D-*threo*-1-*C*-phenylglycerol-1-d_1 (3) and 2,3-*O*-Isopropylidene-D-*erythro*-1-*C*-phenylglycerol-1-d_1 (5) from Compound 11.—An ether solution (10 ml) of compound **11** (0.40 g) was added slowly to a suspension of $LiAlD_4$ (0.15 g) in ether (50 ml). After 24 hr, moist ether was added to destroy the excess $LiAlD_4$ and the inorganic solids were removed by filtration. The filtrate was concentrated *in vacuo* to a syrup (0.37 g). Gas chromatography indicated the presence of two components with the same retention times as **1** and **4**. The isomeric distribution was 67:33 in favor of the crystalline isomer (**3**).

On standing overnight in a little pentane, compound **3** crystallized from solution. The crystals (0.11 g) were isolated by filtration and washed with a little cold pentane. Pure 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol-1-d_1 (**3**) was obtained by sublimation at 0.05 mm (60° bath): mp 74–75°; admixture with compound **1**, mp 74–75°; $[\alpha]^{23}D$ −28.1° (*c*, 3.6, CH_3OH); nmr signals ($DCCl_3$) at δ 1.4 ($-CH_3$), 2.9 (–OH), 3.7 (H_3), 4.2 (H_2), 7.4 (Ar–H).

Anal. Calcd for $C_{12}H_{15}DO_3$: C, 68.87; H + D, 8.19. Found: C, 69.09; H + D, 8.04.

A pure sample of 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol-1-d_1 (**5**) was obtained by preparative glpc. Although chromatographically pure, the syrup could not be induced to crystallize: $[\alpha]^{23}D$ +4.3° (*c* 2.5, CH_3OH); nmr signals ($DCCl_3$) at δ 1.4 ($-CH_3$), 2.5 (–OH), 3.9 (H_3), 4.3 (H_2), 7.3 (Ar–H).

Lithium Aluminum Hydride Reduction of 11 in Benzene.—A benzene solution (1 ml) of **11** (.043 g) was added dropwise to a suspension of $LiAlH_4$ (0.1 g) in benzene (10 ml). The reaction conditions and procedure of the previous experiment were followed. Product analysis by glpc indicated that the reduction favored the crystalline over the liquid isomer in the ratio of 6:4. The crystalline and liquid products were identified as compounds **1** and **4**, respectively, by glpc and ir and nmr spectroscopy.

D-*threo*-1-*C*-Phenylglycerol (6) from 1.—A solution of compound **1** (1.0 g) and 3 *N* HCl (1 ml) in ethanol (20 ml) was refluxed for 1 hr. The solution was neutralized with Ag_2CO_3 and the solids removed by filtration; the filtrate was concentrated *in vacuo* to a syrup (0.71 g), which could not be induced to crystallize. The syrup (0.71 g) was applied to a column of Bio-sil A (80 g), eluting with ethyl acetate–acetone (3:1 v/v) to yield chromatographically pure D-*threo*-1-*C*-phenylglycerol (0.51 g, 62%): tlc, one spot, R_f 0.56 (ethyl acetate); $[\alpha]^{23}D$ −38.6° (*c* 3.5, CH_3OH); nmr signals (D_2O) at δ 3.4 (H_3), 3.9 (H_2), 4.7 (H_1), 7.4 (Ar–H).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 64.38; H, 7.27.

1,2,3-tri-*O*-Benzoyl-D-*threo*-1-*C*-phenylglycerol (8) from 6.—Benzoyl chloride (0.7 ml) was added dropwise to a solution of **6** (0.3 g) in pyridine (15 ml) and the mixture stored at room temperature overnight. Crystalline **8** was obtained, when the reaction mixture was poured into water and stirred to yield 0.8 g, 93%. Two recrystallizations from benzene–pentane gave pure **8**: mp 139–140°; $[\alpha]^{23}D$ +12.2° (*c* 4.42, $HCCl_3$); nmr signals ($DCCl_3$) at δ 4.5 (H_3), 6.1 (H_2), 6.5 (H_1), 7.4 and 8.0 (Ar–H) (lit.[4] mp 110° for *dl-threo*-tribenzoate).

Anal. Calcd for $C_{30}H_{24}O_6$: C, 74.98; H, 5.03. Found: C, 74.54; H, 5.07.

D-*erythro*-1-*C*-Phenylglycerol (9).—The syrupy product (3.0 g), obtained from the phenyllithium addition to 2,3-*O*-isopropylidene D-glyceraldehyde, 3 *N* HCl (4 ml), and ethanol (35 ml) were heated under reflux for 1.5 hr. After neutralization of the acid with Ag_2CO_3 and filteration to remove the inorganic solids, the filtrate was concentrated *in vacuo* to give a syrup (2.3 g) which was dissolved in a small volume of chloroform. Compound **9** crystallized from the chloroform solution and was removed by filtration (0.7 g, mp 97–104°). D-*erythro*-1-*C*-Phenylglycerol was purified by two recrystallizations from acetone: mp 106–107°; $[\alpha]^{23}D$ +19.6° (*c* 6.34, H_2O); nmr signals (D_2O) at δ 3.6 (H_3), 3.8 (H_2), 4.6 (H_1), 7.3 (Ar–H) [lit.[4] mp 105–106°, $[\alpha]D$ +18.4° (10% aqueous), for α-D-phenylglycerol].

D-*erythro*-1-*C*-Phenylglycerol-1-d_1 (10) from 5.—A chromatographically pure sample of **5** (25 mg) and 3 *N* HCl (0.1 ml) were dissolved in ethanol (3.0 ml) and the solution was heated under reflux for 1 hr. The same work-up described for the preparation of **9** was followed to yield 16 mg of syrup, which crystallized upon adding acetone and cooling: mp 106–107°; admixture with **9**, mp 106–107°; $[\alpha]^{23}D$ +19.0° (*c* 1.6, D_2O); nmr signals (D_2O) at δ 3.5 (H_3), 3.8 (H_2), 7.3 (Ar–H).

(*R*)-α,β-Dihydroxypropiophenone (12) from 11.—An acetone solution (5 ml) of **11** (0.20 g) and 1 *N* HCl (0.25 ml) was heated under reflux for 5 min. After neutralization of the acid with Ag_2CO_3 and removal of the solids by filtration, the filtrate was concentrated *in vacuo* to give a syrup (0.12 g). A pure sample of **12** was obtained by chromatographing the syrup (0.12 g) on a column of Bio-sil A (80 g), eluting with ethyl acetate: tlc, one spot, R_f 0.71 (ethyl acetate); $[\alpha]^{23}D$ +72.1° (*c* 8.0, H_2CCl_2); nmr signals ($DCCl_3$) at δ 3.7 (H_β), 4.5 (–OH), 5.1 (H_α), 7.4 and 7.9 (Ar–H).

(*R*)-α,β-Dibenzoyloxypropiophenone (13) from 12.—Standard benzoylation procedure using benzoyl chloride in methylene chloride–pyridine solution converted **12** (0.10 g) into the dibenzoate, which was purified by chromatographing on a Bio-sil A (80 g) column, eluting with benzene–chloroform (1:1 v/v); tlc showed one spot, R_f 0.50 (benzene). Compound **13** could not be induced to crystallize: $[\alpha]^{23}D$ −51.4° (*c* 2.7, H_2CCl_2); nmr signals ($DCCl_3$) at δ 4.8 (H_β), 6.6 (H_α), 7.5 and 8.0 (Ar–H).

Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.67; H, 4.72.

Registry No.—**1**, 16354-89-5; **2**, 16355-01-4; **3**, 16354-90-8; **4**, 16354-91-9; **5**, 16354-92-0; **6**, 16354-93-1; **8**, 16354-94-2; **9**, 16354-95-3; **10**, 16354-96-4; **11**, 16354-97-5; **12**, 16354-98-6; **13**, 16354-99-7; **14**, 16355-00-3.

Rotatory Dispersion Studies. VI.[1a] Phenylosotriazole Derivatives of the Aldo Sugar Family[1b-d]

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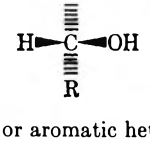
A study of the ORD and CD curves of osotriazole derivatives of sugars having four to six carbon atoms has shown that the phenylosotriazole chromophore is optically anisotropic, producing Cotton effect curves which result in the following rule: a positive Cotton effect at 265 nm will be produced if the C-3 hydroxyl group (α to the aromatic ring) is at the right in a standard Fischer projection [(R) configuration] of the phenylosotriazole derivative. The optical rotatory power of the osotriazoles in four solvents showed a correlation between the dielectric constant and the magnitude of rotation indicating the probability of intramolecular hydrogen bonding. The nmr spectra were consistent with a conformation (B) of the osotriazole in which a hydrogen bond is formed between the 3-hydroxyl group and a nitrogen of the osotriazole ring while the tetraacetyl derivatives appeared to have the usual zigzag conformation. A sector rule has been devised correlating the Cotton effects of the phenylosotriazole chromophoric system with the configuration of the sugar residue in a hydrogen-bonded conformation. The signs and amplitudes of the Cotton effects of all of these compounds were consistent with the sector rule.

The correlation of the absolute configuration of a molecule and its optical rotatory power has been sought in many systems of organic compounds, but it has been successful in relatively few cases. The carbohydrates have been especially attractive for such studies because of the multiplicity of structurally similar chiral centers. The challenge of the carbohydrates led to early considerations of three-dimensional structures, and the correlation of optical rotations with stereochemical assignments resulted in several useful rules, especially those of Hudson.[2] One of the Hudson rules states that the sign of the D-line rotation reflects the absolute configuration of the hydroxyl group on the carbon α to the benzimidazole ring in these derivatives of sugars, thus permitting the configurational assignment at the 2 position of the original sugar.[2b]

An extension of this rule to another cyclic derivative, the phenylosotriazole structure, has been suggested by Khadem[3] and Mills.[4] By the conversion of a sugar into this derivative the configuration at C-3 of the original sugar may be established on the basis of the osotriazole rule. Khadem and El-Shafei[5] have also suggested the general applicability of the rule to all aromatic systems declaring that "the sign of rotation of a heterocyclic or aromatic compound having more than one asymmetric carbon depends only on the configuration of the asymmetric carbon atom attached to the heterocyclic or benzene ring provided no other ring is present in the molecule." The sign of rotation at the D line is correlated with the configuration, below, giving a positive rotation.



benzene or aromatic heterocycle

Where R is a sugar moiety and the aromatic group is the osotriazole ring, the configurational designation is R.[6]

In view of the availability of spectropolarimeters for measurements below 300 nm, it seemed desirable to investigate this correlation, which was based on D-line rotations, with attention to the variation of rotation with the wavelength of the incident polarized light. If the aromatic ring produced a Cotton effect curve whose sign was consistent with the D-line rotation, this would indicate the dominance of the ORD curve by this aromatic chromophore and, perhaps, the possibility of designing a sector rule for this chromophore (*vide infra*). By examining a series of derivatives (1–6) of simple sugars (four to six carbons per sugar molecule) that possess almost all possible combinations of the stereorelationships of adjacent hydroxyl groups, it should also be possible to determine the conformation of the sugar residue from nmr spectral analysis.[7]

Assuming that the aromatic nucleus substituted on the asymmetric carbon atom represented the parent structure, the synthesis of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-triazole (**1**) was carried out. Potato starch was converted into potato oxystarch and thence to a mixture of phenylosazones.[8] A portion of this mixture of osazones was purified by column chromatography to yield D-erythrose phenylosazone free of glyoxal phenylosazone and β-acetylphenylhydrazine which were also isolated and characterized. Either pure erythrose osazone or the osazone mixture was converted into the phenylosotriazole **1** by cyclization with copper(II) sulfate. The crystalline osotriazole **1** was the only derivative which had not been previously reported in this family. The properties are described in the Experimental Section.

The preparation of the phenylosazones of the five-

(1) (a) Part V: G. G. Lyle and W. Gaffield, *Tetrahedron*, **23**, 51 (1967). (b) This study was supported in part by a grant GM-07239 and continuation grants from the National Institutes of Health. (c) Taken in part from the thesis of M. J. P. submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. Degree. (d) Presented before the Carbohydrate Division of the American Chemical Society at the 153rd Meeting, April 1967, Miami, Fla., Abstracts, p C10.

(2) (a) N. K. Richtmyer, *Advan. Carbohyd. Chem.*, **6**, 175 (1951); (b) N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1612 (1942).

(3) H. El Khadem, *J. Org. Chem.*, **28**, 2478 (1963).

(4) J. A. Mills, *Aust. J. Chem.*, **17**, 277 (1964).

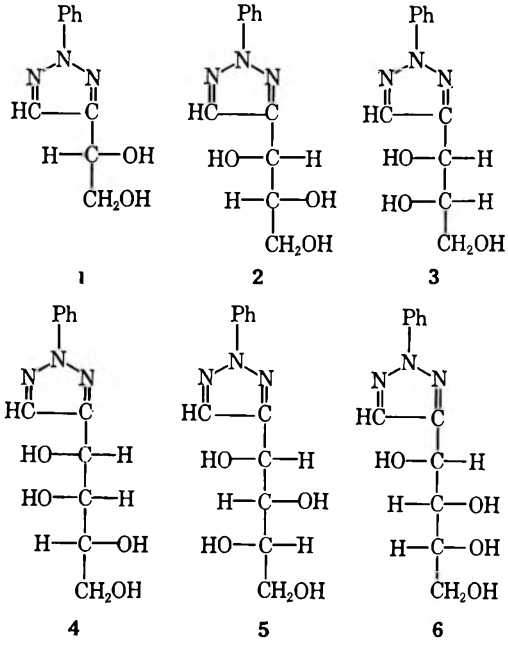
(5) H. El Khadem and Z. M. El-Shafei, *Tetrahedron Lett.*, 1887 (1963).

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

(7) After this manuscript was submitted to the editor, a paper appeared [W. S. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **89**, 4129 (1967)] describing the results of an ORD study of aryl derivatives of carbohydrates. The authors concluded that the aryl substituent would give a Cotton effect whose sign was consistent with the configuration of the chiral group attached to the aromatic ring, and they included one example of a phenylosotriazole derivative. NOTE ADDED IN PROOF.—Two recent publications have described some ORD results [W. S. Chilton and R. C. Krahn, *ibid.*, **90**, 1318 (1968)] and nmr studies in methyl sulfoxide-d_6 [H. S. El Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 734 (1968)] on which conformational preferences have been suggested.

(8) V. C. Barry and P. W. D. Mitchell, *J. Chem. Soc.*, 4020 (1954).

and six-carbon sugars was effected by standard procedures, and they were converted into the cyclic osotriazoles (2–6) by heating with $CuSO_4$. The osotriazoles prepared in this study are listed in the Experimental Section. All possible isomers except D-*ribo*-hexose phenylosotriazole were prepared and subjected to spectropolarimetric study.



A comparison of the rotatory power in four solvents between 600 and 300 nm was carried out, and the data were subjected to analysis by a one-term Drude equation using the procedure previously described.[9] The Drude constants showed little similarity indicating that the data were not amenable to a simple Drude plot. This is probably because of the strong, relatively long wavelength absorption band of the osotriazole ring which is optically anisotropic and dominates the ORD curve in the visible region.

The results showed that the optical rotatory power was generally the lowest in water and the highest in pyridine. The curves for L-*xylo*-hexose phenylosotriazole (**5**) in four solvents are shown in Figure 1. The ORD curves in methanol and acetic acid were quite similar except in the case of the osotriazole **3** derived from arabinose. In this case the ORD curve in methanol showed stronger rotation than in any of the other three solvents. There seems to be no simple explanation for the solvent effects except to assume a change in conformation depending on the solvent. The decreasing rotatory power with increasing dielectric constant suggests that in pyridine the molecules can assume the maximum amount of intramolecular hydrogen bonding, the relative conformational rigidity thus resulting in the larger rotatory power. This is consistent with the pattern which has been observed in which cyclic structures generally show larger D-line rotations than acyclic analogs.[10] In water, however, the solvation of the osotriazole nitrogens as well as the hydroxyl groups would increase the random structure and produce a decrease in the rotatory power.

(9) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

(10) W. J. Kauzmann, J. E. Walter, and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).

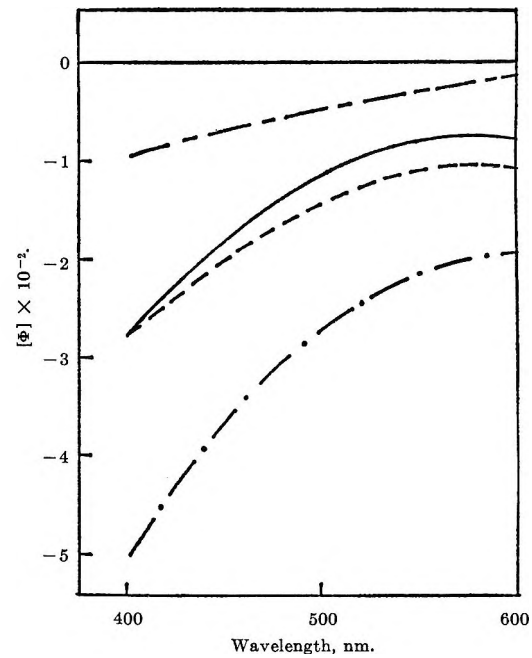


Figure 1.—ORD curves of 4-(L-*xylo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**5**). The curves were obtained from the Rudolph instrument using pyridine (—·—), methanol (——), acetic acid (— — —), and water (— - —) as the solvents.

The ORD curves of the phenylosotriazole derivatives below 400 nm[11] were generally characterized by having the same sign of rotation at 400 nm as the D line and a strong Cotton effect between 250 and 300 nm of the same sign. The midpoints of the Cotton effects occurred at 259–266 nm, in excellent agreement with the maximal ultraviolet absorption at 265–267 nm (ϵ 19,000–24,000) of all six compounds. An experimental complication was noted with these derivatives and should be mentioned. They showed considerable fluorescence above 300 nm which can lead to erroneous readings of the amplitudes of the Cotton effects similar to the errors introduced in measuring uv data of fluorescing species. When the absorbance was kept below **2**, however, the fluorescence gave no problems but, in some low-rotating derivatives, the quantitative values of the amplitudes may be of diminished reliability. The Cotton effects shown by the two pentose phenylosotriazoles (**2** and **3**) have the same sign, thus reflecting the configurations at the α carbon rather than the β carbon where the configurations are opposite (Figure 2). The amplitude of the single Cotton effect of the *threo* isomer **2** was considerably larger than the combined Cotton effects in the same region shown by **3**. In the curves of **5** and **6** as well as **3** the extremum at about 240 nm was split into two peaks (Figure 3). That this indicated more than one Cotton effect was verified by examination of the circular dichroism (CD) spectra[12] of **1** and **6**. The curve of **6** showed three negative maxima and a shoulder between 280 and 240 nm (Figure 4). The uv spectra gave no indication of fine structure in methanol solution, while the ORD suggested and the CD proved the oc-

(11) The generosity of Dr. W. Gaffield of the Western Regional Research Laboratory of the Department of Agriculture, Albany, Calif., and of Professor W. Klyne, Westfield College, University of London, England, for measuring the low-wavelength ORD curves is gratefully acknowledged.

(12) We are grateful to Mr. W. Ungerer of the Jouan Co. for arranging for these curves to be obtained on the Jouan Dichrograph. More recently, Mr. N. Mitchell of Cary Instruments has furnished additional curves which duplicate those reported in this paper.

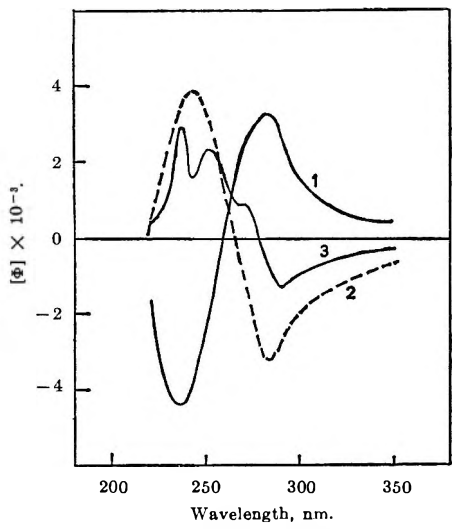


Figure 2.—ORD curves of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1), 4-(D-*threo*-trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (2), and 4-(L-*erythro*-trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (3).

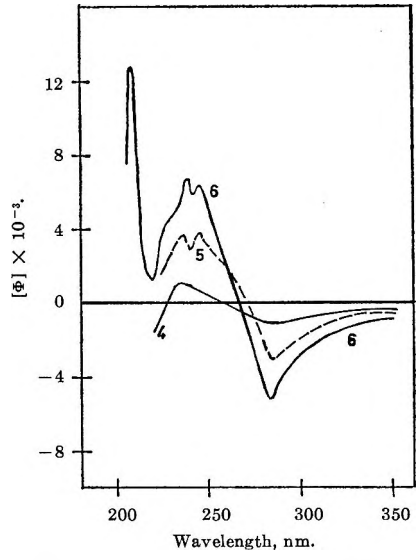


Figure 3.—ORD curves in methanol of 4-(D-*lyxo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (4), 4-(L-*xylo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (5), and 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (6).

currence of more than a single electronic transition in this region. The CD curve also showed a positive Cotton effect at lower wavelength which had been suggested by the appearance of a peak at 207 nm in the ORD curve of **6**. The CD curve of **1** was enantiomeric to that of **6** above 215 nm except for the difference in intensity. A similar difference was noted in the ORD curves. Below 215 nm, both compounds gave a negative direction to the curves which suggests that there is an electronic transition below 200 nm which may have the same sign.

Since the signs of the long-wavelength Cotton effects are the same as the D-line rotations, there is possible a restatement of the osotriazole rule: *The sign of the Cotton effect at 265 nm is positive if the hydroxyl group α to the phenylosotriazole ring is to the right (R configuration) in a standard Fischer projection.* The narrow range of values for the amplitudes of these Cotton

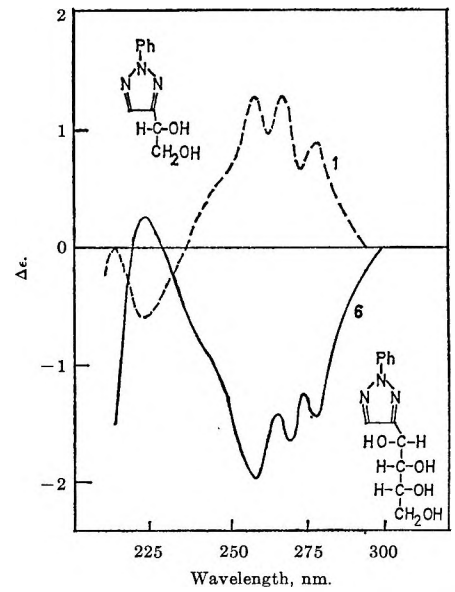
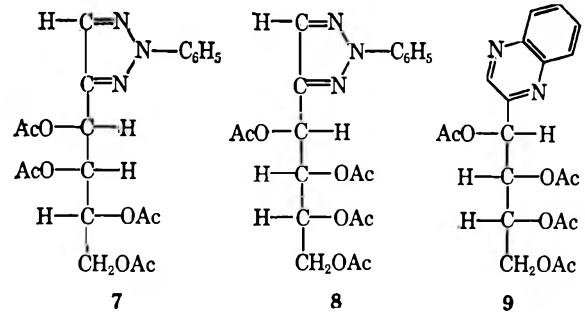


Figure 4.—CD curves in methanol of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1) and 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (6).

effects indicates the dominance of this asymmetric carbon atom.

The ORD curve of D-*lyxo*-hexose phenylosotriazole tetraacetate (**7**) showed a Cotton effect centered at 278 nm which appeared on the side of a larger Cotton effect at lower wavelength. The second Cotton effect probably resulted from the ester bands of the acetate groups but the entire Cotton effect was not visible. The sign of the long-wavelength Cotton effect is the same as that of the osotriazole **4** from which **7** was prepared.



A comparison of the nmr spectra of D-*arabino*-hexose phenylosotriazole (**6**) and its tetraacetate derivative **8** with the analogous quinoxaline derivative **9** indicated that **8** possessed the zigzag conformation (A, Figure 5) similar with that assigned[13] to **9**. The coupling constant of the proton α to the aromatic ring in **8** was 3.9 Hz, close to that in **9**. In view of the correspondence of the remainder of the aliphatic proton parts of the spectra of **8** and **9** in both chemical shift and coupling constant, the zigzag conformation may be assigned to **8**. Examination of the nmr of **7** showed that the coupling constants for the C-3 and C-4 hydrogens corresponded to those anticipated for a zigzag conformation. It is possible for a large number of conformations to exist, but these data suggest that the zigzag conformation is of significance. A comparison of the spectral data for these tetraacetate derivatives is given in the Experimental Section.

(13) D. Horton and M. J. Miller, *J. Org. Chem.*, **30**, 2457 (1965).

TABLE I

APPROXIMATE DIHEDRAL ANGLES OF α- AND β-CH BONDS IN SUGAR PHENYLOSOTRIAZOLES IN VARIOUS CONFORMATIONS[a]

	Dihedral angle and predicted coupling constant							
	Conformation A		Conformation B[b]		Conformation C[b]		α-Proton	
Compd	Angle, deg	J[c]	Angle, deg	J[c]	Angle, deg	J[c]	chemical shift, τ	J[c]
1	*d*		*d*		*d*		4.42	5.6
Pentoses								
2	60	1.8	60	1.8	30	6.1	4.17	3.6
3	180	9.2	150	6.8	150	6.8	4.23	5.9
Hexoses								
4	180	9.2	150	6.8	150	6.8	4.15	7.3
5	60	1.8	40	4.7	20	8.7	4.12	5.1
6	60	1.8	60	1.8	50	3.2	3.85	<2[e]
Tetraacetates								
7	180	9.2					3.30	7.5
8	60	1.8					3.58[f]	3.9
9	60	1.8					3.55[f,g]	3.0[g]

[a] The solvent used was pyridine-d_5. [b] In both hydrogen-bonded conformations the remainder of the sugar chain was assumed to be in conformations which would allow the maximum amount of intramolecular hydrogen bonding and with the minimum of nonbonded interactions. [c] Coupling constants are given in hertz. [d] Two coupling constants and two angles are possible for each conformation. The observed J represents the time-averaged spectrum which prohibits any selection of preferential conformation where the methylene protons are equivalent. [e] Half-band width. [f] The solvent used was $CDCl_3$. [g] Reference 13.

Three conformations of the hexose phenylosotriazole molecules appeared the most plausible. The zigzag conformation (A, Figure 5) would show no intramolecular hydrogen bonding and is the most probable conformation for the tetraacetate molecules **7**, **8**, and **9**. Although the monocyclic sugars may have little or no intramolecular hydrogen bonding in polar solvents,[14] the osotriazoles should show such bonding because of the possibility of O—H···N bonds, these being strong compared to the weaker O—H···O bonds possible in the sugars. Such bonding could occur between the C-3 hydroxyl group and nitrogen to form a five-membered ring (B, Figure 5) or between the C-4 hydroxyl and nitrogen resulting in a six-membered ring (C, Figure 5). Examination of space-filling models shows that the six-membered, hydrogen-bonded ring would be destabilized by the interference of the phenyl group. It apparently becomes impossible for the hydrogen bonding to remain in effect when the phenyl is coplanar with the triazole ring. If a five-membered ring is formed, however, the interfering nonbonded interactions are at a minimum. A decision as to the conformational preference of the hexose osotriazoles was sought *via* analysis of the nmr spectra.

The spectrum of **1** in pyridine-d_5 showed the signal for the C-3 proton as a triplet at τ 4.4 (J = 5.6 Hz). The methylene protons appeared as a doublet at τ 5.56 (J = 5.6 Hz). For the glucose derivative **6**, the C-3 proton was a broad singlet at τ 3.83 with a half-band width of less than 2 Hz, while in pyridine as solvent and on another instrument this single peak was resolved as a doublet (J = 1.5 Hz). The same proton in **5** appeared as a doublet at τ 4.10 (J = 5.1 Hz), whereas in **4** this proton resonated at 4.14 (J = 7.3 Hz). The data for the pentose derivatives are recorded in Table I. The fact that the J values represent time averages of a number of conformations must be emphasized. The dihedral angle of the α and β protons was estimated from Dreiding models of the osotriazoles for each conformer consistent with the spatial requirements estimated from Fisher–Hirschfelder models. Exact measurement was impossible for these flexible hydrogen-bonded models.

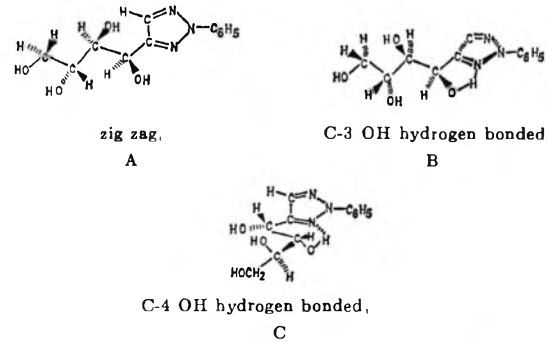


Figure 5.—Possible conformations of 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (6). The hydroxyl groups not hydrogen bonded to nitrogen in B and C may be hydrogen bonded to each other or in a zigzag conformation. The data calculated for Table I assumed conformations approximating the ones drawn based on a minimization of nonbonded interactions as judged from space-filling models.

Using the Karplus correlation[15] the coupling constant was calculated for the angle between the α-CH and β-CH for each conformation (Table I). The correspondence of the values for $J_{\alpha\beta}$ to those for conformation B in preference to A or C is evident in all three hexose phenylosotriazoles. The resolution of the nmr spectra indicates reasonable conformational homogeneity. This, of course, does not exclude other possible conformers but supports a hydrogen-bonded conformation over the zigzag conformation on the nmr time scale for the structures having free hydroxyl groups.

The remainder of the nmr spectra was consistent with the structural assignments for these systems. The proton attached to the osotriazole ring was shifted to low field, τ 1.5–1.6 (1 H), as expected. The phenyl protons appeared as two multiplets, two doublets centered at τ 1.8 (2 H) and a split quartet at 2.7 (3 H). The hydroxyl protons appeared as a broad band at τ 3.4–3.5. The methylene protons generally appeared as a doublet but in **5** they gave only a broad singlet at τ 5.56. Only in the case of **2** was the signal split further and to such an extent that the nonequivalence

(14) A. B. Foster, R. Harrison, J. Lehman, and J. M. Webber, *J. Chem. Soc.*, 4471 (1963).

(15) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

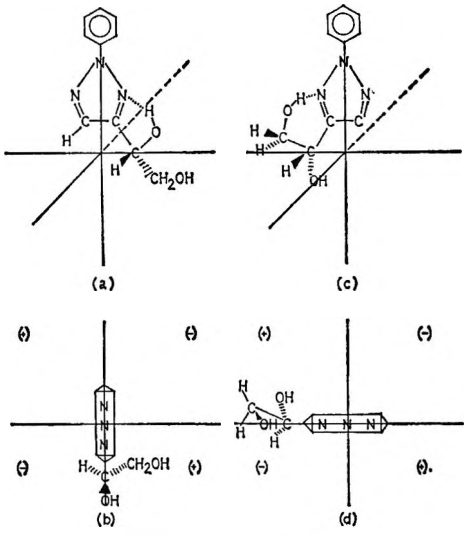


Figure 6.—Orientation of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1) on an eight-sector diagram. In part a this structure assumes a conformation similar to B in Figure 5, whereas the conformation in part c is analogous to C in Figure 5. The diagrams in parts b and d represent views from the *para* position of the benzene ring bisecting the triazole ring. These views maintain the signs of the four pertinent rear sectors and orient the molecules consistent with the experimentally observed positive Cotton effect for 1.

of the methylene protons was apparent. The remaining β and γ protons showed multiplets at τ 5.1–5.4.

The coupling constants of the α protons in the osotriazoles were smaller (2–5 Hz) for the *threo* α,β hydrogens than those for the *erythro* series (6–7 Hz). The range of coupling constants reflects the alterations in dihedral angle imposed by the variety of conformations in the remainder of the molecule which results from the differences in stereochemistry. The zigzag conformation for **3** would require the dihedral angle of α- and β-CH bonds to be 180° with J = 9.2 Hz, whereas in **2** the dihedral angle should be 60° (J = 1.8 Hz) for the same idealized conformation. The hydrogen-bonded conformations for **2** would be relatively similar to those for **5** or **6**, whereas **3** should be similar to **4** (Table I). The values observed indicated that **2** may have any of the three possible conformations, preferably A or B. The conformation of **3**, however, is more probably the hydrogen-bonded (B or C) rather than the zigzag structure. The data for the pentose derivatives are somewhat more equivocal than for the hexose phenylosotriazoles.

In view of the evidence from the ORD and nmr spectra as to the probable conformations of these sugar derivatives, it should be possible to construct a reasonable model by which one may predict the sign of the Cotton effect. Such a design would be analogous to the octant rule established for the carbonyl function.[16] The phenyl and triazole rings may be assumed to be coplanar for maximum π orbital overlap. The symmetry of the phenylosotriazole rings directs one symmetry axis through the *para* position of the phenyl ring, the central nitrogen atom, and between the two carbons of the triazole ring (Figure 6a). A second nodal plane is in the plane of the paper. The exact locations of any other nodal planes are less certain, but the sector diagrams shown in Figure 6 seem most plausible. It is possible that the symmetry may be of the C_{2v} type and a four-sector diagram may provide a satisfactory model. It has been suggested that the monosubstituted benzene would best fit a C_{2v} model,[17] and the triazole ring is, fortunately, of similar symmetry.

In designing a sector rule for the aromatic chromophore attached to an acyclic side chain, the conformational possibilities seem almost limitless. The number of possible conformations of the substituents attached to the asymmetric carbon atom bearing the osotriazole ring must be reduced to a single conformation of substantial probability before such a design is feasible. If the aromatic ring is placed on a three-coordinate axis, the α carbon will have the usual six basic conformations with each substituent either eclipsed by or perpendicular to the aromatic ring. If there is reasonably stabilized hydrogen bonding of the C-3 hydroxyl group to a nitrogen of the osotriazole ring as postulated from the nmr evidence above, the predominant conformation may be assigned to that where the groups which appear in the sectors are the C-3 hydrogen and the $-(CHOH)_n-CH_2OH$ substituents (Figure 5). This situation then requires only the decision as to whether the aromatic moiety be horizontal or vertical on the three-coordinate diagram. Kuriyama, *et al.*,[18] designed an octant rule for the 1,2,4,5-tetrasubstituted aromatic chromophore in alkaloids placing the aromatic ring horizontally. This rule is not applicable to the five-membered, hydrogen-bonded ring of the phenylosotriazole derivatives since the experimental observations do not agree with the predicted signs of the Cotton effects. In view of the difference in the chromophoric system, this is not surprising and it would be very fortuitous if all compounds containing an aromatic chromophore could be correlated by a single sector rule.

The rule proposed herein is, therefore, based on the experimental observation that the configuration of the C-3 carbon determines the sign of the Cotton effect group centered at about 265 nm. The symmetry of the phenylosotriazole chromophore requires that one plane pass vertically through the *para* position of the aromatic ring bisecting the C-1–C-2 bond of the osotriazole ring. This means that the C-3 chiral center does *not* lie at the origin but has one finite coordinate (Figure 6a). Viewing the substituents from the *para* position of the benzene ring, the schematic sector diagram of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (**1**) may be represented as in Figure 6b. The striped area represents the phenylosotriazole chromophore and the C-3 carbon and hydroxyl are in the same nodal plane. If the signs of the sectors are the same as those designated by the octant rule,[16] conformation a (Figure 6) for **1** would be expected to show a positive Cotton effect since the CH_2OH substituent will be in the lower right rear, a positive sector, outweighing the C-3 hydrogen opposite it. The remainder of the molecule will lie in a nodal plane.

It is apparent that the sector diagram having the horizontal aromatic chromophore would be applicable to the phenylosotriazole system provided an alternate conformation were used. The six-membered, hydro-

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gen-bonded ring would fit such a rule and cannot be discarded. The representation is shown in Figure 6c. Since the nmr evidence appeared to support the five-membered hydrogen-bonded ring, it has been used as the primary model. It seems, therefore, that conformation B (Figure 5) drawn on the sector rule of Figure 6a,b is plausible based on the experimental observations of the osotriazole rule. In addition, this conformation is consistent with the data obtained from the nmr study. It represents, therefore, a useful model of this system for study of a sector rule for an aromatic chromophore.

Experimental Section[19]

Potato Oxystarch.—A colloidal suspension of 4.5 g of potato starch and 6.18 g of sodium metaperiodate was kept stirring in the dark for 48 hr. At the end of this time the insoluble oxystarch was separated by filtration and washed with water until free from periodate and iodate. The gelatinous solid was washed with absolute alcohol until a white powder was obtained. The powder was washed with ether and dried by passing air through the filter cake. The yield was quantitative.

Phenylosazone of Potato Oxystarch.—A mixture of 2.3 g of potato oxystarch in 100 ml of water was heated under reflux in 200 ml of ethanol, 25 ml of phenylhydrazine and 30 ml of glacial acetic acid. Solution of the oxystarch took place in about 10 min after which the ethanol was removed under reduced pressure. To the remaining solution was added with rapid stirring 500 ml of cold water producing a golden yellow precipitate. The precipitate was collected by filtration and washed with 50-ml portions of 10% acetic acid followed by two 50-ml portions of cold water, yielding 3.5 g of the phenylosazone which was used without further purification in the following experiment.

D-Erythrose Phenylosazone.—A solution of 2 g of the crude potato oxystarch osazone was dissolved in 100 ml of benzene and absorbed on a 150-g neutral alumina column. The column was eluted with 1 l. of ether or until the initial wide yellow band came off the column. The ether eluted the glyoxal osazone and β-acetyl phenylhydrazine as one band. The column was washed free of the remaining solid with 95% ethanol. The ethanol solution was concentrated under reduced pressure and the erythrose phenylosazone was precipitated by the addition of water to the rapidly stirring solution. The yellow precipitate was collected by filtration and was recrystallized from 60% ethanol–water yielding 0.42 g of D-erythrose phenylosazone, mp 175–177° (lit.[20] mp 175–177°).

4-(D-*glycero*-Dihydroxyethyl)-2-phenyl-1,2,3-triazole (1).—A suspension of 20 g of the crude potato starch phenylosazone and 1800 ml of water was heated to boiling and a solution of 16.7 g of copper sulfate pentahydrate in 100 ml of boiling water was added. After 30 min of heating under reflux, the solution was allowed to cool to room temperature and freed of decomposition products by filtration. Hydrogen sulfide was bubbled through the solution as long as a black precipitate continued to form. The black precipitate was separated by filtration leaving a yellow solution which was boiled with 20 g of barium carbonate until the solution was slightly basic to litmus. After cooling, the mixture was separated by filtration and the filtrate was concentrated to a syrup under reduced pressure. The syrup was extracted with two 250-ml portions of carbon tetrachloride. The combined extracts of carbon tetrachloride were concentrated under reduced pressure and cooled for 2 hr under refrigeration. The white, voluminous precipitate was dried and dissolved in hot isopropyl ether and *n*-hexane was added until the first sign of turbidity appeared. The solution was allowed to cool to room temperature and then refrigerated overnight. The white precipitate was separated by filtration and washed with two 25-ml portions of *n*-hexane yielding 2.5 g of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-triazole (1): mp 64–65°; λ_{max} 265 nm (ε 20,147), 208 (14,117); nmr gave τ 1.63 (1 H) for osotriazole proton, 1.75 (two doublets, 2 H) and 2.6 (multiplet, 3 H) for the phenyl protons, a triplet at 4.42 (1 H, J = 5.6 Hz), and a doublet at 5.55 (2 H, J = 5.6 Hz).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 59.10; H, 5.23; N, 19.83.

Preparation of Osazones.—A mixture of 10 g of the sugar, 20 g of phenylhydrazone hydrochloride, 25 ml of a saturated solution of sodium bisulfite, 30 g of crystalline sodium acetate, and 200 ml of distilled water was heated with stirring on a steam bath for 0.5 hr. The precipitate was separated by filtration, washed with water and combined with a second crop obtained after heating the filtrate for several hours. Recrystallization yielded 56–75% of the phenylosazone whose physical constants agreed with those recorded in the literature.

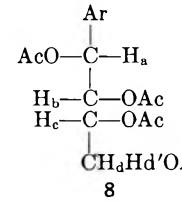
The osazone of arabinose was prepared in methyl cellosolve and precipitated on contact with water. The work-up was comparable with that above, yielding 60% of product, mp 170–171° (lit.[21] mp 172–172°).

Preparation of Phenylosotriazoles.—A mixture of 20 g of the phenylosazone, 16.7 g of $CuSO_4 \cdot 5H_2O$, and 1200 ml of water was heated under reflux for 30–60 min. The color changed from a red to green to yellow green. A red precipitate was removed, hydrogen sulfide was bubbled through the solution, and the CuS was separated by filtration. The filtrate was boiled for 15 min with 10 g of barium carbonate or until the solution was neutral to pH paper. Insoluble material was removed and the filtrate was concentrated to a syrup under reduced pressure. The syrup either deposited crystals or was extracted with ethyl acetate (for **5**) or chloroform (for 4) which yielded the crystalline product. Recrystallization from ether or ether–hexane gave 40–70% of the phenylosotriazoles which agreed in melting point with literature values and are listed with ORD and CD data below.

4-(D-*arabino*-Tetrahydroxybutyl)-2-phenyl-1,2,3-triazole (6).—The insolubility of the osazone from glucose required modification of the above procedure. A mixture of 180 ml of water, 10 ml of 0.5 *N* sulfuric acid, 2 g of the osazone, 6 g of copper sulfate pentahydrate, and 120 ml of isopropyl alcohol was heated under reflux for 1 hr and separated by filtration, and the liquid was concentrated to 50 ml. The tan precipitate was dissolved in water and decolorized with Norit. After being freed from Norit, the crystalline osotriazole (6), 300 mg (20%), melted at 193–193.5° (lit.[20] mp 195–196°).

Preparation of Tetraacetoxy Derivatives of Phenylosotriazoles.—The phenylosotriazoles **4** and **6** were treated with acetic anhydride in pyridine at 20° for 48 hr. The product in each case was extracted into chloroform, dried, and crystallized from dioxane–water to yield (90%) the tetraacetoxy derivatives **7**, mp 104–105° (lit.[22] mp 105–106°), and **8**, mp 81–82° (lit.[20] mp 81–82°).

The nmr of **8** in $CDCl_3$ showed a singlet at τ 2.13 (1 H, osotriazole ring proton), a multiplet at 2.82 (5 H, phenyl), C(=O)-CH_3 at 7.82, 7.87, 7.89, 7.97 (3 H each), and five aliphatic protons of chemical shift and apparent coupling constant as listed under compound **8**. Second-order coupling was disregarded for H_b.



8

H_a, τ 3.55 (d) (J_{ab} = 3.9 Hz)
H_b, τ 4.18 (q) (J_{ab} = 3.9 Hz, J_{bc} = 7.9 Hz)
H_c, τ 4.58 (m)
H_d, τ 5.72 (m)

(19) The ultraviolet absorption spectra were recorded on a Cary 15 instrument using 95% ethanol as solvent. The ORD curves were obtained on a Rudolph recording spectropolarimeter (λ 600–350 nm), a Cary 60 or Bellingham and Stanley Bendix-Ericsson instrument (λ <350 nm) in 10-, 5-, or 1-mm cells, adjusting concentration and path length for maximum signal. The nmr data were recorded on a Varian A-60 (purchased with the assistance of a National Science Foundation Equipment Grant G22718 to the University of New Hampshire) and on a Perkin-Elmer instrument using pyridine-d_5 as the solvent. Grateful acknowledgment is accorded to Mrs. E. Richards and Mr. P. Cherry of Dyson-Perrins Laboratory, Oxford, England, for determining many of these spectra. Microanalyses were by Schwartzkopf Laboratory, Woodside, N. Y.

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The data were compared with those obtained from the analogous quinoxaline derivative **9** analyzed previously[13] and which showed $J_{ab} = 3.0$ Hz and $J_{bc} = 8.5$ Hz. The Karplus equation[15] predicts dihedral angles of 45° for two protons coupled by 3.9 Hz and 51° for those where $J = 3.0$ Hz. The coupling constants for J_{bc} in **8** and **9** correspond, respectively, to dihedral angles of 158 and 164°. These data suggest that there may be slightly more deviation from the ideal staggered conformation in the triazole **8** than in the quinoxaline **9**. The difference between the two seems relatively minor as compared with the deviation from ideal. The data, of course, merely reflect an average of a large number of conformations and suggest only that of the extremes possible the staggered conformation predominates.

The nmr data for the tetraacetate derivative **7** which has the *lyxo* stereochemistry (H_{ab} *erythro*) instead of the *arabino* stereochemistry of **8** and **9** (H_{ab} *threo*) showed in pyridine-d_5 τ 1.72 (1 H, osotriazole proton), a complex aromatic region centered approximately at 2.24 (5 H), and four acetyl groups at 7.88 (3 H), 7.92 (3 H), and 7.98 (6 H). The five aliphatic protons showed signals for H_a at τ 3.30 (d) ($J_{ab} = 7.5$ Hz); H_b at 3.76 (q) ($J_{ab} = 7.5$ Hz, $J_{bc} = 3.5$ Hz); H_c at about 4.0 (m); and H_d at 5.40 (q). The quartet for H_d shows the nonequivalence of these methylene protons ($J_{dd'} = 13$ Hz, $J_{cd} = 7$ Hz). The dihedral angles for the H_{ab} and H_{bc} bonds are calculated to be approximately 155 and 48°, respectively, which suggests the staggered conformation very similar to that shown by the osotriazole **7** and reflecting the enantiomeric configuration at C-4.

Optical rotatory dispersion data were recorded on a Cary 60 spectropolarimeter in methanol solution.

4-(D-*glycero*-Dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (**1**), mp 64–65°, *c* 0.07, had the following ORD values: $[\Phi]_{350}$ +435, $[\Phi]_{282.5}$ +3280, $[\Phi]_{235}$ −4550, $[\Phi]_{222}$ −1640.

4-(D-*threo*-Trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (**2**), mp 87–88.5° (lit.[22] mp 88–89°), *c* 0.043, had the following ORD values: $[\Phi]_{350}$ −670, $[\Phi]_{285}$ −3240, $[\Phi]_{241}$ +3880, $[\Phi]_{220}$ 0.

4-(L-*erythro*-Trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (**3**), mp 65–68.5° (lit.[20] 69–70°), *c* 0.084, had the following ORD values: $[\Phi]_{350}$ −296, $[\Phi]_{289}$ −1340, $[\Phi]_{270-265}$ +894, $[\Phi]_{250}$ +2350, $[\Phi]_{242.5}$ +1670. $[\Phi]_{237}$ +2900, $[\Phi]_{220}$ +190.

4-(D-*lyxo*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**4**) mp 108–109° (lit.[22] 110–111°), *c* 0.045, had the following ORD values: $[\Phi]_{350}$ −284, $[\Phi]_{284}$ −1154, $[\Phi]_{234}$ +1036, $[\Phi]_{220}$ −1508.

4-(D-*lyxo*-Tetraacetoxybutyl)-2-phenyl-1,2,3-osotriazole (**7**), *c* 0.085, had the following ORD values: $[\Phi]_{350}$ −589, $[\Phi]_{285}$ −2117, $[\Phi]_{270}$ +1650, $[\Phi]_{264}$ +1303, $[\Phi]_{236}$ +5781, $[\Phi]_{221}$ 0.

4-(L-*xylo*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**5**), mp 151–152° (lit.[22] mp 158–159°), *c* 0.0045, had the following ORD values: $[\Phi]_{350}$ −559, $[\Phi]_{285}$ −3108, $[\Phi]_{245}$ +3768, $[\Phi]_{240}$ +2828, $[\Phi]_{235}$ +3676, $[\Phi]_{225}$ +1884.

4-(D-*arabino*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**6**), *c* 0.131, had the following ORD values: $[\Phi]_{350}$ −910, $[\Phi]_{283}$ −5250, $[\Phi]_{245}$ +6410, $[\Phi]_{241}$ +5830, $[\Phi]_{239}$ +6700, $[\Phi]_{217}$ 0, $[\Phi]_{207}$ +12,800, $[\Phi]_{205}$ +7860.

Circular dichroism data were recorded in methanol on a Jouan Dichrograph Model 185. The following values were recorded: for compound **6**, 300 nm ($\Delta\epsilon$ 0), 277 (−1.43), 274 (−1.24), 270 (−1.84), 265 (−1.42), 258 (−1.93), 244 [−0.90 (sh)], 227 (0), 223 (+0.27), 219 (0), 213 (−1.52); for **1**, 295 nm ($\Delta\epsilon$ 0), 277 (+0.90), 273 (+0.66), 265 (+1.28), 262 (+0.96), 258 (+1.26), 248 [+0.60 (sh)], 236 (0), 222 (−0.58), 213 (0), 210 (0.24).

Ultraviolet absorption spectra were recorded in 95% ethanol on the Cary 15 or Perkin-Elmer 4000 instrument. The λ_{max} (ϵ) values for the osotriazole derivatives follow: **1**, 265 nm (20,150); **2**, 267 (20,240); **3**, 266 (19,830); **4**, 266 (19,550); **5**, 266 (18,810); **6**, 267 (24,450); **7**, 264 (22,070).

Registry No.—**1**, 16336-37-1; **2**, 15476-33-2; **3**, 15476-35-4; **4**, 15476-32-1; **5**, 15476-34-3; **6**, 16346-56-8; **7**, 6341-06-6; **8**, 7770-63-0; **9**, 4710-99-0.

The Conformation of α-D-Idopyranose Pentaacetate[1,2]

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The proton nmr spectrum of α-D-idopyranose pentaacetate (**1**) at 220 MHz in acetone-d_6 or chloroform-*d* is completely first order and shows that the *C1* chair conformation, having the acetoxymethyl group equatorial and the four acetoxy groups axial, is the favored conformation. In addition to the normal spin couplings of vicinal protons, long-range ^4J couplings are observed between the equatorial protons H-1 and H-3, and similarly between H-2 and H-4. A ^5J coupling between H-1 and H-4 is also observed. The alternative chair (*1C*) conformation, having all groups equatorial except the acetoxymethyl group, is considerably less stable than the *C1* form.

Conformational analysis of polysubstituted chains and ring systems may be studied conveniently by use of various types of carbohydrate derivative. Such compounds offer the advantage that several stereoisomers, and frequently complete sets of stereoisomers, are available in a given system. A program in this laboratory has been concerned with determination of favored conformation and conformational populations at equilibrium, in highly substituted tetrahydropyran ring systems, as provided by pyranoid sugar derivatives,[1] and in the open-chain structures of acyclic derivatives of sugars.[6]

Polysubstituted tetrahydropyran derivatives may be formulated in two energetically nonequivalent chairlike conformations and in a flexible cycle of skew forms interconvertible through the boat forms.[7,8] Conformers in the flexible cycle are generally considered to be of higher energy than the favored chairlike conformer, except perhaps for certain fused-ring derivatives.[9] A rationale for predicting the favored chair conformation for pyranose sugars and their derivatives

(1) This paper is part of a series "Application of 220-MHz Nmr to the Solution of Stereochemical Problems." For previous papers from this laboratory concerned with conformations of pyranoid sugar derivatives see (a) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965); (b) C. V. Holland, D. Horton, and J. S. Jewell, *ibid.*, **32**, 1818 (1967); (c) N. S. Bhacca and D. Horton, *Chem. Commun.*, 867 (1967); (d) C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32**, 3077 (1967); (e) N. S. Bhacca and D. Horton, *J. Amer. Chem. Soc.*, **89**, 5993 (1967).

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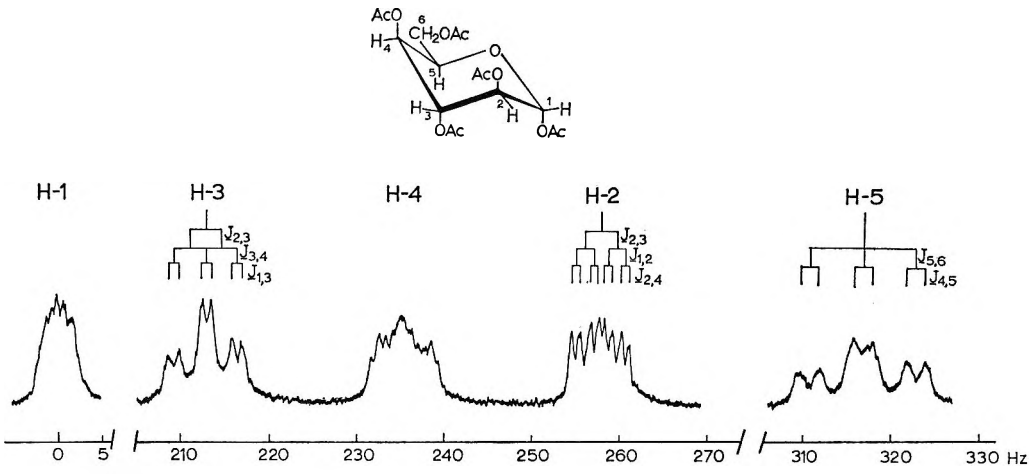

Figure 1.—The low-field portion of the 220-MHz nmr spectrum of α-D-idopyranose pentaacetate (1) in acetone-d_6 at 15°. The scale divisions give chemical shifts in hertz upfield from the H-1 signal. The H-6 signal (not shown) appears as a two-proton doublet, width 6.0 Hz, at 402 Hz upfield from the H-1 signal.

was put forward by Reeves,[10] based on summation of a set of conformational "instability factors." The conformational assignments upon which Reeves' correlations were based were made from data on the formation or nonformation of cuprammonium–diol complexes. The fact that the cuprammonium reagent may itself influence the conformation of a sugar introduces complications in the interpretation of such data. The advent of nmr techniques for the study of conformations in solution has removed this objection from conformational assignments, and it is usually possible to make a clear-cut assignment of one chair conformer or the other, based on the values of vicinal proton–proton spin couplings.[1,11,12]

In certain cases spin-coupling data suggest that the less-favored chair conformer is present in substantial proportion in equilibrium with the favored form, and such a conformational equilibrium has recently been demonstrated directly, for β-D-ribopyranose tetraacetate, by low-temperature nmr spectroscopy at 220 MHz.[1e]

One of the most significant factors to emerge from conformational studies on pyranose sugars and their derivatives is the observation that the favored conformation is not necessarily that chairlike conformer having the greater number of bulky substituents oriented equatorially. An extreme case is tri-*O*-acetyl-β-D-xylopyranosyl chloride (2). This tetrasubstituted, pyranose sugar derivative has, in various solvents, all four substituents axial in the favored conformation;[1b,13] the energy difference between this form and the all-equatorial form is sufficient that the proportion of the latter form statistically present is too small to be observed by conventional low-temperature nmr spectroscopy.[2] There appears to be a strong driving force (anomeric effect)[1a,14,15] for a polar group at C-1 of an aldopyranose derivative to adopt the axial orientation.

Based on the principle that various conformational elements in a polysubstituted, six-membered ring system give rise to additive elements of conformational destabilization, relative to a hypothetical system having no interacitons between substituents, values have been estimated for the conformational free energies of substituent groups in various environments in substituted, pyranose sugars dissolved in organic solvents[15] and in free sugars in aqueous solution.[8] These values, which include a term for the anomeric effect, permit calculation of a predicted, relative free energy for each chair conformer of a given pyranose sugar or its peracetate. The predicted $\Delta G°$ value for one chair conformer is generally considerably less than that of the other chair conformer. Direct observation of the favored conformation by nmr spectroscopy has provided, in many instances, experimental verification of the conformations predicted.

α-D-Idopyranose is a key compound in conformational studies on the six-carbon, pyranose sugars because the favored chair conformation of this sugar and its pentaacetate can be supposed, based on algebraic summation of estimated values for conformational free energies of the ring substituents,[8,10,15] to be the reverse of that chair conformer shown to be the stable form in the common D-hexopyranoses and their pentaacetates. Of the two possible chairlike conformations of α-D-idopyranose, the *C1* (D) conformer (*CA* in the Isbell–Tipson[16] system of conformational nomenclature[17]) has the hydroxymethyl group oriented equatorially and the four hydroxyl groups oriented axially. The alternative *1C* (D) conformer has the four hydroxyl groups equatorial and the hydroxymethyl group axial. By the "instability factors" of Reeves,[10] or by the conformational free-energy values of Angyal,[8] the *1C* (D) conformation is predicted to be favored strongly over the

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TABLE I

CHEMICAL-SHIFT DATA FOR α-D-IDOPYRANOSE PENTAACETATE (1) IN ACETONE-d_6 AT 20° AND 220 MHZ

Solvent	Scale	Chemical shifts of protons H-1	H-2	H-3	H-4	H-5	H-6[a]	CHOAc	CH_2OAc
$(CD_3)_2CO$	Hz upfield from H-1	0	257	213	235	317	402		
	Ppm upfield from H-1	0	1.17	0.97	1.07	1.45	1.83		
	τ scale	4.02	5.19	4.99	5.09	5.47	5.85	7.87,[b] 7.89[b]	8.00[c]
$CDCl_3$	Hz upfield from H-1	0	260	218	248	350	412		
	Ppm upfield from H-1	0	1.18	0.99	1.13	1.59	1.87		
	τ scale	3.93	5.11	4.92	5.06	5.52	5.80	7.89,[d] 7.90[c]	7.94[c]

[a] Doublet, lower-field peak approximately twice the intensity of the higher-field peak. [b] Integral, six protons. [c] Integral, three protons. [d] Integral, nine protons.

C1 (D) conformation, in aqueous solution. For the corresponding pentaacetate, in chloroform solution, the estimated conformational free energies[15] would also indicate that the *1C* (D) conformation is the stable form, if it can be assumed that an axial acetoxymethyl group exerts a steric effect at least as great as that of an acetoxy group.

The pentaacetate (1) of α-D-idopyranose has been characterized on a crystalline basis,[18] and the present report describes conformational assignments from nmr spectroscopic data measured at 220 MHz. The results indicate that substance **1**, in acetone-d_6 or chloroform-*d*, adopts the *C1* (D) conformation, having four axial substituents and one equatorial substituent, as the favored form. This result is the opposite of that predicted by summation of conformational free-energy values.

Spectral Interpretations.—The pmr spectrum (Figure 1) of α-D-idopyranose pentaacetate (**1**), at 220 MHz in acetone-d_6, is completely first-order. Chemical-shift data are listed in Table I; Table II gives coupling constants. Each of the methine protons gives rise to a multiplet that is well separated from neighboring signals, so that no significant virtual coupling[19] is possible, and the couplings derived by first-order analysis should be close to the absolute $|J|$ values. The methylene group gives rise to a two-proton signal that appears as a doublet, indicating that the two C-6 protons are equivalent. The spacing of this doublet gives the $J_{5,6}$ coupling constant. The highest field, methine proton signal, that of H-5, appears as a triplet of narrow doublets, through coupling with H-6 and with H-4, and the small splitting gives the $J_{4,5}$ coupling constant. Another triplet of doublets, observed at next to lowest field, is assigned to H-3; the triplet structure arises through equal coupling of H-3 with H-2 and H-4, and the additional splitting arises by long-range coupling with H-1 (W arrangement[20,21] of H-1 and H-3). The eight-peak multiplet to lower field of the H-5 signal is assigned to H-2, and the multiplicity arises by unequal coupling of H-2 with three other protons. The largest splitting is caused by the $J_{2,3}$ coupling, and a smaller splitting gives $J_{1,2}$; the smallest splitting is attributable to long-range coupling of H-2 with H-4 (W arrangement[20,21]).

TABLE II

PROTON–PROTON COUPLING CONSTANTS FOR α-D-IDOPYRANOSE PENTAACETATE (1) IN ACETONE-d_6

Vicinal couplings, Hz					Long-range couplings, Hz		
$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,3}$	$J_{1,4}$	$J_{2,4}$
2.1	3.6	3.5	2.1	6.0	1.0	0.6	0.9

Of the two remaining methine proton signals, that at lowest field can be assigned to H-1, and the multiplet between the H-3 and H-2 signals must, therefore, be that of H-4. On the basis of the couplings already assigned, the H-1 signal should appear as a quartet of width 3.1 Hz and the H-4 signal should appear as an octet of width 5.6 Hz. The observed signals, however, indicate that there is a small, additional coupling of about 0.6 Hz between H-1 and H-4. On this basis the H-1 signal should appear as an octet and the H-4 signal as a 16-line multiplet; the small difference in magnitude between the long-range splittings prevented each of these multiplets from being resolved completely.

The acetyl-group signals appear as a high-field singlet, assigned to the primary acetoxy group, and a partially resolved group of signals at lower field that was assigned to the four acetoxy groups attached axially to the ring; the latter were not assigned individually.

Addition of a few drops of benzene-d_6 to the prepared sample caused the C-6 protons to become slightly nonequivalent, as observed in a doubling of the higher field peak of the H-6 signal and concomitant increase in complexity of the H-5 signal.

The nmr spectrum in chloroform-*d* is similar to that observed in acetone-d_6 and the H-6 protons are still equivalent in this solvent. Some differences in chemical shifts are observed (Table I); notably the separation of the H-2 and H-4 signals is smaller.

The advantages of measurements at 220 MHz is well illustrated by the separation of the H-3, H-4, and H-2 signals shown in Figure 1. Although the separation of the H-3 and H-2 signals is a mere 0.20 ppm, the three signals are completely separated and there is hardly any buildup in intensity of the inner portions of the H-3 and H-2 signals. In contrast, a comparable spectrum measured at 100 MHz (Varian HA-100 spectrometer) showed the three multiplets almost contiguous, with strong intensity buildup of the inner portions of the H-3 and H-2 signals.

Discussion

The small magnitudes (2.1–3.6 Hz) of the vicinal couplings observed for **1** in acetone-d_6 clearly exclude the *1C* (D) conformation which, with the axial arrangement of H-1, H-2, H-3, and H-4, would have given a series of large (8–10 Hz) vicinal couplings. The couplings observed are fully consistent with the *C1* (D) conformation

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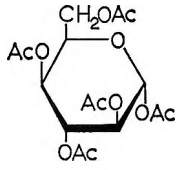
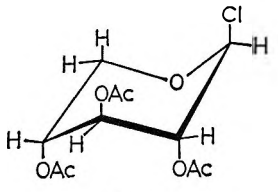
having H-1, H-2, H-3, and H-4 equatorial.[22] The data are not in accord with formulation of **1** in a skew conformation because such a structure would be expected to give rise to one or more large, vicinal couplings.[23]

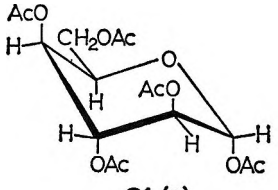


1

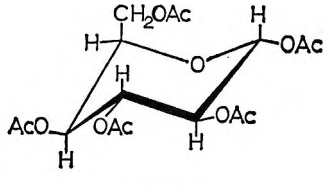


2

In view of the fact that the molecule of α-D-idopyranose pentaacetate in the favored *C1* (D) conformation



C1 (D)
favored



1C (D)
not favored

has the supposedly strong destabilizing influence of two pairs of *syn*-diaxial acetoxy groups, it is difficult to reconcile the observed behavior with the predictions based on current theory.[24] It does not appear probable that the anomeric effect is alone responsible for controlling the conformation of **1**. It has been observed[1b] that a related example, tri-*O*-acetyl-β-D-xylopyranosyl chloride (**2**), favors the all-axial *1C* (D) conformation even in rather polar solvents such as acetone and acetonitrile, although the anomeric effect is considered[8,15] to be diminished on passing from solvents of low polarity to solvents of high polarity. It may be noted that the *C1* (D) conformation is also favored in the case of the penta-*O*-benzoyl analog[25] of **1** and also with 1,2,3,6-tetra-*O*-acetyl-α-D-idopyranose.[18]

Possibly there are attractive interactions between axial acetoxy groups and other groups in the molecule, or repulsive interactions between vicinal, equatorial groups, that should be considered in any model for predicting favored conformation. Detailed speculation on this point is not warranted until data on conformational and configurational equilibria in a series of related compounds become available.

Extensive long-range couplings through the W arrangement of bonds are commonly observable in bridged ring systems,[20,21] and ^5J couplings have also been observed in some bridged ring systems.[26] The present example is unusual, however, in that such couplings are here exhibited by a pyranoid ring-system that is not bridged. This observation suggests that the molecule of **1** may be conformationally quite rigid, with libration about the shape corresponding to the minimum energy being energetically unfavorable.

Experimental Section

Nmr spectra were measured at 220 MHz with a Varian spectrometer equipped with a superconducting solenoid.[27] The sample of α-D-idopyranose pentaacetate (**1**) had mp 94–95° and $[\alpha]^{20}D$ +55.2° (*c* 0.8, chloroform), in good agreement with literature values.[18] The concentration of sample was ~10% and tetramethylsilane (τ 10.00) was used as the internal standard for spectra measured in chloroform-*d*. Spectra were measured at 15–20°, and coupling constants (Table II) were measured directly from spectra recorded at 100-Hz sweep width. Data on chemical shifts are given in Table I.

Registry No.—1, 16299-15-5.

(22) A small proportion of the *1C* (D) conformer undoubtedly exists in equilibrium with the favored *C1* (D) form, but the proportion of the nonfavored form can be expected to be not more than 10% and it may be considerably less than this.

(23) A nonchair conformation has been proposed [R. Bentley, *J. Amer. Chem. Soc.*, **82**, 2811 (1960)], based on cuprammonium-complexing data, for methyl β-D-idopyranoside in aqueous solution, and the α-D anomer was considered to adopt the *1C* conformation.

(24) Since this manuscript was submitted for publication a paper has appeared by P. R. Sundarajan and V. S. R. Rao [*Tetrahedron*, **24**, 289 (1968)] that describes potential energy calculations for the aldohexopyranoses and aldopentopyranoses. If polar interactions are ignored completely, and Kitaigorodsky-type functions are used to determine the nonbonded interaction energies, it can be calculated that the lowest energy conformer for all D-aldohexopyranoses would be the *C1* (D) chair form. However, since there is abundant evidence[1,8,15] that polar factors are significant in influencing conformation, a complete theoretical model for predicting favored conformation would have to include terms for polar interactions. The quantitative significance of polar factors, in relation to steric factors, is difficult to assess.

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The Synthesis of 3-β-(3′-Deoxy-D-ribofuranosyl)adenine, an Isomer of Cordycepin[1]

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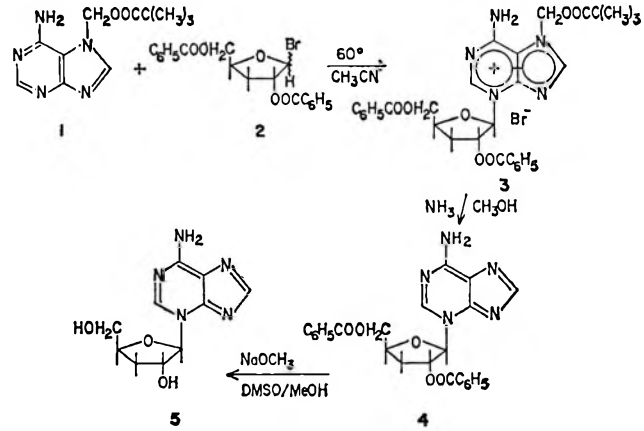
In an application of the use of the pivaloylcxymethyl protecting group, 3-β-(3′-deoxy-D-ribofuranosyl)adenine (**5**), an isomer of cordycepin, has been synthesized in good yield. The route involves the alkylation of 7-pivaloyloxymethyladenine (**1**) with 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) to give 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine (hydrobromide **3**) and successive removal of the pivaloyloxymethyl and benzoyl groups.

Interest in 3′-deoxyribofuranosyl nucleosides stems from the identification[2,3] of the metabolite cordycepin from *Cordyceps militaris* (Linn.) Link[4-6] and from the fermentation broth of *Aspergillus nidulans* (Eidam) Wint. as 9-β-(3′-deoxy-D-ribofuranosyl)adenine[7-12] (3′-deoxyadenosine). This 3′-deoxyribofuranosyl nucleoside inhibits nucleic acid synthesis in Ehrlich ascites cells[13-18] and in *Bacillus subtilis*.[19] Parallel interest has developed in the isonucleosides of adenine in which the sugar moiety is attached to N-3 instead of N-9, such as 3-β-D-ribofuranosyladenine (3-isoadenosine)[20] and 3-β-(2′-deoxy-D-ribofuranosyl)adenine[21] especially because of the unusual biological activity exhibited by the former.[20c,22-24] Accordingly, we were encouraged to prepare 3-β-(3′-deoxy-D-ribofuranosyl)-adenine (**5**) (3′-deoxy-3-isoadenosine or 3-isocordycepin), which contains the characteristic structural features of both cordycepin and 3-isoadenosine.

The mild synthetic route to 3-substituted adenine derivatives employing the pivaloyloxymethyl (Pom) protecting group[21] seemed eminently suited for the preparation of **5**. Of the several synthetic procedures developed for providing a 3-deoxypentose moiety on purine or pyrimidine bases,[7-12,25-31] that involving alkylation by a preformed 3-deoxyribofuranosyl halide[10,26] appeared simplest. 7-Pivaloyloxymethyladenine (**1**), obtained from sodium adenide and chloromethyl pivalate,[21] was treated with 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**)[10] in acetonitrile at about 60°. The reaction was essentially complete within 5 min, and crude product (**3**) was obtained in



1 2 3 5 4

yields up to 95%. Characterization of the product as 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine hydrobromide (**3**) followed from the ultraviolet[32] and nmr spectra. Since the compound showed instability in solution, it was not purified further but was subjected directly to reaction with methanolic ammonia at room temperature. This treatment led to rapid removal of the 7-pivaloyloxymethyl group but gave, in place of the expected nucleo-

(1) This work was supported by Research Grant USPHS-GM-05829 from the National Institutes of Health, U. S. Public Health Service, to whom we are pleased to acknowledge our thanks.

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side **5**, a mixture of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) and 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-N_6-pivaloyladenine (N^6-pivaloyl derivative of **4**) in a ratio of about 4:1. The latter, minor component, formed by intermolecular rearrangement of the pivaloyl group,[21] was readily separated from the sparingly soluble **4** and was identified by its spectroscopic characteristics. The debenzoylation of **4**, isolated in 59% yield from the ammonia–methanol treatment, was accomplished with sodium methoxide in dimethyl sulfoxide–methanol at room temperature in 79% yield.

The structure of the debenzoylated product, mp 224.5–225°, homogeneous by tlc, was indicated as 3-β-(3′-deoxy-D-ribofuranosyl)adenine (**5**) by microanalysis and the route of synthesis. The position of attachment of the sugar to adenine was confirmed as **3** by the nmr and uv spectral data.[33,34] The assignment of the β configuration required further inspection. Participation of the 2′-*O*-benzoyl group during the alkylation reaction (**1** + **2**) should have given preponderantly the β anomer, following the *trans* rule.[35,36] Similar use of 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) had produced the β-ribofuranoside cordycepin,[10] and direct alkylation of adenine with 2,3,5-tri-O-benzoylribofuranosyl bromide had given two β-ribofuranosides, precursors of adenosine and 3-isoadenosine.[20b] In the light of the synthetic precedents, the fairly high over-all yield from 7-pivaloyloxymethyladenine of pure **5** (43%), with its sharp melting point and homogeneity indicated by tlc, was suggestive of the β configuration. The ORD curve for **5** was difficult to measure owing to the high $\epsilon/[M]$ ratios in the region of the absorption maximum but indicated a negative Cotton effect. Application of Hudson's rules of isorotation[38] is not secure for a new, single example as represented by **5**, and anomeric assignments by ORD have been limited mainly to cyclo nucleosides, pyrimidine nucleosides, purine N-9 nucleosides,[39,40] and series of nucleosides containing unnatural sugar moieties.[41] From our experience with 3-substituted adenines.[20b,21] we consider the optical rotation data to be further suggestive of the β configuration in **5**.

Further support for the assignments of anomeric configuration emerges from the nmr spectrum through judicious application of the Karplus equations[42,43] to the relation between the coupling constant $J_{1',2'}$ and the dihedral angle between the intersecting planes defined by H-1′–C–C and H-2′–C–C and empirically by analogy. In the nmr spectra of several anomeric pairs of 3′-deoxyribofuranosylpyrimidine nucleosides[26] there appears to be a small but distinct difference between the *trans* $J_{1',2'}$ coupling, 1.3–1.8 cps, of the β anomers and the *cis* $J_{1',2'}$ coupling, 3.5–3.9 cps, of the α anomers. The related 9-β-(3′-deoxy-D-ribofuranosyl)adenine (cordycepin) in D_2O has been noted[44] to have a low $J_{1',2'}$ coupling, 2.2 cps, relative to that of adenosine, 6.1 cps. The value of $J_{1',2'}$ which we observed for 3′-deoxy-3-isoadenosine (**5**) in hexadeuteriodimethyl sulfoxide was 3.2 ± 0.5 cps, which did not permit a firm conclusion concerning the anomeric configuration. However, the observed $J_{1',2'}$ coupling was solvent dependent, and the addition of a few drops of deuterium oxide to the DMSO-d_6 solution of **5** caused $J_{1',2'}$ to decrease to 2.7 cps. Moreover, the signal for the anomeric C-1′ proton of **5** in D_2O acidified with deuteriosulfuric acid occurred as a broadened *singlet* with half-height width of 2.2 cps.[45] Supportive nmr evidence was also available from the signal for the C-1′ proton in the precursors **4** (singlet) and **3** (broad singlet). Further, the chemical shift of H-1′ appears in the region to be expected for a proton *cis* to the C-2′ hydroxyl group.[21,44,46] The chemical shift and coupling constant are consistent with a β configuration for **5**, but no final correlation between nmr spectra and configuration can be made in the absence of the α anomer. In conclusion, the structural formulas **3**, **4**, and **5** indicate the most probable stereochemistry of the products synthesized in this sequence, which, by the use of the Pom protecting group, provides a good yield of 3-β-(3′-deoxy-D-ribofuranosyl)adenine.[47]

Experimental Section[48]

2,5-Di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) was obtained as a pale brown oil by following the ten-step procedure of Walton, Holly, Boxer, Nutt, and Jenkins[10] (4.6% over-all yield from D-xylose).

3-β-(2′,5′-Di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine Hydrobromide (**3**).—To a solution of 0.611 g (2.46 mmol) of 7-pivaloyloxymethyladenine (**1**)[21] in 100 ml of anhydrous acetonitrile at 57° was added 1.8 g (4.4 mmol) of 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide[10] in 10 ml of acetonitrile. After 10 min at 57–60°, the solution was cooled and then evaporated *in vacuo* (below 30°). The residual foam was dissolved in 10 ml of acetonitrile, and the solution was diluted with *ca.* 100 ml of ether. After trituration, the crude product was collected by filtration as fawn-colored microcrystals, yield 1.488 g (94%), which softened at 115°, gradually decomposed above *ca.* 150°, and melted with evolution of a gas and extensive decomposition at *ca.* 206° (rapid heating): λ_{max} 228, 279, and 288 (sh) mμ, λ_{min} 250, λ_{max} (pH 1) 229, 277, and 288 (sh), λ_{min} 250, λ_{max} (pH 13) (unstable) *ca.* 275 (sh), 281, and 326, λ_{min} 258 and

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(47) This compound has been mentioned by H. T. Shigeura and S. D. Sampson, *Nature*, **215**, 419 (1967), in the summary of their study on the structural basis for phosphorylation of adenosine congeners.

(48) All melting points are corrected. The ir spectra were recorded as Nujol mulls on a Perkin-Elmer 337 grating infrared spectrophotometer at slow scan. The uv spectra were recorded on a Cary Model 15 spectrophotometer on samples dissolved in 95% aqueous ethanol and 0.1 *M* hydrochloric acid in 95% aqueous ethanol (pH 1).[32] The pmr spectra were determined with a Varian A-60A spectrometer. Chemical shifts are reported in δ units (ppm downfield from internal tetramethylsilane) and coupling constants in cps with estimated error ±0.5 cps. The following conventions for abbreviations are used: m = multiplet, e = envelope, t = triplet, d = doublet, s = singlet, b = broad, p = pseudo, D = signal disappears on exchange with D_2O, sh = shoulder, st = strong, med = medium, v = very. Thin layer chromatography (tlc) was performed on Eastman silica gel strips (with fluorescent indicator) routinely using 1:19 to 1:4 methanol–chloroform solvent systems.

ca. 290; nmr ($CDCl_3$) δ 1.16 [9H, s, $(CH_3)_3CCOO$], 2.1–3.4 (2H, vbm, 3′-CH_2), 4.80 [3H, e, 5′-CH_2 and 4′-CH(?)], 6.04 [1H, e, 2′-CH(?)], 6.57 (1H, bs, 1′-CH), 6.88 (2H, bs, $COOCH_2$-N), 7.23–7.67 (6H, m, *m*- and *p*-C_6H_5COO), 7.88–8.20 (4H, m, *o*-C_6H_5COO), 8.48 and 9.20 (1H each, s,s, purine H's), 9.05 (2H, be, NH_2). The resolution of the nmr spectrum was low owing to slow decomposition and precipitation of solid from the solution. Compound **3** was essentially pure as judged by tlc and was used directly in the next reaction.

3-β-(2′,5′-Di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (4).—Compound **3** (4.26 g, 6.51 mmol) was dissolved in 12 ml of methanol saturated with ammonia. After 40 min at room temperature, the reaction mixture was filtered, giving 2.31 g of almost colorless microcrystals. Nmr spectroscopy (trifluoroacetic acid solution) established this material to be a mixture of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) and its N^6-pivaloyl derivative in a ratio of about 4:1. The crude product was triturated with 30 ml of boiling chloroform, and this mixture was evaporated on a water bath with periodic addition of methanol until most of the chloroform had been replaced by methanol. Filtration of the cooled mixture then gave 1.775 g (59%) of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) as colorless microcrystals: mp 244–246° dec; ν_{max} 3220 cm^{-1} (b, NH_2), 1724 (sh), 1716, 1272, and 1261 (st, ester) 1686 and 1621 (med, purine); λ_{max} 230 mμ (ε × 10^{-3} 33.8), 274–282 (13.5), *ca.* 293 (sh, 10.7), λ_{min} 251 (5.6), λ_{max} (pH 1) 229 (33.8) and 277 (20.2), λ_{min} 250 (8.7); nmr (CF_3COOH) δ 2.70 (2H, m, 3′-CH_2), 4.78 (2H, m, 5′-CH_2), 5.13 (1H, e, 4′-CH), 5.86 [1H, bps, 2′-CH(?)], 6.75 (0.8H, s, 1′-CH), 7.35–7.80 (6H, m, *m*- and *p*-C_6H_5COO), 8.00–8.28 (4H, m, o-C_6H_5-COO), 8.87 and 9.24 (1H each, s,s, purine H's).

Anal. Calcd for $C_{24}H_{21}N_5O_5$: C, 62.74; H, 4.61; N, 15.24. Found: C, 62.53; H, 4.64; N, 15.34.

From the original chloroform–methanol mother liquors long needles (0.166 g) deposited on standing. Recrystallization from acetonitrile gave glistening colorless needles of nearly pure **3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-N^6-pivaloyladenine**: softens and melts indistinctly at 113°; λ_{max} 229, 283 (sh), and 295 mμ, λ_{min} 255, λ_{max} (pH 1) 228, 283 (sh), 293, and 302 (sh), λ_{min} 251, λ_{max} (pH 13) 228, 273 (sh), 282 and 329, λ_{min} 263 and 288; nmr ($CDCl_3$) δ 1.46 (9H, s, $(CH_3)_3CCON$), 2.22–3.22 (2H, m, 3′-CH_2), 4.72 (2H, ps and d, J = ~4.2 cps av, 5′-CH_2), 4.68–5.22 (1H, m, 4′-CH), 6.02 and 6.11 (1H, d of bpt, J = 5.2, 1.5 cps, 2′-CH), 6.48 (1H, bs half-height width 2.5 cps, 1′-CH), 6.87–7.22 (1H, e, NH), 7.22–7.63 (6H, m, *m*- and *p*-C_6H_5COO), 7.92–8.13 (4H, m, o-C_6H_5COO), 8.14 and 8.81 (1H each, s,s, purine H's).

3-β-(3′-Deoxy-D-ribofuranosyl)adenine (5).—Sodium methoxide (0.206 g, 3.81 mmol) in 15 ml of methanol was added to a stirred suspension of 0.372 g (0.81 mmol) of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) in 5 ml of dimethyl sulfoxide. The reaction mixture became homogeneous after being stirred for 40 min at room temperature and was treated with 7 drops of glacial acetic acid. The resulting solution was concentrated *in vacuo* (30°) to a translucent gel. This crude product was suspended in 50 ml of 19:1 chloroform–methanol, and the suspension was applied to a column of silica gel (70 g). Elution with 1:4–3:7 methanol–chloroform gave 0.185 g (91%) of pale cream crystals. Recrystallization from absolute ethanol gave 0.132 g of **3-β-(3′-deoxy-D-ribofuranosyl)adenine (5)** as analytically pure, glistening, colorless plates: mp 222–223° dec (further recrystallization raised the melting point to 224.5–225°); ν_{max} 2300–3500 cm^{-1} (b, st, NH_2 and OH); λ_{max} 214 mμ (ε × 10^{-3} 16.1) and 277 (12.9), λ_{min} 244 (2.9), λ_{max} (pH 1) 219 (sh, 11.4) and 276 (17.6), λ_{min} 237 (3.2); nmr (DMSO-d_6) δ 1.67–2.50 (2H, m, 3′-CH_2), 3.27–4.07 (2H, m, 5′-CH_2), 4.32–5.00 (2H, m, 2′-CH and 4′-CH), 5.84 and 6.12 [*ca.* 0.8H each, e (D), e (D), 2′-COH and 5′-COH], 5.96 (1H, d, J = 3.2 cps, 1′-CH), 8.21 [1.4H, e (D), NH_2], 7.85 and 9.05 (1H each, s,s, purine H's).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.98; H, 5.25; N, 27.98.

Increased yields of the nucleoside **5** could be obtained by using small solvent/solute ratios. Under these more concentrated conditions the reaction mixture would not become homogeneous but, after 2 hr or less, substantially pure nucleoside **5** could be obtained directly by filtration. Work-up of the filtrate would then give additional amounts of **5**.

Registry No.—**3**, 16136-37-1; **4**, 16136-34-8; **5**, 16136-35-9; 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl-N^6-pivaloyladenine, 16136-36-0.

Branched-Chain Sugar Nucleosides. IV. 2′-*C*-Methyladenosine

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The synthesis of 2′-*C*-methyladenosine is described. The required derivative of the previously unknown 2-*C*-methyl-D-ribofuranose was prepared starting with 2-*C*-methyl-D-ribono-γ-lactone. The lactone was completely benzoylated and the benzoyl derivative was reduced with bis(3-methyl-2-butylborane) which produced a mixture of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose and 3,5-di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose. This mixture was benzoylated to give a mixture of α and β tetrabenzoates which was converted into 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride. The chloro sugar reacted with chloromercuri-6-benzamidopurine to give the completely acylated nucleoside. Catalytic removal of the benzoyl blocking groups with sodium methoxide in methanol led to the isolation of crystalline 2′-*C*-methyladenosine. From nmr spectral measurements and consideration of steric interactions, it is suggested that 2′-*C*-methyladenosine exists in a 2′-*exo*,3′-*endo* (T_2^3) conformation and is, therefore, conformationally unrelated to adenosine.

In a preliminary communication,[1] we reported the synthesis of 2′-*C*-methyladenosine (**13**), the second of a series of branched-chain sugar nucleosides. We now wish to describe the synthesis of **13** in detail.

Our interest in 2′-*C*-methyladenosine stemmed from the biological activity evinced by 3′-*C*-methyladenosine,[1] the first compound of this series. Our objective in the synthesis of a 2′-*C*-methyl nucleoside was to produce a compound which might mimic a 2′-deoxy nucleoside, either through the lowered chemical activity of the tertiary 2′-hydroxyl or because conformational changes produced by the steric interaction of the 2′-*C*-methyl group with the purine moiety might move the 2′-hydroxyl group to a location where it would no longer be recognized enzymically as the 2′-hydroxyl group of a normal nucleoside. There is evidence that a tertiary alcohol in a nucleoside is not a satisfactory substrate for enzymic reactions in the finding that 5′,5′-di-*C*-methyladenosine,[2] a branched-chain sugar nucleoside having a tertiary C-5′ hydroxyl, is not phosphorylated by Ehrlich ascites cells.[3] It seemed possible that a nucleoside possessing a non-

(1) (a) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Amer. Chem. Soc.*, **88**, 4524 (1966).

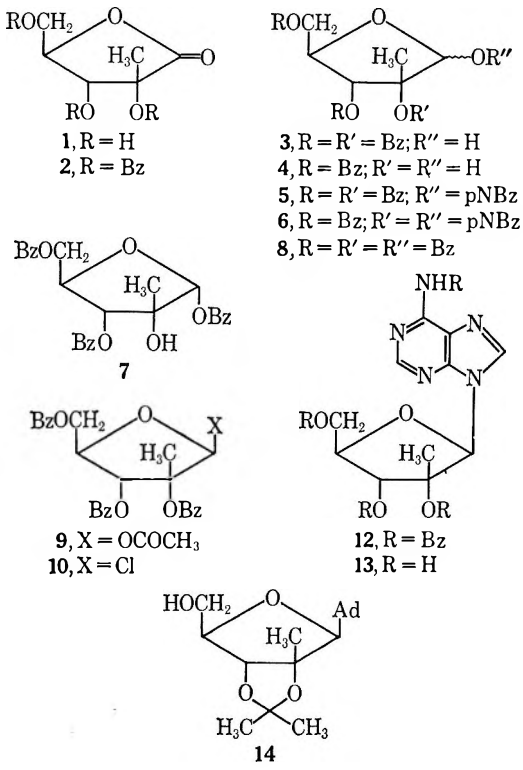
(2) R. F. Nutt and E. Walton, *J. Med. Chem.*, **11**, 151 (1958).

(3) H. T. Shigeura and S. D. Sampson, *Nature*, **215**, 419 (1967).

functioning 2′-hydroxyl group might indeed resemble a 2′-deoxy nucleoside in biological systems.

For the synthesis of 2′-*C*-methyladenosine, a source of the previously undescribed 2-*C*-methyl-D-ribofuranose was required. Aldoses branched at C-2 are not completely unknown. The naturally-occurring sugar hamamelose, 2-*C*-hydroxymethyl-D-ribose, has been available for some time and its synthesis in the pyranoid form was described by two groups[4a,b] of workers.

More recently the synthesis of methyl 3,4-*O*-isopropylidene-2-*C*-methyl-β-L-ribopyranoside was reported.[4c] The method of introducing branching at C-2 used by these workers involved addition of suitable reagents to a 2-keto aldopyranose. This approach might have been useful in the synthesis of 2′-*C*-methyl-D-ribofuranose, but what appeared to be a more attractive starting point was found in 2-*C*-methyl-D-ribono-γ-lactone (**1**) (α-glucosaccharinic acid lactone). This lactone, easily prepared[5a] in low yield by an alkaline rearrangement of invert sugar, has been known for about 90 years[5b] although its exact structure was finally proven only recently.[5c] Reaction of **1** in pyridine with benzoyl chloride gave the 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribono-γ-lactone (**2**). Although benzoylation of the primary C-5 hydroxyl and the secondary C-3 hydroxyl proceeded at 25°, acylation of the tertiary C-2 hydroxyl required heating at 70° for several hours. The tri-*O*-benzoyllactone (**2**) was then reduced to the corresponding aldose using disiamylborane (bis-3-methyl-2-butylborane). This reagent had been used previously[6] in the reduction of several straight-chain poly-*O*-acyl-hexono-γ-lactones. The reduction of **2** yielded, along with the expected 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (**3**), a considerable amount of 3,5-di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (**4**). Not all of the di-*O*-benzoyl derivative (**4**) resulted from hydrolysis of the 2-*O*-benzoyl group but was produced in great measure by reductive cleavage as demonstrated by the isolation of benzyl benzoate following rebenzoylation of the crude reduction mixture. The 2,3,5-tri-*O*-benzoyl and 3,5-di-*O*-benzoyl derivatives (**3** and **4**) could be separated by chromatography on silica gel from which the α and β anomeric mixtures **3** and **4** were isolated as oils. For further characterization, both **3** and **4** were completely acylated with *p*-nitrobenzoyl chloride and crystalline 2,3,5-tri-*O*-benzoyl-1-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (**5**) and 3,5-di-*O*-benzoyl-1,2-di-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (**6**) were obtained, respectively. For preparative purposes, the mixture of **3** and **4** was benzoylated in pyridine at 70° to produce a mixture of α- and β-1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**8**) from which most of the β anomer (β **8**) was separated by crystallization from ether. The pure α anomer (α **8**) was obtained by chromatography of the residue obtained from the filtrate from the crystallization. In an attempt to separate the α and β anomers of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**3**) by chromatography on acid-washed alumina, a rearrangement occurred and practically all of the product was converted into 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (**7**) by a migration of the 2-*O*-benzoyl group to the anomeric position. Only one anomer was obtained and, as the migration undoubtedly occurred through a cyclic intermediate, it must be the α anomer.



Both anomers of **8** were convertable into 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride (**10**); however, the reaction conditions required for the conversion of α **8** were quite different from those used for β **8**. In the case of β **8**, **10** was obtained in good yield by treatment with ethereal hydrogen chloride at 25° for about 2 hr. Under the same conditions, α **8** remained virtually unchanged after 5 days. Even when hydrogen chloride in acetic acid was used, 24 hr at 25° was required for complete conversion of α **8** into a mixture of **10** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**9**). Retreatment of this mixture with ethereal hydrogen chloride at 25° for 2 hr resulted in complete conversion into **10**.[7]

From both α **8** and β **8** only one anomer, 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride, is obtained. This is also true of the 1-*O*-acetyl intermediate (**9**) formed during the first stage of conversion of α **8** into **10**. Ness and Fletcher[8] have reported that the reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with water in acetone leads to the formation of approxi-

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(5) (a) R. L. Whistler and J. N. BeMiller, *Methods Carbohyd. Chem.*, **2**, 484 (1963); (b) E. Peligot, *Compt. Rend.*, **89**, 918 (1879); (c) J. C. Sowden and D. R. Strobach, *J. Amer. Chem. Soc.*, **82**, 3707 (1960).

(6) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **86**, 1457 (1964); P. Kohn and L. M. Lerner, *J. Org. Chem.*, **31**, 1503 (1966).

(7) Tlc of the acetic acid, hydrogen chloride reaction solution in the conversion of α **8** into **10** showed a sizable zone for **10** at R_f 0.3 and a moderate zone for **9** at R_f 0.5. However, tlc of the product obtained after concentration of the reaction solution indicated that almost all of the isolated product was **9** and very little was **10**. This was confirmed by the nmr spectra, which indicated a ratio of **9** to **10** of about 9:1. This reversion of **10** to **9** during work-up is reasonable if one assumes that the reaction mixture is a mobile equilibrium. During concentration Cl^-, as volatile hydrogen chloride, is removed faster than AcO^- thereby driving the reaction in the direction of **9**. In the reaction carried out in ether solution, there is no competing anion, and **10** is the sole product isolated after concentration of the reaction solution.

(8) R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **78**, 4710 (1956).

mately equal amounts of 2,3,5-tri-*O*-benzoyl-D-ribofuranose and 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose. We have repeated this reaction using the chloro sugar in place of the bromo sugar and have obtained a similar result. However, when **10** was subjected to the same conditions, 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose was the only product. In the case of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride and bromide, the rearranged product 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose arises from the β-glycosyl halide *via* a cyclic carbonium ion whereas the 2,3,5-tri-*O*-benzoyl-D-ribofuranose comes from unassisted hydrolysis of the α anomer of the chloro sugar. The quantitative recovery of rearranged product **7** from **10** indicates that **10** is entirely in the β form.

The assignment of anomeric configurations to β **5**, β **6**, α **8**, β **8**, and **10** is based in part on the obvious α configuration of the rearrangement product **7**. The nmr spectrum of **7** shows the C-3 proton resonance as a broad singlet; the C-3 proton resonance of α **8** is also a broad singlet. On the other hand, all of the β anomers show the C-3 proton resonance as a doublet ($J_{3,4}$ = 7.3–7.5 cps). The resonance for the C-1 proton of both α and β anomers appears as a singlet because of the absence of vicinal protons at C-2. It was noted that the resonances for H-1 of the β anomers were about 0.2 ppm downfield relative to the resonances for H-1 of the related α anomers.

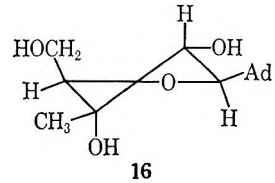
Benzoylation of **7** in pyridine with benzoyl chloride produced mainly α **8**; however, this does not constitute an unambiguous proof of the configuration of α **8** because a sizable amount of β **8** was also recovered from the reaction products. It is assumed that β **8** was obtained from 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**3**) produced by reconversion of **7** into **3** during the essentially basic (pyridine) conditions of the benzoylation reaction. It has been reported[8] that 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose is rearranged to 2,3,5-tri-*O*-benzoyl-D-ribofuranose under basic conditions.

Additional confirmation of the anomeric configurational assignments of α and β **8** is obtained from the difference in the ease of conversion of these two compounds into the halo sugar **10**. Neighboring-group assistance in the β *trans* anomer of **8** would be expected to result in easy conversion into **10**, whereas the unassisted reaction in the case of the α anomer would be expected to require more strenuous conditions. The quite different experimental conditions required for the preparation of **10** from α and β **8** are in keeping with the configurational assignments.

Reaction of **10** in boiling xylene with chloromercuri-6-benzamidopurine (**11**)[9] gave 6-benzamido-9-(2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl)purine (**12**) which was purified by chromatography on silica gel. Attempts to purify **12** on acid-washed alumina led to extensive decomposition into 6-benzamidopurine and a carbohydrate fragment whose physical properties indicated that it was 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (**7**).

Following purification, **12** was deblocked in methanol with a catalytic amount of sodium methoxide and 2′-*C*-methyladenosine (**13**) was isolated and crystallized from water.

Configurational Assignment.—The assignment of the β configuration to 2′-*C*-methyladenosine (**13**) was based on the following: (1) the *trans* rule;[10] (2) the negative Cotton effect shown by ORD measurements is consistent with the proposals advanced[11] for purine β-D-nucleosides; (3) the facile decomposition of the polyacylated nucleoside (**12**) on acid-washed alumina giving **11** and **7**, which undoubtedly requires the anchimeric assistance of the neighboring 2′-acyloxy moiety, is in keeping with a *trans* configuration of the functional groups at C-1′ and C-2′. Although nmr measurements were of little direct value toward establishing the anomeric configuration of **13**, the magnitude of $J_{3',4'}$ (8.8 cps) is of interest. In the case of 5′,5′-di-*C*-methyladenosine (**15**)[2] $J_{1',2'}$ was found to be about 7.0 cps whereas $J_{3',4'}$ was about 1.5 cps. On the other hand, 3′-*C*-methyladenosine (**16**)[12] showed $J_{1',2'} \simeq$ 8.2 cps. The rather large value for $J_{1',2'}$ in both **15** and **16** indicated a rather large dihedral angle for the *trans* protons on C-1′ and C-2′, and led to the proposal that C-2′ in these compounds, is in an *endo*[13] conformation. In 2′-*C*-methyladenosine (**13**), however, the dihedral angle H-3′–H-4′, is large, ∽155°,[14] and is in keeping with a C-3′ *endo*[13] conformation. The potential steric interaction of the C-2′ methyl group with the purine moiety at C-1′ would be maximumly relieved if C-2′ were *exo*.[15] For these reasons, and examination of molecular models, it is proposed that **13** exists in a twist conformation wherein C-2′ is *exo* and C-3′ is *endo* (T_2^3),[16] which would make 2′-*C*-methyladenosine the "conformational mirror image" of 3′-*C*-methyladenosine, and is, therefore, not related to adenosine conformationally.



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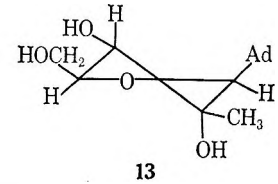

13

2′-*C*-Methyladenosine (**13**) was converted, by a modification of the method of Hampton,[17] into its 2′,3′-*O*-isopropylidene derivative (**14**). As in the synthesis of 2′,3′-*O*-isopropylidene-3′-*C*-methyladenosine,[12] the conversion was very slow and gave a low yield of product. The nmr spectrum of **14** showed that $J_{3'4'}$ was 2.1 cps, a considerable reduction from the value of 8.8 cps shown by **13**, and indicates a reduction in the dihedral angle H-3′–H-4′ from 155° in **13** to ∽115° in **14**. As was proposed in the case of 3′-*C*-methyladenosine,[12] this would be accompanied by a reduction in the dihedral angle O–C-2′–C-3′–O to a size which would accommodate a dioxolane ring. The resultant flattening of the furanose ring would increase steric contacts between the

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(10) B. R. Baker, Ciba Foundation Symposium, Chemistry and Biology of Purines; Little, Brown and Co., Boston, Mass., 1957, p 120.

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purine and sugar moieties[15] which impedes the conversion of **13** into **14**.

Experimental Section[18]

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-D-ribono-γ-lactone (2).—A solution of 5 g (30.8 mmol) of **1**[5] in 100 ml of dry pyridine was cooled, stirred, and treated with 17 ml of benzoyl chloride. The mixture was heated at 65–70° for 4 hr, then cooled, and stirred while 20 ml of water was added. After 25 min, the mixture was concentrated to a thick semisolid which was dissolved in 100 ml of chloroform and washed with three 50-ml portions of 10% hydrochloric acid, two 50-ml portions of 1 *N* sodium hydrogen carbonate, and two 50-ml portions of water. The dried chloroform layer was concentrated and the residue was crystallized from ether. The yield of **2** was 10.8 g (74%): mp 141–142°; $[\alpha]_D$ −79° (*c* 1, chloroform); λ_{max}^{Nujol} 5.57 (lactone) and 5.70 and 5.78 μ (ester); τ^{CDCl_3} 4.48 (d, C-3 H, $J_{3,4}$ = 6.0 cps), 4.82 (m, C-4 H), 5.25 (m, C-5 H_2), 8.06 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67. Found: C, 68.26; H, 4.76.

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (3) and 3,5-Di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (4).—To a stirred solution of 30 g (63 mmol) of **2** in 125 ml of dry tetrahydrofuran at 0° under a nitrogen atmosphere was added dropwise 175 ml of 1 *M* bis(3-methyl-2-butyl)borane. After 16 hr at 25°, the reaction solution was cooled to 0° and 26 ml of water was carefully added. After the evolution of gas had subsided, the mixture was refluxed for 30 min and concentrated and the residual oil was dissolved in 250 ml of acetone and 75 ml of water. The solution was cooled (0–5°) and stirred during the dropwise addition of 33 ml of 30% H_2O_2 while the pH was maintained between 7 and 8 by the addition of 3 *N* NaOH. The excess H_2O_2 was decomposed at 25° by the cautious addition of 500 mg of 5% platinum on carbon. Stirring was continued until the evolution of gas was complete. The catalyst was removed and the filtrate was extracted with four 200-ml portions of chloroform. The chloroform solution was concentrated to a residual oil (42 g). Tlc in chloroform–ethyl acetate (19:1) showed zones at R_f 0.7 (by-product), 0.5 (**3**), 0.4 (**4**), 0.2, and 0.1 (by-products).

The residue was chromatographed on 650 g of silica gel in chloroform–ethyl acetate (99:1). Fractions containing materials of R_f (tlc) 0.7, 0.5, and 0.4 were combined and concentrated to an oil (32 g). Rechromatography of the oil on 650 g of silica gel in benzene–ethyl acetate (19:1) gave 15 g of a mixture of **3** and **4** which was satisfactory for use in the preparation of **8**.

A similar reduction of 5.5 g (11 mmol) of **2** gave 6 g of crude product which showed tlc zones at R_f 0.0, 0.18, 0.33, 0.45, and 0.65, on silica plates in benzene–ethyl acetate (4:1). It was chromatographed on 300 g of silica gel in the same solvent system which yielded 1.9 g of **3** (R_f 0.65) and 0.5 g of **4** (R_f 0.33) as oils which were further characterized by the synthesis of crystalline *p*-nitrobenzoyl derivatives **5** and **6** described below.

2,3,5-Tri-*O*-benzoyl-1-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (5).—A solution of 0.5 g (1 mmol) of **3** in 8 ml of pyridine was treated with 370 mg (2 mmol) of *p*-nitrobenzoyl chloride. After being kept at 25° for 16 hr, the reaction was worked up in the usual manner. Crystallization of the crude product from ether gave 200 mg of **β 5**: mp 211–212°; $[\alpha]_D$ +70°; $[\alpha]_{578}$ + 74° (*c* 1, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.77 μ (C=O); R_f 0.55, tlc in benzene–ethyl acetate (19:1); τ^{CDCl_3} 2.90 (s, C-1 H), 4.00 (d, C-3 H, $J_{3,4}$ = 7.5 cps), 5.20 (m, C-4 H and C-5 H_2), 8.04 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{34}H_{27}NO_{11}$: C, 65.28; H, 4.35; N, 2.24. Found: C, 65.30; H, 4.38; N, 2.37.

The filtrates from the crystallization of **β 5** were concentrated and the residue (400 mg) was chromatographed on 20 g of silica gel in benzene–ethyl acetate (9:1). Fractions were obtained from which 100 mg of **α 5** was obtained as an oil: R_f 0.6, tlc in benzene–ethyl acetate (19:1); λ^{CDCl_3} 3.08 (s, C-1 H), 4.30 (broad s, C-3 H, w_h = 4.5 cps), 5.16 (s, C-4 H and C-5 H_2), 8.01 ppm (s, C-2 CH_3).

3,5-Di-*O*-benzoyl-1,2-di-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (β 6).—A solution of 290 mg (0.78 mmol) of **4** in 10 ml of dry pyridine was treated with 445 mg (2.4 mmol) of *p*-nitrobenzoyl chloride. After being heated at 45° for 3 hr the mixture was worked up in the usual manner. The crude product, as a residual oil, crystallized on the addition of ether. The solid was recrystallized from benzene–petroleum ether (30–60°) which gave 102 mg (20%) of **β 6**: mp 207–208°; $[\alpha]_D$ +80°, $[\alpha]_{578}$ +85° (*c* 1, $CHCl_3$); τ^{CDCl_3} 2.97 (s, C-1 H), 4.02 ppm (d, C-3 H, $J_{3',4'}$ = 7.5 cps).

Anal. Calcd for $C_{34}H_{26}N_2O_{13}$: C, 60.89; H, 3.91; N, 4.18. Found: C, 61.09; H, 3.69; N, 4.12.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (8).—A mixture of 15 g (~32 mmol) of **3** and **4** in 250 ml of dry pyridine was treated with 15.2 ml of benzoyl chloride. The mixture was heated for 5 hr at 80°, and the product was worked up as in the preparation of **2**. The chloroform solution of the product was concentrated and the residue (18 g) was dissolved in 55 ml of ether and kept at 5° for several hours. The precipitated **β 8** (8.25 g, 23%) was removed by filtration: mp 156.5–157.5°; $[\alpha]_D$ +68°, $[\alpha]_{578}$ +72° (*c* 1, $CHCl_3$); R_f 0.8, tlc in chloroform–ethyl acetate (19:1); τ^{CDCl_3} 2.90 (s, C-1 H), 4.02 (d, C-3 H; $J_{3,4}$ = 7.3 cps), 5.14 (m, C-4 H), 5.33 (m, C-5 H_2), 8.04 ppm (s, C-2 CH_3); λ_{max}^{Nujol} 5.72 and 5.80 μ (C=O).

Anal. Calcd for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.22; H, 4.84.

The combined filtrates were concentrated to a residual oil (10 g) containing mostly **α 8** and a small amount of the **β 8**. Chromatography of the oil on 650 g of silica gel in chloroform–ethyl acetate (19:1) gave 9 g (25%) of pure **α 8**: $[\alpha]_D$ +68°, $[\alpha]_{578}$ +71° (*c* 1, $CHCl_3$); R_f 0.65, tlc in chloroform–ethyl acetate (19:1); τ^{CDCl_3} 3.12 (s, C-1 H), 4.30 (broad s, w_h = 4.5 cps), 5.17 (s, C-4 H and C-5 H_2), 8.02 ppm (s, C-2 CH_3); $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Found: C, 69.90; H, 4.98.

Rearrangement of 2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (3) to 1,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7).—A 3.1-g sample of **3** (R_f 0.5, tlc on alumina in chloroform) was chromatographed on 120 g of acid-washed alumina (Merck) in chloroform. All of the material obtained from the column had R_f 0.7. The column fractions were combined and concentrated and gave 2.9 g (95%) of **7** as an oil: $[\alpha]_D$ +92°, $[\alpha]_{578}$ +96° (*c* 1, $CHCl_3$); τ^{CDCl_3} 3.68 (s, C-1 H), 4.78 (broad s, C-3 H, w_h = 4.5 cps), 5.28 (s, C-4 H and C-5 H_2), 8.34 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 68.00; H, 5.16.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (8) from 1,2,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7).—A solution of 1.9 g (4.0 mmol) of **7** in 32 ml of pyridine was treated with 1.5 ml of benzoyl chloride and heated at 80° for 5 hr. The reaction mixture was worked up in the usual manner and the crude product (2.2 g) was dissolved in a small amount of ether and cooled. Crystalline **β 8** {$[\alpha]_D$ +66°, $[\alpha]_{578}$ +70° (*c* 0.65, $CHCl_3$), R_f 0.8, tlc on silica in chloroform–ethyl acetate (19:1) (400 mg, mp 155–156°)} was obtained. The filtrate was concentrated and the residue was chromatographed on 100 g of silica gel in chloroform–ethyl acetate (19:1) and fractions were obtained which on concentration yielded 800 mg of **α 8**: $[\alpha]_D$ +67°, $[\alpha]_{578}$ +71° (*c* 1, $CHCl_3$); R_f 0.65, tlc on silica gel in chloroform–ethyl acetate (19:1).

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10). From 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (β 8).—To 300 ml of dry ether saturated at 0° with hydrogen chloride in a round-bottomed flask was added 12 ml of acetyl chloride and 6 g (10 mmol) of **β 8**. The flask was tightly stoppered and kept at 25° for 2.5 hr. The tetra benzoate dissolved during the first hour. The solvent was removed and 75 ml of dry toluene distilled from the residue. The residue was dissolved in 300 ml of dry ether and rapidly extracted with three 120-ml portions of cold, saturated $NaHCO_3$ and two 120-ml portions of cold water. The ether layer was dried ($MgSO_4$) and concentrated and the product (**10**, 5.0 g) was obtained as an oil: tlc on alumina in benzene–chloroform (1:1), R_f 0.3; τ^{CDCl_3} 3.13 (s, C-1

(18) Microanalyses were performed by Mr. R. N. Boos and his associates, and the ultraviolet spectral measurements were done by Mr. E. A. MacMullin and his associates. The ORD curve was determined by Dr. J. J. Wittick. All melting points were determined on a micro hot stage and are corrected. Except where noted, silica gel was used for tlc and the zones were made visible with I_2 vapor. The naphthalene-1,2-diol spray used previously[3] was not useful with the 2-*C*-methyl sugars in that the colors were slow to develop and very weak. Fritted-glass Büchner funnels of medium porosity were used for column chromatographic separations. The silica gel (J. T. Baker, 100–200 mesh) packing had a height to diameter ratio of about 1:1. Unless noted otherwise, all concentrations were carried out in a rotary evaporator at reduced pressure. The nmr values were determined with a Varian Associates Model A-60 spectrometer.

H), 3.92 (d, C-3 H, $J_{3,4}$ = 7.5 cps), 5.27 (m, C-4 H and C-5 H_2), 8.02 ppm (s, C-2 CH_3).

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10). From 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (α 8).—A solution of 5.9 g (10 mmol) of α **8** in 105 ml of acetic acid containing 5 ml of acetyl chloride was added to 260 ml of ether containing 4 ml of acetyl chloride saturated with hydrogen chloride at 0° in a round-bottomed flask. The flask was tightly stoppered and kept at 25° for 48 hr. The solvents were removed and the residue was dissolved in 150 ml of ether and was extracted with three 75-ml portions of cold, saturated $NaHCO_3$ and three 75-ml portions of cold water. The ether layer was dried ($MgSO_4$) and concentrated. The residue (5.8 g) which consisted of a mixture of **10** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**9**) [τ^{CDCl_3} 3.14 (s, C-1 H), 4.15 (d, C-3 H, $J_{3,4}$ = 7.0 cps), 5.30 (m, C-4 H and C-5 H_2), 7.98 (s, C-1 CH_3COO), 8.16 ppm (s, C-2 CH_3)] was dissolved in 250 ml of ether containing 0.5 ml of acetyl chloride and saturated with hydrogen chloride. After being kept at 25° for 2.5 hr, the solution was concentrated. Three 50-ml portions of dry toluene were distilled from the residue at reduced pressure. The residual **10** (5.5 g) had the same physical properties as the product obtained from β **8**.

1,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7) from 2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10).—A solution of 200 mg of **10** in 0.5 ml of acetone was treated with 0.03 ml of water. Tlc on alumina in benzene–chloroform (1:1) indicated that the reaction was essentially complete in 10 min. The reaction solution was diluted with 25 ml of chloroform and washed with cold dilute HCl, $NaHCO_3$, and water. Concentration of the chloroform solution gave 175 mg of essentially pure **7** with physical properties identical with those of an authentic sample of **7**.

6-Benzamido-9-(2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl)purine (12).—About 400 ml of xylene was distilled, at atmospheric pressure, from a suspension of 4.86 g (10.3 mmol) of finely powdered chloromercuri-6-benzamidopurine (**11**). The last 90 ml of xylene distilled was used to dissolve 5.5 g of chloro sugar **10**, and the solution of **10** was added to the stirred xylene suspension of **11** at 60–80°. The mixture was heated to the reflux temperature and refluxing was continued for 1.25 hr. The mixture was concentrated to 150 ml and partially cooled, and 500 ml of petroleum ether was added. After being kept at 5° several hours, the precipitate was removed and added to 200 ml of chloroform. A small amount of chloroform-insoluble material was removed and the filtrate was washed with three 150-ml portions of 30% KI and two 150-ml portions of water. Concentration of the dried ($MgSO_4$) chloroform layer gave a residual glass (5.7 g). Tlc in chloroform–ethyl acetate (9:1) showed a large zone for **12** at R_f 0.3 and faint zones due to impurities at R_f 0.0, 0.1, 0.5, and 0.9. The crude product was chromatographed on 200 g of silica gel in chloroform–ethyl acetate (4:1) and 4.4 g (61%) of purified **12** was obtained: $[\alpha]_D$ −66°, $[\alpha]_{578}$ −66° (*c* 1, $CHCl_3$); λ_{max}^{MeOH} mμ (ε × 10^{-3}), 278 (12.5), 262 (8.0), 231 (27); τ^{CDCl_3} 3.13 (s, C-1 H), 3.22 ppm (d, C-3 H, $J_{3',4'}$ = 6.0 cps).

Anal. Calcd for $C_{39}H_{31}N_5O_8$: C, 67.14; H, 4.48; N, 10.04. Found: C, 67.42; H, 4.71; N, 9.74.

Decomposition of 12 on Acid-Washed Alumina.—A 1.37-g sample of **12** was chromatographed on 50 g of acid-washed alumina (Merck) in chloroform–ethyl acetate (9:1). Several fractions were obtained which contained only the desired product (**12**), R_f 0.6 − tlc on alumina. These fractions were concentrated and gave a total of 580 mg (24%) of **12**. All of the remaining fractions from the column showed three distinct tlc zones when the plates were viewed in ultraviolet light. These zones were scraped from the tlc plates and eluted with methanol. The ultraviolet and infrared spectra as well as R_f values indicated that the zone at R_f 0.1 was 6-benzamidopurine, that at R_f 0.6 was **25**, and that at R_f 0.8 was **7**.

2′-*C*-Methyladenosine (13).—To a suspension of 4.4 g (6.3 mmol) of **11** in dry methanol was added a solution prepared from 240 mg (10.5 mg-atom) of sodium and 50 ml of dry methanol. The solution was refluxed for 30 min and concentrated, and the residue was dissolved in 66 ml of water. The pH was adjusted to 7 with acetic acid and the water solution was extracted with four 100-ml portions of ether. The water layer was concentrated to ~20 ml during which process the product precipitated. After the mixture was kept at 5° for several hours, the product (1.35 g) was removed and recrystallized from 30 ml of hot water. The cooled mixture was filtered and 1.3 g (74%) of **13** was obtained: mp 256–258°; $[\alpha]_D$ −21°, $[\alpha]_{578}$ −22° (*c* 0.5, water); [φ] (λ, mμ), −1000° (292), −2250° tr (278), 0° (267), +8900° pk (248), 6950° tr (235) (*c* 0.0516, H_2O); $\lambda_{max}^{H_2O}$ mμ (ε × 10^{-3}), pH 1 258 (15.1), pH 7 260 (15.1), pH 13 260 (14.9); $\tau^{deuteriopyridine}$ 3.10 (s, C-1′ H), 4.93 (d, C-3′ H, $J_{3',4'}$ = 8.8 cps), 5.22 (d, C-4 H), 5.52 (s, C-5 H_2), 8.65 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.77; H, 5.26; N, 25.20.

2′,3′-*O*-Isopropylidene-2′-*C*-methyladenosine (14).—A suspension of 150 mg (0.52 mmol) of **13** in 12 ml of dry acetone, 0.7 ml of 2,2-dimethoxypropane and 436 mg (1.28 mmol) of di-*p*-nitrophenylphosphoric acid was stirred at 25° for 3.5 days at which time a small amount of **13** [R_f 0.33, tlc on silica gel in ethyl acetate–ethanol (4:1)] remained unreacted. Complete solution was obtained in 1 hr. The reaction mixture was neutralized with 20 ml of 0.1 *N* $NaHCO_3$, and the acetone was removed at reduced pressure. The aqueous solution was extracted with three 40-ml portions of chloroform which were combined and washed with 40 ml of water. The chloroform was removed and the residue was dissolved in 8 ml of methanol, concentrated to 3 ml and kept at 5° for 20 hr. The crystalline product (88 mg) was removed and recrystallized from 1.5 ml of methanol, which yielded 77 mg (45%) of **14**: mp 291–292°; $[\alpha]_D$ −89° $[\alpha]_{578}$ −94° (c 0.5, CH_3OH); λ_{max}^{MeOH} mμ (ε × 10^{-3}), 0.1 *N* HCl 211 (20.0), 257.5 (14.8), neutral 260 (15.1), 0.1 *N* NaOH 259 (14.9); $\tau^{deuteriopyridine}$ 3.20 (s, C-1′ H), 5.02 (d), C-3′ H, $J_{3',4'}$ = 2.1 cps), 5.33 (m, C-4′ H), 5.84 (m, C-5′ H_2), 8.31 (s, C-2′ CH_3), 8.55 ppm [s, >C $(CH_3)_2$].

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.77; H, 5.87; N, 22.14.

Registry No.—**2**, 7392-74-7; α **5**, 16434-45-0; β **5**, 16434-46-1; β **6**, 16434-47-2; **7**, 16434-48-3; α **8**, 15397-16-7; β **8**, 15397-15-6; **10**, 16434-51-8; **12**, 16434-52-9; **13**, 15397-12-3; **14**, 16434-54-1.

Photochemical Addition of Phosphines to 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose

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Photochemical addition of phosphine to 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose produces, presumably, a mixture of 5,6-dideoxy-1,2-*O*-isopropylidene-6-phosphine-α-D-*xylo*-hexofuranose and bis-6-(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose)phosphine. They are characterized as the cyclohexylamine salt of the corresponding phosphonous acid and phosphine oxide, respectively. Phenylphosphine also adds photochemically to produce phenyl-6-(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose)phosphine which is converted into its oxide for isolation.

Synthesis of sugars containing a carbon–phosphorus bond in various positions of hexose and pentose sugars by the addition of phosphines to carbon–carbon double bonds has not been reported. However, addition of phosphines to olefin hydrocarbons has been accomplished in the presence of radical initiators[1-3] or under the influence of acid catalysts.[4,5] Carbohydrate phosphines would possess phosphorus in its lowest oxidation state and could be used as starting materials for the synthesis of a variety of phosphorus containing sugar derivatives by modification of either the phosphorus group or the sugar moiety. Consequently, an investigation of the addition of phosphines to the 5,6-unsaturated bond in a hexose was undertaken and the results are reported here.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enfuranose (I) was used as the olefinic substrate because it has an exposed terminal exocyclic double bond which would aid the addition.

When compound I is exposed to ultraviolet radiation in the presence of phosphine a reaction takes place with the formation of two major products, as indicated by thin layer chromatography. With ethyl ether as the irrigant they had approximate R_f values of 0.25 (component A) and 0.02 (component B), respectively. A minor amount of material remained stationary (component C). Addition of ether to the reaction product caused precipitation of component B. After recrystallization from ethanol, it was identified as bis(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6)-phosphine oxide (V). The isolation of V suggests that phosphine adds to I, producing the secondary phosphine, III, which during isolation takes up an oxygen atom to form the oxide. It is known that secondary phosphines readily undergo air oxidation to their corresponding secondary phosphine oxides.[6]

An attempt to separate component A from component C by fractionation on silica gel yielded no pure fractions. Passage of air or oxygen through the alcoholic solution slowly converts component A into an oxidized product (component C) which causes the solution to become acidic. After application to an anion-exchange column, component C is eluted with ammonia and converted into a crystalline cyclohexylamine salt. The isolation and identification of this material suggests that component A and C are the corresponding primary phosphine (II) and phosphonous acid (IV), respectively. Primary phosphines have been shown to undergo air oxidation readily to the corresponding phosphonous acid.[7]

Reaction conditions and yields of the phosphine addition are shown in Table I. Higher yields of the primary phosphine (II) result when a high ratio of phosphine to compound I is employed.

TABLE I

PHOTOCHEMICAL ADDITION OF PHOSPHINE TO 5,6-DIDEOXY-1,2-*O*-ISOPROPYLIDENE-α-D-*xylo*-HEX-5-ENOFURANOSE

Compound I, mol	Phosphine, mol	Irradiation time, hr	Yield, % IV[a]	Yield, % V
0.01	0.01	11	1	15
0.01	0.06	40	24	6

[a] Based on the isolated cyclohexylamine salt.

Phenylphosphine behaves similarly with phosphine when treated with compound I in the presence of ultraviolet light to produce an unstable syrupy material which was not characterized. An attempt to crystallize it from benzene and Skellysolve B slowly produced crystalline material which was identified as the secondary phosphine oxide (VII), obtained in 75% over-all yield. Although phenylphosphine has been shown to be readily added to various olefinic compounds in the presence of peroxides and/or at high temperatures,[8-11] its addition by photochemical irradiation has not been reported.

The infrared spectra of all three isolated phosphine derivatives exhibits an absorption maximum between 2300 and 2340 cm^{-1}, which is attributed to the P–H stretching vibration.[12] The infrared spectra of compound VII has a phosphoryl absorption at 1210 cm^{-1}, in agreement with absorptions shown by Bellamy.[12] However, the phosphoryl absorptions of compound V and the cyclohexylamine salt of IV are observed at 1630 and 1635 cm^{-1}, respectively. 5-Deoxy-5-(diethyl

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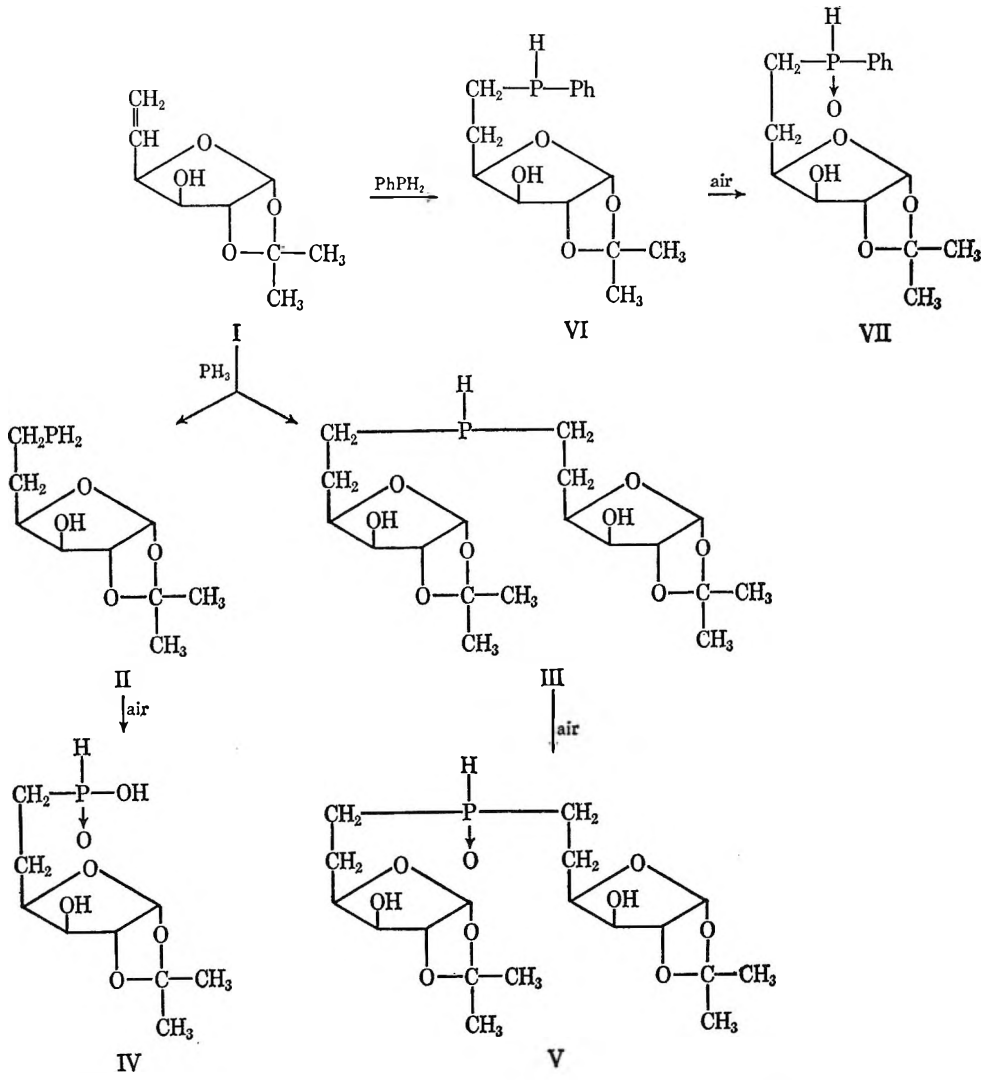

phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose and 5,6-dideoxy-6-(diethyl phosphonate)-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose,[13] recently synthesized in this laboratory, also exhibit phosphoryl absorptions in the region of 1630–1640 cm^{-1}. Other deviations of the phosphoryl absorption from those shown by Bellamy are reported by Rauhut and Currier,[6] who showed that the phosphoryl absorptions appear at 1655 to 1670 cm^{-1}.

None of these isolated phosphine derivatives shows an nmr signal in the region τ 8.9, where a doublet for a terminal methyl group would be expected[14–17] had the addition produced a 6-deoxy-5-phosphino structure. Thus, the addition takes place in anti-Markownikoff fashion as has been observed by others examining phosphine addition to terminal olefins.[2,3]

Experimental Section

Analytical Methods.—Melting points measured on a calibrated Fisher–Johns melting point apparatus were corrected. Infrared spectra were obtained on a Perkin-Elmer Model 521 and nmr spectra on a Varian A-60 spectrometer. Chemical-shift values are given on the τ scale, and correspond to the midpoint of each singlet or symmetrical multiplet. For unsymmetrical multiplets, the chemical shifts are given as weighted mean values. Purity of products was determined by thin layer chromatography on silica gel G[18] after activation of plates for 1 hr at 105°. Phosphorus compounds were detected by spraying the plates with cobalt chloride solution[19] and heating.

Materials.—Phenylphosphine was prepared as described by Mann and Millar[20] and stored in sealed weighed ampoules. Liquid phosphine, obtained from the Matheson Co., Inc., was used without additional purification.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (I) was prepared by a modification of the procedure of Hall, Hough, and Pritchard.[21] 5,6-Di-*O*-*p*-tolylsulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (1.70 g) and sodium iodide (8.0 g) were refluxed for 3 hr with constant stirring in ethyl methyl ketone (50 ml) which was previously dried over calcium sulfate. Sodium tosylate was filtered off and the filtrate was concentrated to a brown residue which was partitioned between a 10% aqueous solution of sodium thiosulfate (50 ml) and chloroform (30 ml). The aqueous layer was extracted twice with 30-ml portions of chloroform and the combined chloroform extracts were washed twice with water and dried over calcium sulfate. Concentration produced a yellow syrup. Methanol (20 ml) was added and the insoluble material removed by filtration. The filtrate was evaporated to a dry solid (0.55 g, 93% yield), mp 58–62°. Sublimation at 60° (bath) (0.3 mm) produced needles (0.5 g, 85%), mp 62–66°. Resublimation gave compound I: mp 65–66°, $[\alpha]^{25}D$ −56.4° (*c* 1.7, chloroform).

Literature values reported for I are as follows: mp 61–65°,

(13) C.-C. Wang and R. L. Whistler, unpublished results.
(14) T. H. Siddall, III, and C. A. Prohaska, *J. Amer. Chem. Soc.*, **84**, 3467 (1962).
(15) T. H. Siddall, III, and C. A. Prohaska, *ibid.*, **84**, 2502 (1962).
(16) T. H. Siddall, III, *J. Phys. Chem.*, **70**, 2249 (1966).
(17) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963).
(18) Brinkman Instruments, Inc., Great Neck, N. Y.
(19) R. Donner and K. Lohs, *J. Chromatog.*, **17**, 349 (1965).
(20) F. A. Mann and I. T. Millar, *J. Chem. Soc.*, 3039 (1952).
(21) L. D. Hall, L. Hough, and R. A. Pritchard, *ibid.*, 1537 (1961).

$[\alpha]_D$ −51.5° (c 11., chloroform);[21] mp 64°, $[\alpha]^{25}_D$ −60.5° (c 2.0, water);[22] mp 70–71°, $[\alpha]^{22}_D$ −57.3° (c 2.8, chloroform).[23]

Reaction of Phosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—Reactions involving phosphine were conducted in a closed glass system. Measured amounts of compound I and phosphine were introduced together in a small Vycor tube cooled in liquid nitrogen, cyclohexanol (5 ml) being used as the solvent. After sealing, the tubes were allowed to warm to 25° in an iron pipe containing a 2 × 10 cm slit and irradiated from a 200-W Hanovia S 654A-36 lamp at a distance of about 15 cm. At the end of irradiation, the unreacted phosphine was evacuated and cyclohexanol was distilled off. Addition of four volumes of ethyl ether precipitated a crude amorphous compound (V). The ether soluble portion was filtered and the filtrates were combined with the washings and evaporated to a yellow syrup which was dissolved in ethanol and oxidized by passing air or oxygen through the solution for 4–6 hr. The solution was then flowed through an Amberlite IR-45 column, eluted with 5% ammonium hydroxide solution and finally washed with water to neutrality. Redistilled cyclohexylamine was added to the collected effluent which was concentrated to a crystalline solid, and was recrystallized from an ethanol–acetone mixture to yield the pure cyclohexylammonium salt of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6-phosphonous acid (IV): mp 166°, $[\alpha]^{25}_D$ −10.9° (c 1.46, methanol).

Anal. Calcd for $C_{15}H_{30}NO_8P$: C, 51.25; H, 8.55; N, 3.99; P, 8.83. Found: C, 51.03; H, 8.47; N, 4.12; P, 8.47.

The infrared spectrum of the compound (potassium bromide pellet) showed absorption maxima at ν 3230 (OH), 2300 (P—H), 1635 (P=O), 1382, 1370 (CMe_2) cm^{-1}. Nmr data in deuterium oxide gave signals at τ 4.09 (one-proton doublet, $J_{1,2}$ = 3.6 Hz, H-1), 5.44 (one-proton doublet overlapping with OD peak), 5.91 (two-proton multiplet, H-3,4), 8.35 (15-proton multiplet, H-5,5′, H-6,6′, C_6H_{11}), 8.58, 8.75 (three-proton singlet, CMe_2), and 2.76 (one-proton doublet, J_{P-H} = 550 Hz, P–H).

The ether-insoluble material was recrystallized from hot ethanol to yield bis(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6)phosphine oxide (V): mp 190°, $[\alpha]^{25}_D$ −22.5° (c 1.70 in water).

Anal. Calcd for $C_{18}H_{31}O_9P$: C, 51.18; H, 7.35; P, 7.35; mol wt, 422. Found: C, 51.60; H, 7.46; P, 6.91; mol wt 412.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3350 (OH), 2340 (P—H), 1630 (P=O), 1368, 1380 (CMe_2) cm^{-1}.

Reaction of Phenylphosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—A 10-ml quartz tube was charged with 1.2 g of I, 6 g of phenylphosphine, and 0.5 ml of methanol and sealed with a rubber cap. The tube was irradiated with uv light from a 200-W Hanovia S 654-36 lamp at a distance of about 10 cm. After 48 hr, 50 ml of methanol was added and the azeotropic mixture of phenylphosphine and methanol was removed under reduced pressure (6 mm, 50°) to give a syrupy residue which was dissolved in benzene, and Skellysolve B was added to near turbidity. Compound VII slowly crystallized in the refrigerator to yield 1.56 g (75%). It was recrystallized from methanol–benzene–Skellysolve B: mp 145–147°, $[\alpha]^{25}_D$ −13.2° (c 0.64, methanol).

Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.70; H, 6.73; P, 10.06. Found: C, 57.74; H, 6.69; P, 9.58.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3190 (OH), 2330 (P—H), 1590 (C_6H_5), 1382, 1370 (CMe_2), 1210 (P=O) cm^{-1}.

The nmr spectra in methanol showed one peak at τ −1.68, which is due to the phosphorus-bonded hydrogen. H-1 was observed at τ 4.08 as a doublet ($J_{1,2}$ = 3.05 Hz); isopropylidene protons were observed at τ 8.43 and 8.58. The rest of protons were obscured by the solvent peaks. Yields were not changed in several other runs using one-fourth the amount of reactants without the addition of methanol.

Preparations on a smaller scale, with irradiation from an ultraviolet handlamp, gave comparable yields of VII after longer periods of irradiation.

Registry No.—I, 7284-07-3; IV cyclohexylamine, 16355-03-6; V, 16355-04-7; VII, 16355-05-8.

Acknowledgment.—This work was supported by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-7662(71) (Journal Paper No. 3234 of the Purdue Agricultural Experiment Station, Lafayette, Ind.), administered by the Northern Regional Laboratory, Peoria, Ill.

(22) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *J. Org. Chem.*, **29**, 1083 (1964).

(23) D. Horton and W. N. Turner, *Carbohyd. Res.*, **1**, 444 (1966).

The Pyrolysis and Structure of Jesaconitine

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Received November 24, 1967

The structure of jesaconitine has been determined by an examination of the nmr spectrum of this alkaloid and its pyrolysis products. The pyrolysis was carried out in an nmr tube and continuously monitored by nmr spectroscopy to provide evidence for the elimination product. This method of pyrolysis constitutes a rapid and convenient way of establishing the presence of certain C-8 ester groups in these diterpene alkaloids using small amounts of material.

Jesaconitine (*Aconitum fischeri* Reich,[2] A. subcunlatum,[3,4] A. sachalinense,[3,4] A. yesoense,[3] and A. mitakense[5]) on hydrolysis affords acetic acid, anisic acid, and the amino alcohol aconine (I).[4] Since the absolute stereochemistry of aconine (Figure 1) is known from X-ray crystallographic studies,[6] the structure of jesaconitine follows once the placement of the two ester groups on the aconine skeleton is determined.

Jesaconitine has been reported to undergo pyrolysis to form pyrojesaconitine.[4] Pyrolysis is a well-characterized reaction for aconitine-type alkaloids bearing an ester functional group at C-8.[7,8] When a C-16 hydroxyl is present, the pyrolytic product exists in the keto form.[9,10] Unfortunately, early workers did not report whether acetic acid or anisic acid was the elimination product of the pyrolysis. However, as a

(1) To whom correspondence regarding this paper should be addressed.

(2) K. Makoshi, *Arch. Pharm.* (Weinheim), **247**, 243 (1909); *Chem. Abstr.*, **3**, 2707 (1909); **5**, 674 (1911).

(3) H. Suginoma and S. Imato, *J. Fac. Sci. Hokkaido Univ., Ser. III*, **4**, 33 (1950); *Chem. Abstr.*, **46**, 1008 (1952).

(4) R. Majima, H. Suginome, and S. Morio, *Ber.*, **57B**, 1486 (1924); *Chem. Abstr.*, **19**, 291 (1925).

(5) E. Ochiai, T. Okomoto, and S. Sashi, *J. Pharm. Soc. Jap*, **75**, 545 (1955); *Chem. Abstr.*, **50**, 5695 (1956).

(6) M. Przybylska and L. Marion, *Can. J. Chem.*, **37**, 1843 (1959).

(7) K. Wiesner, F. Bickelhaupt, and Z. Valenta, *Tetrahedron*, **4**, 418 (1958).

(8) K. Wiesner, F. Bickelhaupt, and D. R. Babin, *Experientia*, **15**, 93 (1959).

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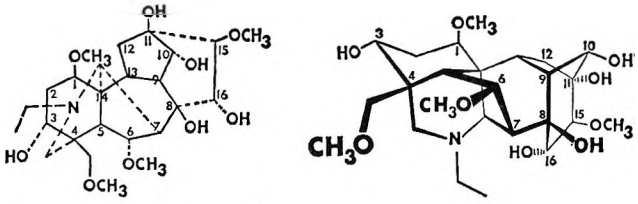
(10) D. J. McCaldin and L. Marion, *Can. J. Chem.*, **37**, 1071 (1959).



I

Figure 1.—The structure of aconine.

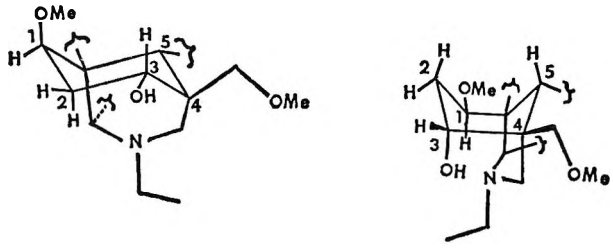
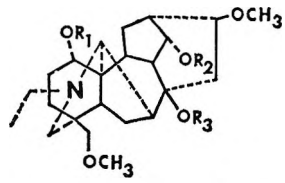


Figure 2.—The conformations of ring A.

working hypothesis it was assumed that one of the two ester moieties is located at C-8.

It then became apparent that the second site of esterification should be relatively easily deduced from the nmr spectrum of jesaconitine itself, for, based on the data gathered from the nmr spectra of other diterpene alkaloids of this type, some rather accurate predictions can be made as to the chemical shift, signal pattern, and coupling constants of the proton geminal to the ester moiety at each of the four possible remaining sites in aconine (C-3, C-10, C-11, C-16). If the second ester group is at C-3, the geminal proton of that position would be expected to exhibit a signal at τ 5.1–5.4 which should be either a quartet, triplet, or a broad multiplet, depending upon the conformation of ring A. If ring A exists in the chair conformation (Figure 2), the dihedral angles between the geminal C-3 proton and the adjacent C-2 equitorial and axial protons are quite different and the signal should be split into a quartet with coupling constants of about 7 and 10 Hz. If ring A is in the boat conformation where the two dihedral angles in question are nearly the same (50–60°), the signal would be expected to be a triplet with a coupling constant of about 3 Hz, and, if ring A is in a rapid equilibrium between the two conformations, the signal of the C-3 geminal proton would be a multiplet. The basis for the above predictions can be discerned from molecular models and is substantiated by a study of the nmr spectra of some ring-A acetate and benzoate esters of condelphine (II) and isotalatizidine (III).[11,12]



II, $R_1 = R_3 = H$; $R_2 = Ac$

III, $R_1 = R_2 = R_3 = H$

IV, $R_1 = R_2 = R_3 = Ac$

(11) S. W. Pelletier, L. H. Keith, and P. C. Parthasarathy, *Tetrahedron Lett.*, **35**, 4217 (1966).

(12) S. W. Pelletier, L. H. Keith, and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, **89**, 4146 (1967).

Although the later alkaloids bear no C-3-hydroxyl group, their corresponding geminal C-1 hydrogen is β, as is the geminal C-3 hydrogen of jesaconitine, and models show that the dihedral angles involved, as well as the magnetic environments, are the same between the C-3 proton and the C-2 protons of jesaconitine as between the C-1 proton and the C-2 protons of condelphine and isotalatizidine. Actually, if the C-3 hydroxyl of jesaconitine were esterified, the expected conformation of ring A would be the chair form for there would then be no possible intramolecular hydrogen bonding to help offset the higher energy of the boat conformation.[12]

If the second ester is substituted at C-10, the signal of the geminal proton should be split into a doublet, coupling with the C-9 bridgehead proton, with a coupling constant of about 4.5 Hz. The basis of this prediction is the correlation of the signals of the C-10 geminal protons of a number of diterpene alkaloids which are esterified at C-10.[12,13] In each case, a doublet or triplet was observed (depending on whether C-11 is substituted with a hydroxyl group or a hydrogen) with a coupling constant of 4.5 Hz.

If the second ester is located at C-11, there would be no signal arising from a geminal proton since there is none present.

If the C-16 hydroxyl is the second site of esterification, the signal of the geminal proton should be a very close doublet with a coupling constant of only about 1.0 Hz since the dihedral angle between this proton and the C-15 proton is about 70°. However, esterification of this hydroxyl might also be expected to interfere with the pyrolysis reaction.

An examination of the nmr spectrum of jesaconitine (Figure 3) immediately revealed the position of the second ester moiety as C-10; the signal of the geminal proton appears as a doublet (J = 4.5 Hz) at τ 5.38. Also evident are the two low field doublets of the aromatic protons, the doublet at τ 2.11 (J = 9 Hz) being attributed to the two protons (H_a) flanking the carbonyl group and the doublet at τ 3.15 (J = 9 Hz) arising from the two protons (H_b) flanking the methoxyl. The five singlets at τ 6.19, 6.28, 6.76, 6.78, and 6.87 are assigned to the five methoxyl groups, the one at lowest field being the aromatic methoxyl. The triplet at τ 8.91 (J = 7 Hz) is characteristic of an N-ethyl group and close to it at 8.64 is the highly shielded signal of the acetoxy protons. This highly shielded signal is further confirmation of a C-8–C-10-diester substitution. Analogous shielding has been observed in all diterpene alkaloids examined which contain a C-10-benzoyloxy–C-8-acetoxy substitution pattern. This phenomenon was first noted by Tsuda and Marion[13] who explained that the upfield shift is caused by the diamagnetic anisotropy of the aromatic ring which can easily come in close proximity to the acetoxy protons. The normal signal of the C-8-acetoxy protons of triacetylisotalatizidine (diacetylcondelphine) (IV) appears at τ 8.07.[12]

At this point there was still no rigorous proof that the aromatic and aliphatic ester moieties of jesaconitine were not switched from their usual deployment in other alkaloids of this type, for a C-8-*p*-methoxybenzoyloxy group and a C-10-acetoxy would be expected to show

(13) Y. Tsuda and L. Marion, *Can. J. Chem.*, **41**, 1634 (1963).

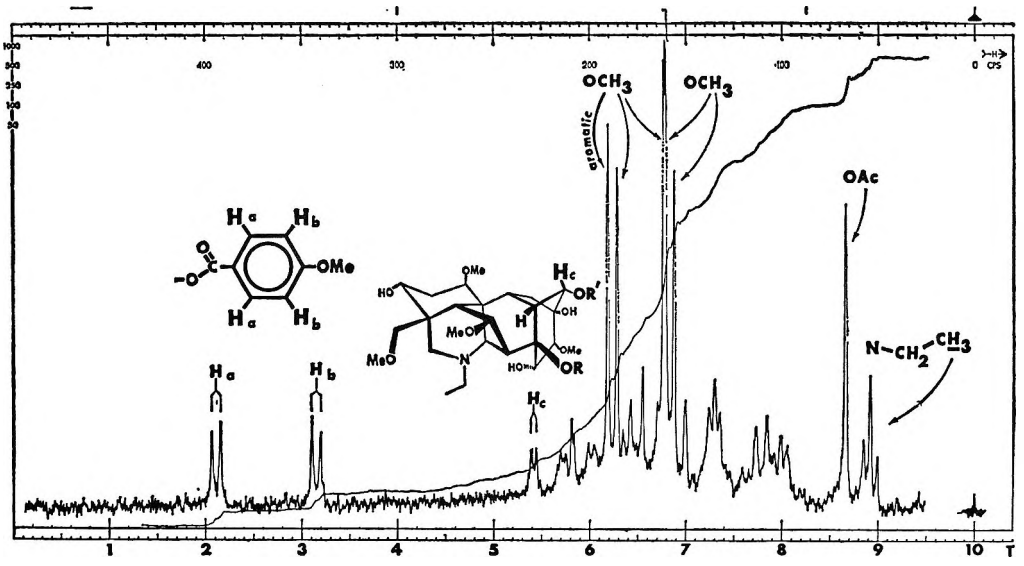
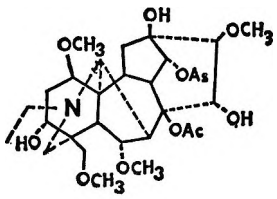


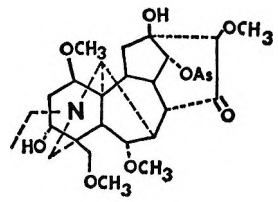
Figure 3.—The 100-MHz spectrum of jesaconitine in carbon tetrachloride at 28°.

the same highly shielded acetoxy signal as a C-8-acetoxy and a C-10-*p*-methoxybenzoyloxy substitution.

Accordingly, in order to determine the exact deployment of the two ester moieties between C-8 and C-10, 10 mg of jesaconitine was pyrolyzed in an nmr tube and the reaction was continuously monitored by nmr over a 2-hr period.[14] The shielded acetoxy signal at τ 8.46 was observed to slowly disappear while another signal at 7.98 correspondingly appeared and grew to the approximate height of the former signal (Figure 4). There was no change in the signals of the aromatic protons. Acetic acid under conditions identical with those described above exhibited a signal at τ 7.98 thus confirming the elimination of acetic acid during the pyrolysis as well as confirming the site of the acetoxy group at C-8. The *p*-methoxybenzoyloxy group is then at C-10. The structures of jesaconitine and pyrojesaconitine are thus V and VI, respectively.

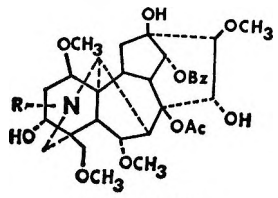


V



VI

The applicability of this method for the determination of similar C-8–C-10 aliphatic–aromatic ester substitutions in aconitine-type alkaloids was confirmed by subjecting 10-mg samples of aconitine (VII) and mesaconitine (VIII) to the pyrolytic conditions described above and monitoring the pyrolysis by nmr spectroscopy. The acetoxy signals at τ 8.48 and 8.49



VII, R = C_2H_5
VIII, R = CH_3

(14) L. H. Keith and S. W. Pelletier, *Chem. Commun.*, 993 (1967).

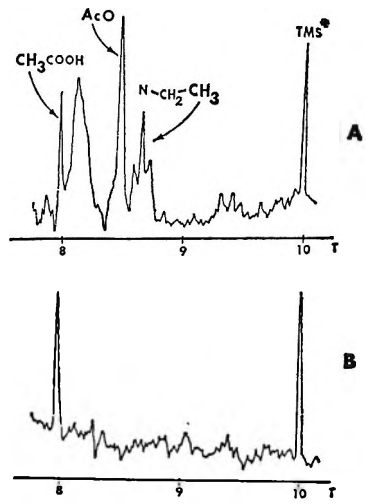


Figure 4.—(A) The nmr spectrum of jesaconitine during pyrolysis (after 45 min); (B) the nmr spectrum of acetic acid under the identical conditions of pyrolysis.

in aconitine and mesaconitine, respectively, were observed to slowly disappear while the corresponding signal of acetic acid at 7.98 appeared and grew to the approximate size of the former signals. This method of monitoring the pyrolysis by nmr presents a rapid and convenient way of establishing the presence of certain C-8-ester groups in the aconitine-type skeleton without sacrificing relatively large amounts of material as required for conventional studies of the pyrolytic products of these alkaloids.

Experimental Section

The spectra were obtained with a Varian HA-100 spectrometer. The samples (10 mg) were dissolved in 0.4 cc of glycerol containing a trace of D_2SO_4 and 2–3 mg of the sodium salt of 3-(trimethylsilyl)propanesulfonic acid as an internal standard. The methylene proton signal of the solvent supplied the lock signal. Pyrolysis was carried out by maintaining the sample temperature at 185° over a 2-hr period.

Registry No.—V, 16298-90-1; VI, 16298-91-2.

Acknowledgment.—This work was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service.

Total Synthesis of Petaline[1]

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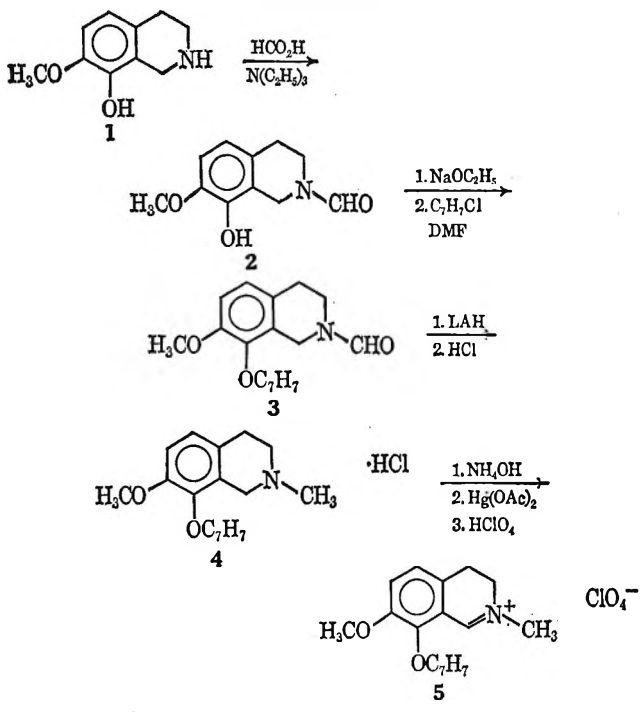
Received January 19, 1968

A total synthesis of petaline is described.

The quaternary benzylisoquinoline alkaloid petaline had attracted our attention because of its 7,8-oxygenation pattern which is unusual for benzylisoquinoline alkaloids. The alkaloid in the form of its chloride or reineckate was isolated[2] from extracts made from the fresh tuberous roots of *Leontice leontopetalum* Linn., a plant which grows wild in Lebanon. The extracts are used there as a folk remedy for grand mal epilepsy. The structure of petaline (**12a**) was elucidated by McCorkindale and coworkers[3] and its absolute configuration (*R*) was recently established by Craig and coworkers[4] using ORD techniques.

The total synthesis of petaline iodide (**12a**) has been achieved by the sequence of reactions in Schemes I and II.

SCHEME I



Formylation of the readily available 7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline **1**[5,6] with a mixture of formic acid and triethylamine[7] gave the crystalline N-formyl derivative **2**, the sodium salt of which was benzylated with benzyl chloride in dimethylformamide. The crude O-benzyl derivative **3**, upon reduction with lithium aluminum hydride in tetrahydrofuran, afforded 8-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, characterized as the crystalline hydrochloride **4**. Mercuric acetate dehydrogenation of the free base of **4** in 10% aqueous acetic acid at 75° led to the 3,4-dihydroisoquinolinium salt **5**, isolated as the crystalline perchlorate. The subsequent Grignard reaction was carried out by adding the solid perchlorate **5** in small portions to an excess of *p*-methoxybenzylmagnesium chloride[8] in ether. The resulting 1-benzyltetrahydroisoquinoline was isolated in the form of its hydrochloride **6** and hydrogenated in glacial acetic acid over palladium on carbon to give the debenzylated product **7a**. For its characterization the maleate **7b** was prepared. The crude free base **7a** yielded upon methylation with methyl iodide in methanol *rac*-petaline iodide, which after crystallization from acetone was isolated as hemiacetonate, mp 134–138°. The acetone content was determined spectroscopically by nmr (methyl group at 2.17 ppm, integrating for three protons) and ir (carbonyl stretching vibration at 1710 cm^{-1}) spectra and by glpc (calcd 5.99%, found 4.7%). All of the spectroscopical data (compare Experimental Section) were in accord with structure **8a**. In the low resolution mass spectrum the base peak appears at *m/e* 327 which can be assigned to a charged fragment of structure **9** which is formed formally by Hofmann degradation. The *rac*-petaline iodide was converted into *rac*-petaline reineckate (**8b**), a pink amorphous compound, mp 178–181° dec, the infrared and ultraviolet spectra of which were superimposable with those of authentic optically active material.[9] Further proof that the synthetic product represents *rac*-petaline iodide (**8a**) was provided by Hofmann degradation to petaline methine **9** on a column of Amberlite anion-exchange resin IRA-400 (OH).[3] The crystalline product obtained showed mp 119–120° and it was identical in all respects with authentic material.[9] The fragmentation pattern of the low resolution mass spectrum was very similar to that of petaline iodide; the molecular ion peak appears at *m/e* 327. The *trans*-stilbene configuration was ascertained by spectroscopic data: the ir spectrum ($CHCl_3$) showed bands at 1610 and 973 cm^{-1} and the nmr spectrum ($CDCl_3$) exhibited an AB pattern at 7.07 and 7.37 ppm (J = 16.5 cps) with integration for two protons.

For the synthesis of petaline the free base **7a** was resolved into its enantiomers by use of dibenzoyl-*d*-

(1) Presented in part at the Natural Products Symposium in Kingston, Jamaica, Jan 1966, by A. B. and at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967, by G. G., Abstracts, p 101. The synthesis of *rac*-petaline iodide was subject of a short communication: G. Grethe, M. Uskoković and A. Brossi, *Tetrahedron Lett.*, 1599, (1966).

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(3) N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Lett.*, 3841 (1964).

(4) J. C. Craig, M. Martin-Smith, S. K. Roy, and J. B. Stenlake, *Tetrahedron*, **22**, 1335 (1966).

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

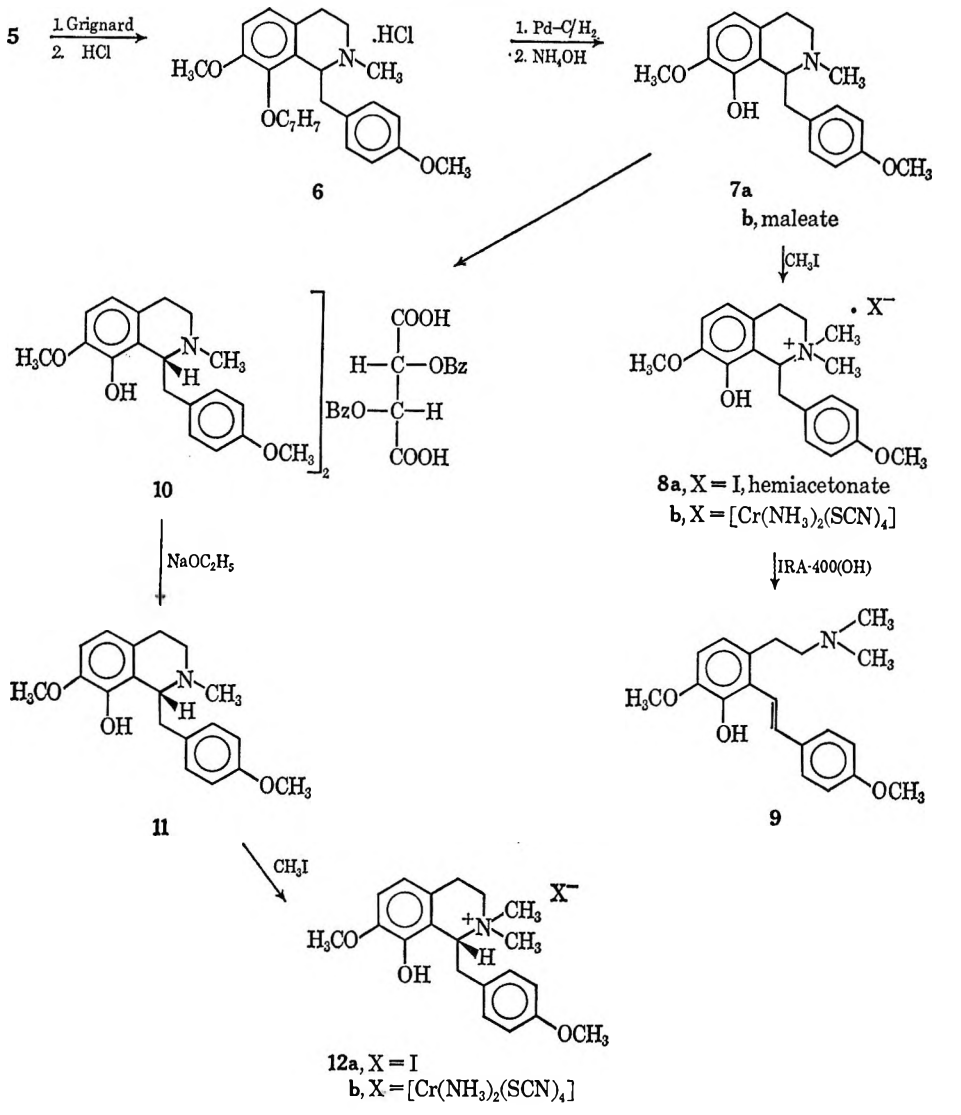
(6) G. Grethe, V. Toome, H. L. Lee, M. Uskoković, and A. Brossi, *ibid.*, **33**, 504 (1968).

(7) S. Durand, X. Lusinchi, and R. C. Moreau, *Bull. Soc. Chim. Fr.*, 270 (1961).

(8) R. C. Elderfield and V. B. Meyer, *J. Amer. Chem. Soc.*, **76**, 1886 (1954).

(9) We are grateful to Professor McCorkindale for providing us with authentic samples of petaline reineckate and petaline methine.

SCHEME II



tartaric acid. The desired diastereoisomer **10** was obtained optically pure after repeated crystallization from methanol: mp 191–192°, $[\alpha]^{24.4}D$ −62.8° (*c* 0.258, MeOH). The absolute configuration was established by ORD measurements. The ORD curve of **10** (Figure 1) showed three negative Cotton effects at 218, 242, and 293 mμ. This according to Craig and coworkers[4] indicated that **10** possesses the *R* configuration at C-1. The small distortion of the curve in the 280–290-mμ region may be attributed to superposition of the ORD curve of the tertiary amine with the one of dibenzoyl-*d*-tartaric acid which showed a strong negative Cotton effect at 241 mμ.

The dibenzoyl tartrate **10** was carefully converted into the free base **11** by treatment with 2 equiv of sodium ethoxide. The yellow oil thus obtained, $[\alpha]^{24.9}D$ −32.2° (*c* 0.165, $CHCl_3$), also exhibited in its ORD curve three negative Cotton effects at 216, 244, and 292 mμ (Figure 2). An ethereal solution of **11**, upon treatment with excess methyl iodide, gave the desired petaline iodide as a yellow, amorphous compound, $[\alpha]^{23}D$ −4.4° (*c* 0.455, 95% ethanol). The melting ranges of synthetic and natural petaline iodide were identical, 127–131° *vs.* 126–130°, and a mixture melting point showed no depression.[10] Identity was also confirmed by thin layer chromatography on silica gel G with methanol–chloroform (4:1) as the mobile phase. In this system both compounds have R_f 0.64.[10]

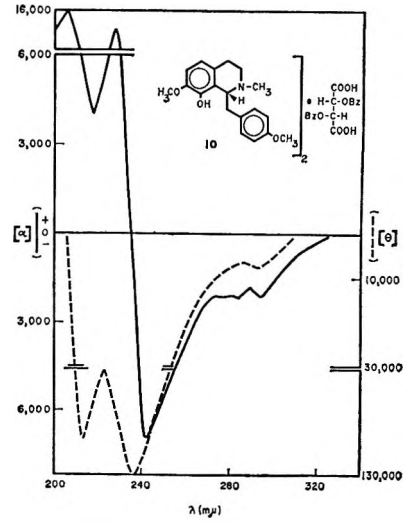


Figure 1.—ORD (—) and CD (---) curve of **10** (*c* 0.0848, CH_3OH).

(10) J. C. Craig, School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco Medical Center, San Francisco, Calif., personal communication, 1967. We are thankful to Professor Craig for checking the identity of synthetic with natural petaline iodide.

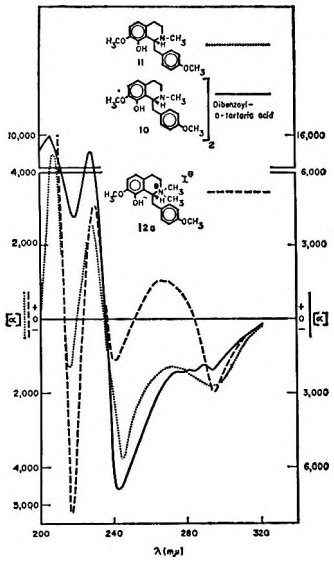


Figure 2.—ORD curves of **11** (···) (c 0.0464, ethanol), **10** (—) (*c* 0.0848, methanol), and **12a** (---) (*c* 0.455, 95% ethanol).

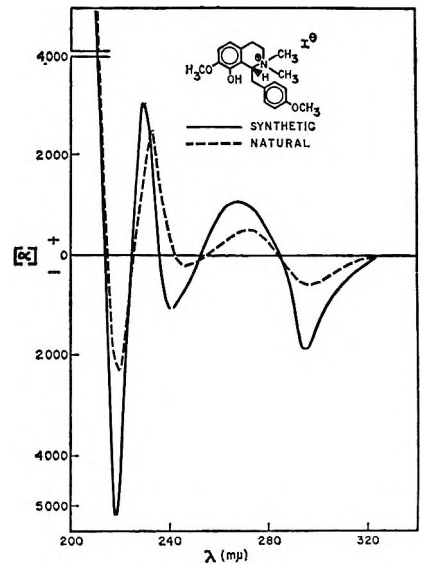


Figure 3.—ORD curves of synthetic (—) and natural (---) petaline iodide in 95% ethanol.

Furthermore, the ORD spectrum of **12a** was in good agreement with the published one[4] (Figure 3). The spectrum again showed three negative Cotton effects in the 200–300-mμ region. A comparison of the ORD curves of **10**, **11**, and **12a** (Figure 2) confirmed the findings of Craig and coworkers[4] that the absolute configuration at C-1 of 1-benzyl-1,2,3,4-tetrahydroisoquinolines can be deduced from the ORD curves of either the free base, its salt, or its methiodide.

Optically active petaline iodide finally was converted into the reineckate **12b**, a pink, amorphous compound. Its infrared spectrum was superimposable with that of natural material.[9]

Experimental Section[11]

2-Formyl,1,2,3,4-tetrahydro-7-methoxy-8-isoquinolinol (2).—To a mixture of formic acid and triethylamine prepared by the dropwise addition of 145 ml (3.84 mol) of formic acid (98–100%) to 111 ml (0.8 mol) of ice-cold triethylamine was added in small portions 66.3 g (0.375 mol) of **1**. After complete addition, the mixture was refluxed for 18 hr. Upon cooling to room temperature a crystalline precipitate was obtained, collected by filtration, and washed with acetone and subsequently with ether to give 68.3 g (89%) of the N-formyl derivative **2**, mp 174–177°. A sample after recrystallization from methanol afforded analytically pure **2**: mp 177–179°; $\nu_{max}^{CHCl_3}$ 3545 (OH), 1670 (C=O), and 1285 and 1240 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 230 mμ (ε 6800) (sh), 280 (2300); $\lambda_{max}^{0.1\ N\ KOH}$ 246 mμ (ε 7200), 292 (4500); nmr ($CDCl_3$),[12] δ 2.82 (2 H, rough triplet, J = 6 cps, CH_2-4), 3.63 and 3.78 (2 H, 2 t, J = 6 cps, CH_2-3), 3.88 (3 H, s, OCH_3), 4.55 and 4.68 (2 H, 2 s, CH_2-1), 5.72 (1 H, exchange, s, OH), 6.70 (2 H, barely resolved AB pattern, CH-5 and CH-6), 8.22 and 8.28 (1 H, 2 s, CHO).

Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.93; H, 6.49; N, 6.61.

8-Benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4).—To a solution of 68.3 g (0.33 mol) of **2** in 2.5 l. of methanol was added 17.8 g (0.33 mol) of sodium methoxide. The mixture was kept at room temperature for 1 hr followed by removal of the solvent under reduced pressure. In order to assure dryness of the solid sodium salt *ca.* 500 ml of benzene was added to the residue and then removed under reduced pressure. This procedure was repeated twice. The residue then was suspended in 1.8 l. of freshly distilled dimethylformamide, 37.9 ml of benzyl chloride was added, and the mixture was stirred at 100° for 70 hr. After removing the solvent at 45° under a pressure of 1 mm, 500 ml of benzene was added to the residue and the insoluble parts were removed by filtration. The filtrate was evaporated to dryness under vacuum to give 104 g of crude oily **3**. This was dissolved in 3.2 l. of anhydrous tetrahydrofuran, and to the cooled solution was added cautiously 26.3 g of lithium aluminum hydride in small portions. After complete addition the stirred mixture was refluxed overnight in a nitrogen atmosphere. Stirring was continued while the mixture was cooled in an ice bath and a saturated aqueous solution of sodium sulfate was added cautiously until the hydrogen evolution ceased. The mixture then was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 200 ml of methanol and excess isopropyl alcoholic hydrogen chloride was added. Upon addition of ether to the solution a crystalline precipitate was formed which when filtered gave 56 g (53%) of **4**, mp 187–189°. An analytical sample after recrystallization from methanol showed the following properties: mp 191.5–192.5°; $\nu_{max}^{CHCl_3}$ 2350 (broad, *t*-amine salt), 1500 (phenyl), and 1285 and 1245 cm^{-1} (OCH_3 and OC_7H_7); $\lambda_{max}^{isopropyl\ alcohol}$ 230 mμ (ε 8210) (sh), 282 (2220); nmr ($CDCl_3$), δ 2.71 (3 H, d, J = 5 cps, ^+N–CH_3), 2.8–3.7 (4 H, m, CH_2-3 and CH_2-4), 3.87 (3 H, s, OCH_3), 3.70 and 4.37 (2 H, AB part of ABX pattern, J_{AB} = 15 cps, $J_{AX,BX}$ = 3 cps, CH_2-1), 5.01 and 5.12 (2 H, AB pattern, J = 11 cps, O–CH_2), 6.88 (2 H, s, CH-5 and CH-6), 7.35 (5 H, s, phenyl), 12.68 (1 H, b, $^+$NH).

Anal. Calcd for $C_{18}H_{21}NO_2 \cdot HCl$ (319.84): C, 67.61; H, 6.93; N, 4.38. Found: C, 67.37; H, 7.23; N, 4.36.

8-Benzyloxy-7-methoxy-2-methyl-3,4-dihydroisoquinolinium Perchlorate (5).—To a methanolic solution of 13.4 g (0.42 mol) of **4** was added 95 ml of ethanol containing 2.84 g (0.42 mol) of sodium ethoxide. The solvent was removed under reduced pressure and the residue was treated with methylene chloride. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The oily residue was dissolved in 240 ml of 10% acetic acid, a solution of 53.5 g (0.168 mol) of mercuric acetate in 240 ml of 10% acetic acid was added, and the

(11) Melting points were taken in capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were determined with a Beckman infrared spectrophotometer, Model IR-9. The uv spectra were recorded on a Cary Recording spectrophotometer, Model 14 M. Rotatory dispersion curves were measured at 23° with a Durrum-Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Specific rotations are given for the highest and lowest wavelength measured, for intersections, and for peaks and troughs. Circular dichroism curves were measured on the same instrument and they are recorded in molecular ellipticity units [Θ]. Optical rotations were measured on a Perkin-Elmer polarimeter, Model 141. Nuclear magnetic resonance spectra were obtained on a Varian Associates spectrophotometer, Model A-60 or HA-100, and chemical shifts are reported in δ using tetramethylsilane as internal reference (δ 0). The following abbreviations are used in connection with the nmr data: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (b) broad featureless peak, (cp) complex band pattern, (m) multiplet. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe.

(12) The nmr spectrum indicates that in solution **2** exists in two isomeric forms in about a 1:1 ratio. Some of the corresponding signals overlap each other and the integration is therefore given of the total protons of each group.

mixture was stirred in a nitrogen atmosphere at 75° for 40 hr. The precipitated mercurous acetate was removed by filtration, and hydrogen sulfide was passed into the filtrate. The black precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in methanol, excess isopropyl alcoholic hydrogen chloride and acetone was added, and the mixture was kept at 5° overnight. The solution was decanted from the small amounts of precipitate formed and evaporated to dryness under reduced pressure, and the residue was dissolved in water. Upon addition of excess 60% perchloric acid an oil was precipitated which slowly crystallized on standing at room temperature. The precipitate was collected by filtration and recrystallization from methanol gave 8.3 g (52%) of **5**, mp 178–180°. For analysis a sample was recrystallized from methanol: mp 181–183°; ν_{max}^{KBr} 1665 (C=$^+$N), 1605, 1580 and 1500 (phenyl), and 1285 and 1258 cm^{-1} (OCH_3 and OC_7H_7); λ_{max} 239 mμ (ε 13,200), 301 (11,760), 379 (2700); nmr (DMSO-d_6), δ 3.07 (2 H, t, J = 8 cps, CH_2-4), 3.76 (3 H, s, $^+$N–CH_3), 3.93 (3 H, s, OCH_3), ~3.9 (2 H, t, J = 8 cps, partially hidden by the $^+$N–CH_3 and OCH_3 signals, CH_2-3), 5.22 (2 H, s, OCH_2–C_6H_5), 7.13 and 7.47 (2 H, AB pattern, J = 8 cps, CH-5 and CH-6), 7.43 (5 H, s, phenyl).

Anal. Calcd for $C_{18}H_{20}ClNO_6$ (381.83): C, 56.62; H, 5.28; N, 3.67. Found: C, 56.87; H, 5.39; N, 3.44.

1-(4-Methoxybenzyl)-8-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6).—To 56.5 g (2.32 g-atoms) of magnesium turnings covered with 250 ml of anhydrous ether was added 0.5 g of iodine and 4 g of *p*-methoxybenzyl chloride.[13] The reaction started immediately. Without stirring the mixture was refluxed for 10 min and then 14.2 g of the chloride (total 0.116 mol) in 110 ml of dry ether was added over 30 min with vigorous stirring. After stirring and refluxing for an additional 40 min the mixture was allowed to settle. The clear solution was carefully decanted from the residue and filtered through a Büchner funnel (fritted disk) under slight nitrogen pressure. To the stirred filtrate was added within 15 min 10 g (26.2 mmol) of **5** under nitrogen atmosphere. With continued stirring the mixture was then refluxed for 1 hr and cooled to room temperature. After 20 ml of methanol was added cautiously the ethereal solution was decanted and treated with excess isopropyl alcoholic hydrogen chloride. Oily material precipitated which slowly crystallized to give 6.3 g of **6**, mp 170–180°. The residue was treated with chloroform, and the organic layer was washed successively with 3 *N* hydrochloric acid and water, dried, filtered, and evaporated to dryness under reduced pressure. The oily residue was dissolved in methanol, the solution was treated with isopropyl alcoholic hydrogen chloride and on addition of ether another 3.1 g of crystalline hydrochloride **6**, mp 186–192°, was obtained. The two crystalline fractions were combined and recrystallized from methanol–ether to furnish in two crops (6.2 g with mp 191–193° and 2.9 g with mp 185–190°) a total of 9.1 g (79%) of **6**. An analytical sample recrystallized from methanol–ether showed the following properties: mp 191–193°; $\nu_{max}^{CHCl_3}$ 2420 (broad, *t*-amine salt), 1613, 1580 and 1510 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OC_7H_7); $\lambda_{max}^{isopropyl\ alcohol}$ 229 mμ (ε 25,200), 278 (4560), 283–284 (4490); nmr ($CDCl_3$), δ 2.2–5.0 (5 H, cp, CH-1, CH_2-3, and CH_2-4), 3.43 (3 H, d, J = 5 cps, $^+$N–CH_3), 3.74 (3 H, s, OCH_3-4), 3.96 (3 H, s, OCH_3-7), 5.08 (2 H, s, OCH_2–C_6H_5), 6.6–7.5 (6 H, cp, aromatic protons), 7.30 (5 H, s, phenyl), 12.4 (1 H, b, $^+$NH).

Anal. Calcd for $C_{26}H_{29}NO_3 \cdot HCl$ (440.00): C, 70.97; H, 6.87; N, 3.18. Found: C, 70.71; H, 6.82; N, 3.17.

1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol Maleate (7b).—A solution of 12.8 g of **6** in 650 ml of glacial acetic acid was hydrogenated over 3 g of 10% palladium on carbon at atmospheric pressure and at an initial temperature of 70°. During the hydrogenation the mixture was allowed to cool to room temperature. After the hydrogen uptake ceased (~6 hr), the catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The oily residue was taken up in 100 ml of water, 100 ml of chloroform was added, and the vigorously stirred suspension was treated with an excess of sodium bicarbonate. The chloroform layer was separated, and the aqueous phase was washed with three 100-ml portions of chloroform. The combined organic solution was washed with water, dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure to give 10.7 g of the free base **7a** as a brown oil. This material could be used for the next step without further purification. For characterization the maleate **7b** was prepared. To a solution of 1.72 g of the oil in ether was added a solution of 700 mg of maleic acid in 50 ml of ether. The precipitated solid material was collected by filtration and crystallized from ethanol–ether to give 2 g of **7b**, mp 152–155° with softening at 80°. After two recrystallizations from ethanol–ether analytically pure **7b** showed two melting points at 77–79 and 155°; $\nu_{max}^{CHCl_3}$ 3540 (OH), 2450 (broad, *t*-amine salt), 1710 (COOH), 1620 (COO^-), 1610, 1580 and 1510 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{CH_3OH}$ 225 mμ (ε 26,000) (sh), 278 (4000), 284 (3800); $\lambda_{max}^{0.1\ N\ KOH}$ 250 mμ (ε 8000) (sh), 275 (4200) (sh), 283 (4700), 293 (4400) (sh).

Anal. Calcd for $C_{19}H_{23}NO_3 \cdot C_4H_4O_4$ (429.47): C, 64.33; H, 6.34; N, 3.26. Found: C, 64.28; H, 6.66; N, 3.46.

Racemic Petaline Iodide Hemiacetonate (8a).—A solution of 1.375 g of the crude free base **7a** and 3.5 ml of freshly distilled methyl iodide in 50 ml of methanol was refluxed overnight. The solvent was removed under reduced pressure and the oily residue was triturated with 5 ml of acetone to give 1.555 g (78%) of crystalline **8a**, mp 134–138° dec. The volume of a solution of 250 mg of this material in 250 ml of acetone was reduced to 100 ml by evaporation under reduced pressure at room temperature. The crystalline material obtained on standing was collected by filtration and dried for 50 hr at 50° under vacuum to give analytically pure **8a**: mp 134–138° dec; $\nu_{max}^{CHCl_3}$ 3530 (OH), 1710 (acetone, C=O), 1610, 1510 and 1500 (phenyl), and 1285 and 1250 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 223 mμ (ε 28,200), 279–280 (3980), 284–285 (3980); nmr ($CDCl_3$), δ 2.17 (3 H, s, acetone), 3.35 and 3.50 (3 H each, s, $^+$N–CH_3), 3.77 and 3.92 (3 H each, s, OCH_3), 2.9–4.4 (4 H, cp, partially buried, CH_2-3 and CH_2-4), 5.07 (1 H, b, CH-1), 6.23 (1 H, s, OH), 6.5–7.4 (6 H, cp, aromatic protons); mass spectrum, fragments at m/e 327 (base peak), 206, 192, 177, 142, 121, and 58; acetone determination by glpc (calcd 5.9% w/w), found 4.7% w/w.

Anal. Calcd for $C_{20}H_{26}NO_3I \cdot {}^1/_2CH_3COCH_3$ (484.39): C, 53.31; H, 6.04; N, 2.89. Found: C, 53.47; H, 6.14; N, 2.93.

Racemic Petaline Reineckate (8b).—Treatment of an aqueous solution of **8a** with a saturated aqueous solution of ammonium reineckate afforded a pink amorphous solid which was further purified by precipitation from an aqueous solution with acetone. The racemic petaline reineckate (**8b**) thus obtained showed the following properties: mp 178–181° dec; ν_{max}^{KBr} 3500 (OH), 2080 (SCN), 1610, 1520 and 1500 (phenyl), and 1288, 1255, and 1242 cm^{-1} (OCH_3 and OH); λ_{max} (isopropyl alcohol + 10% Methyl Cellosolve) 233 mμ (ε 35,800), 280 (12,000), 284 (12,100), 311 (17,600).

Petaline Methine (9).—A solution of 7.5 g of racemic petaline iodide in 75 ml of 80% ethanol was applied to a column of 1000 ml of Amberlite anion exchange resin IRA-400 (OH) and left there for 15 hr. Elution with 900 ml of 80% ethanol at a rate of 3 ml/min and evaporation of the eluate under reduced pressure gave an oily residue. Trituration of the residue with 50 ml of ethanol afforded 4 g (79%) of crystalline petaline methine (**9**), mp 120–122°. An analytical sample was recrystallized twice from methanol–water and showed the following properties: mp 119–120°; $\nu_{max}^{CHCl_3}$ 3530 (OH), 1610 and 973 (C=C, *trans*-stilbene), 1605, 1580 and 1515 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 214 mμ (ε 30,500), 240 (11,900) (sh), 300 (24,900), 321 (21,000) (sh); $\lambda_{max}^{0.1\ N\ KOH}$ 251 mμ (ε 19,600), 290 (16,700), 357 (8200) (sh); nmr ($CDCl_3$), δ 2.32 [6 H, s, $N(CH_3)_2$], 2.75 (4 H, m, CH_2–CH_2), 3.83 and 3.88 (3 H each, s, OCH_3), 6.42 (1 H, s, OH), 6.72 (2 H, s, CH-5 and CH-6), 6.88 and 7.37 (4 H, A_2B_2 pattern, J = 9 cps, CH-2′, CH-3′, CH-5′ and CH-6′), 7.07 and 7.37 (2 H, AB pattern, J = 16.5 cps, *trans* CH=CH); mass spectrum, fragments at m/e 327 (molecular ion), 206, 177, 121, and 58.

Anal. Calcd for $C_{20}H_{25}NO_3$ (327.43): C, 73.37; H, 7.70; N, 4.28. Found: C, 73.36; H, 7.43; N, 4.31.

(*R*)-(−)-1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol Dibenzoyl-*d*-tartrate (10).—The oily free base **7a**, obtained from 3.7 g of **6** as previously described, was dissolved in 100 ml of ether. Addition of 3.3 g of dibenzoyl-*d*-tartaric acid in 50 ml of ether gave a solid precipitate which, recrystallized from hot methanol, afforded 1.414 g of dibenzoyl-*d*-tartrate **10**, $[\alpha]^{25}D$ −60.4° (*c* 0.262, MeOH). Several recrystallizations to constant rotation yielded analytically pure material: mp 191–192°; $[\alpha]^{24.4}D$ −62.8° (c 0.258, MeOH), $[\alpha]_{365}^{24.4}$ −326° (*c* 0.258, MeOH); ORD and CD curve, see Figure 1; λ_{max}^{MeOH}

(13) J. Lee, A. Ziering, L. Berger, and S. D. Heineman, *Festschr. Emil Barrel*, 264 (1946); *Chem. Abstr.*, **41**, 6252 (1947).

227–228 mμ (ε 68,500), 278 (9500), 284 (8800) (sh); $\lambda_{max}^{0.1\ N\ KOH}$ 225 mμ (ε 67,500) (sh), 276 (11,100) (sh), 282–283 (11,800), 296 (9000) (sh); ν_{max}^{KBr} 2550 (broad, *t*-amine salt), 1720 (ester C=O), 1625 and 1615 (COO^-), 1617, 1585 and 1505 (phenyl), and 1280 cm^{-1} (broad, ester, OCH_3, and OH).

Anal. Calcd for $C_{38}H_{46}N_2O_6 \cdot C_{18}H_{14}O_8$ (985.12): C, 68.28; H, 6.14; N, 2.84. Found: C, 68.47; H, 6.08; N, 3.02.

(*R*)-(−)-1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol (11).—To a solution of 281.5 mg (0.285 mmol) of 10 in 200 ml of methanol was added 5.15 ml of ethanol containing 38.85 mg (0.572 mmol) of sodium ethoxide. The solvent was removed under reduced pressure and the residue was extracted with ether to give 162 mg of 11 as a yellow oil: $[\alpha]^{24.9}D$ −32.2° (*c* 0.165, $CHCl_3$), $[\alpha]_{365}^{24.9}$ −326° (*c* 0.165, $CHCl_3$); for the ORD curve see Figure 2; CD (*c* 0.0464, ethanol), $[\theta]_{300}$ 0, $[\theta]_{278}$ −2829, $[\theta]_{255}$ −1338, $[\theta]_{235}$ −19,624, $[\theta]_{230}$ −9366; $\nu_{max}^{CHCl_3}$ 3545 (OH), 1610, 1588, 1515 and 1495 (phenyl), and 1280 and 1250 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{CH_3OH}$ 226 mμ (ε 21,300), 278 (3900), 284 (3600); nmr ($CDCl_3$), δ 2.31 (3 H, s, N-CH_3), 2.2–3.3 (6 H, cp, methylene protons), 3.72 and 3.81 (3 H each, s, OCH_3-4 and OCH_3-7), 4.00 (1 H, q, J = 4.5 cps, CH-1), 5.82 (1 H, b, OH), 6.55 and 6.68 (2 H, AB pattern, J = 8.5 cps, CH-5 and CH-6), 6.77 and 7.17 (4 H, A_2B_2 pattern, J = 8 cps, CH-2′, CH-3′, CH-5′ and CH-6′); mass spectrum, fragments at *m/e* 313, 312, 192 (base peak), 177.

Petaline Iodide (12a).—To the oily free base 11 (150 mg) in 20 ml of anhydrous ether was added within 20 min a solution of 1 ml of freshly distilled methyl iodide in 3 ml of anhydrous ether. The mixture was left at room temperature overnight, and the amorphous yellow precipitate was collected by filtration and washed thoroughly with ether to give 168 mg of 12a melting between 107 and 116° after drying at 40° for 3 days under reduced pressure: for the optical rotatory dispersion curve see Figures 2 and 3; $[\alpha]^{23}D$ −4.4° (*c* 0.455, 95% ethanol); CD (*c* 0.455, 95% ethanol), $[\theta]_{310}$ 0, $[\theta]_{288}$ −9108, $[\theta]_{253}$ −528, $[\theta]_{235}$ −21,120, $[\theta]_{225}$ −5280, $[\theta]_{212}$ −84,480, $[\theta]_{205}$ 0.

Petaline Reineckate (12b).—To 25 ml of an aqueous solution of 12a (140 mg) was added a saturated aqueous solution of ammonium reineckate until no more material was precipitated. The amorphous pink precipitate was collected by filtration and dried 3 days at 50° under reduced pressure to give 128 mg of 12b, melting between 135 and 145° dec; a mixture melting point with authentic material[9] showed no depression and the infrared spectra (KBr) were superimposable. Reprecipitation from an aqueous solution with acetone afforded, after drying at room temperature for 80 hr under reduced pressure, 12b which melted between 126 and 134°: $[\alpha]^{23}D$ −1.5° (*c* 0.647, ethanol); ORD (*c* 0.647, ethanol), $[\alpha]_{320}$ −386°, $[\alpha]_{292}$ −850° (tr), $[\alpha]_{284}$ 0°, $[\alpha]_{270}$ +540° (pk), $[\alpha]_{253}$ 0°, $[\alpha]_{241}$ −540° (tr), $[\alpha]_{235}$ 0°, $[\alpha]_{228}$ +1620° (pk), $[\alpha]_{216}$ −1390° (tr), $[\alpha]_{212}$ −773°; CD (*c* 0.647, ethanol), $[\theta]_{305}$ 0, $[\theta]_{288}$ −7920, $[\theta]_{268}$ 0, $[\theta]_{235}$ −23,100, $[\theta]_{223}$ −1320, $[\theta]_{215}$ −42,900.

By paper chromatography (descending, pyridine–water 1:4, Whatman No. 1 paper), 12b was identical with authentic material,[9] R_f 0.83. The spots were developed with modified Dragendorff reagent.[14]

Registry No.—2, 6068-43-5; 4, 6077-99-2; 5, 5890-46-0; 6, 5890-47-1; 7b, 16336-16-6; 8a, 16350-27-9; 8b, 15612-34-7; 9, 2609-29-2; 10, 16346-57-9; 11, 16336-17-7; 12a, 6392-37-6; 12b, 16351-46-5.

Acknowledgment.—The authors thank Miss Nancey Radimer for skillful technical assistance. They also thank Dr. P. Bommer and his staff, especially Dr. V. Toome for the uv, ORD, and CD spectra, Mr. S. Traiman for the ir spectra, Dr. F. Vane for the mass spectral data, Dr. T. Williams for the nmr spectra, and Dr. F. Scheidl and his staff for performing the elemental analyses. We appreciate the help of Dr. Rachlin and his group in preparing larger amounts of starting material.

(14) B. Franck and G. Blaschke, *Ann. Chem.*, **695**, 144 (1966).

Synthetic Quinine Analogs. I. The Synthesis and Some Chemical Transformations of 6′-Methoxy-7-oxo-8-rubene[1]

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Sodium ethoxide-catalyzed condensation of 6-methoxyquinoline-4-carboxaldehyde with 3-quinuclidinone produces 6′-methoxy-7-oxo-8-rubene in high yield. Of the two possible geometrical isomers, only that with the ketone function *trans* to the quinoline ring is formed. Reduction of the ketone affords an allylic alcohol whose *p*-nitrobenzoate is completely isomerized to the opposite geometrical isomer in refluxing acetic acid. The ketone is not ketalized by 1,2-ethanedithiol in refluxing trifluoroacetic acid but instead undergoes a remarkable condensation reaction involving one molecule of ketone, two of 1,2-ethanedithiol, and one of trifluoroacetic acid. A by-product of the reaction results from the condensation of three molecules of 1,2-ethanedithiol with two of trifluoroacetic acid. Pyrazoline derivatives of the ketone resulting from 1,3-dipolar addition of diazomethane and condensation with hydrazine are described.

As a sequel to their brilliant degradative studies which elucidated the structure of quinine,[3] Rabe and his coworkers undertook its synthesis in the 1920's.[4] While this substance constituted a rather ambitious synthetic objective for the time, a general route to the quinine skeleton was developed by which total syntheses of dihydroquinine and dihydroquinidine were accomplished in 1931.[5] In its basic form [Claisen condensation of a β-(4-piperidyl)propionate with ethyl quininate followed by decarboxylation, bromination, and cyclization], the Rabe route formed the cornerstone of most of the subsequent synthetic work in the area. Both Rabe[6] and Prelog,[7] *et al.*, used this route extensively for the preparation of synthetic quinine analogs and, in the hands of Woodward and Doering,[8] it was utilized to effect the total synthesis of quinine itself.

Much of the more recent synthetic work on the

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) National Science Foundation Undergraduate Research Participant.

(3) P. Rabe, *Ber.*, **41**, 62 (1908).

(4) P. Rabe, K. Kindler, and O. Wagner, *ibid.*, **55**, 532 (1922).

(5) P. Rabe, W. Huntenburg, A. Schultze, and G. Volger, *ibid.*, **64**, 2487 (1931).

(6) (a) P. Rabe and G. Hagen, *ibid.*, **74**, 636 (1941); (b) P. Rabe and W. Schuler, *ibid.*, **76**, 318 (1943).

(7) (a) V. Prelog, P. Stern, R. Sewerth, and S. Heimbach-Juhasz, *Naturwissenschaften*, **28**, 750 (1940); (b) V. Prelog, P. Stern, R. Sewerth, and S. Heimbach-Juhasz, *Ber.*, **74**, 647 (1941).

(8) R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, **66**, 849 (1944); **67**, 860 (1945).

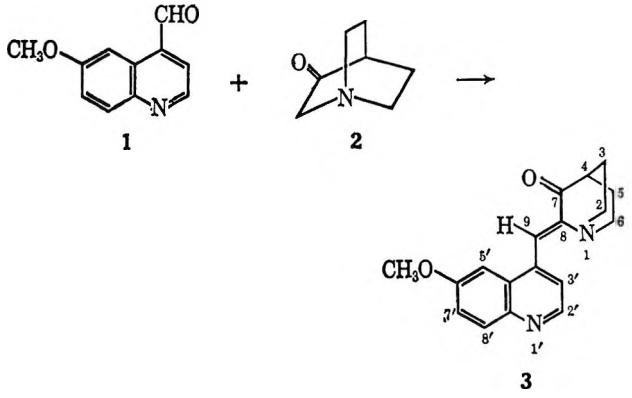
cinchona alkaloids has been directed toward the indole group. The transformation of members of the quinoline group to the indole group[9] and a total synthesis of cinchonamine,[10] the parent alkaloid of the latter, have been described.

Interest in synthetic routes to quinine and its analogs disappeared as its importance in the chemotherapy of malaria declined.[11] However, by 1963 it was clearly recognized that drug resistant strains of Plasmodium falciparum had evolved. While malarial infections with these microorganisms responded to treatment with quinine, the snythetic antimalarials which had largely replaced quinine during the two previous decades were quite ineffective.[12] As a result, quinine once again assumed a position of central importance in malaria chemotherapy. At the same time, the search for new synthetic antimalarials was taken up again and has already yielded the highly effective diaminodiphenyl sulfones.[13]

We have recently undertaken the development of new synthetic routes to the basic quinine skeleton with the twofold objective of synthesizing racemic quinine and of providing general synthetic methods for the preparation of quinine analogs. Enzymic oxidation to a carbostyril[14] seriously curtails the activity of quinine whence antipodal and racemic quinines might conceivably be far superior antimalarials to the natural product. Results from the investigation of one synthetic approach and the partial realization of the second objective are described in this paper.

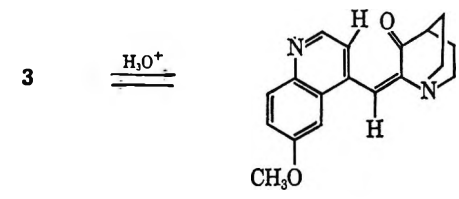
Discussion

3-Quinuclidinone (2), because of its ready availability,[15] represents an attractive precursor to the alicyclic portion of the quinine molecule. Its active methylene group is known to condense readily with aldehydes[16] and moreover the condensation, in modest yield, with quinoline-4-carboxaldehyde has been described.[17] 6-Methoxyquinoline-4-carboxaldehyde (1) was obtained by selenium dioxide oxidation of 6-methoxylepidine[18] which in turn was synthesized from *p*-anisidine and ethyl acetoacetate as first described by Rabe[5] and later modified by Elderfield and coworkers.[19] The aldehyde **1** and ketone **2** condense, in 90% yield, with sodium ethoxide as catalyst giving 6′-methoxy-7-oxo-8-rubene (**3**).



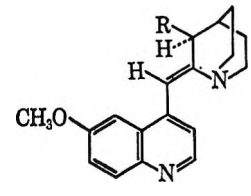
1 **2** **3**

Under acid catalysis, the α,β-unsaturated ketone **3** can be transformed into an equilibrium mixture of the two possible geometric isomers. However, under the conditions of the condensation reaction, only the indicated isomer (*vide infra*) of **3** is formed.

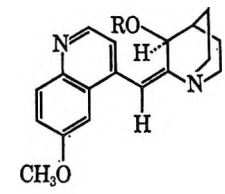


3 **4**

Samples of isomer **4**, isolated by preparative layer chromatography, slowly rearranged to isomer **3** on standing. The assignment of structures **3** and **4** to the two ketones can be made on the basis of their ultraviolet absorption spectra. There are no serious steric interactions to inhibit coplanarity of the α,β-unsaturated ketone function and quinoline ring in ketone **3** and the resulting conjugation is reflected in an ultraviolet absorption maximum at 362 mμ. However, ketone **4** suffers severe steric interactions when these functions are coplanar and the resulting steric inhibition of resonance manifests itself in the absence of an absorption maximum above 337 mμ, the longest wavelength absorption maximum of 6-methoxyquinolines (compounds **6**, **8**, **13**, **16**, and **18** as well as **4** all show maxima between 335 and 340 mμ). The maximum at 337 mμ in compound **4** shows sufficient tailing into the visible to impart its yellow color.



5 R = OH
6, R = *p*-nitrobenzoyloxy
10, R = Cl
11, R = acetoxy



7, R = H
8, R = *p*-nitrobenzoyloxy

The α,β-unsaturated ketone **3** possesses a plane of symmetry whereby its sodium borohydride reduction produces a single (racemic) alcohol (**5**). The utilization of this alcohol as a precursor of quinine has been explored to some extent. In principle the hydroxy group can be used as a "handle" for the functionalization of C_3 (required for the introduction of a vinyl group) and can then be migrated to C_9 *via* an allylic rearrangement. Treatment with *p*-nitrobenzoyl chloride in pyridine transforms the alcohol **5** into its

(9) E. Ochiai, H. Kataoka, T. Dodo, and M. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 76 (1962).

(10) C.-B. Chen, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR*, **123**, 707 (1958); *Chem. Abstr.*, **53**, 7919 (1959).

(11) P. B. Russel in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 814.

(12) E. H. Sadun, *Amer. J. Trop. Med. Hyg.*, **13**, 145 (1964).

(13) See E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965), for leading references.

(14) K. Lang and H. Keuer, *Biochem. Z.*, **329**, 277 (1957).

(15) H. U. Daeniker and C. A. Grob, *Org. Syn.*, **44**, 86 (1964); Aldrich Chemical Co., Inc., Milwaukee, Wis.

(16) (a) C. A. Grob and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963); (b) A. T. Nielsen, *J. Org. Chem.*, **31**, 1053 (1966).

(17) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).

(18) (a) C. E. Kwartler and H. G. Lindwall, *J. Amer. Chem. Soc.*, **59**, 524 (1937); (b) M. Levitz and M. T. Bogert, *J. Org. Chem.*, **10**, 341 (1945).

(19) K. N. Campbell, R. S. Tipson, R. C. Elderfield, B. K. Campbell, M. A. Clapp, W. J. Gensler, D. Morrison, and W. J. Moran, *ibid.*, **11**, 803 (1946).

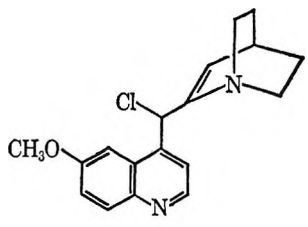
p-nitrobenzoate **6**. When this derivative was exposed to sodium acetate in refluxing acetic acid for 6 hr, it failed to yield any detectable amount of a rearranged acetate; indeed, it failed to yield any acetate. The product, compound **8**, is that resulting from isomerization of the olefinic linkage. Assignment of structures **6** and **8** to the starting material and product, respectively, is based on the nmr spectra of the two esters. Whereas the four protons of the *p*-nitrobenzoyl group appear as a singlet at 8.25 ppm in ester **6**, they give rise to a multiplet superimposed on the multiplet arising from the quinoline protons (centered at *ca.* 7.5 ppm) in the isomeric ester **8**. This is interpreted as a consequence of the close proximity of the quinoline ring and *p*-nitrobenzoyl group in ester **8**.

Both hydrolysis of *p*-nitrobenzoate **8** and sodium borohydride reduction of ketone **4** gave the same alcohol, compound **7**.

The SNi′ reaction of allylic alcohols with thionyl chloride[20] suggested a second method of transposing the oxygen function at C_7 in alcohol **5** to C_9. Treatment with thionyl chloride did in fact give some of the rearranged chloride **9**, but as a minor product. The major product was the chloride **10**. The two chlorides **9** and **10** form partially overlapping spots on thin layer chromatography and were therefore not amenable to separation. The nmr spectrum of the mixture showed signals at 3.96, 4.90, and 6.98 ppm which can be assigned to the methoxyl, C_7, and vinyl protons, respectively, of compound **10** and signals at 3.89, 6.11, and 6.48 ppm which can be assigned to the methoxyl, C_9, and vinyl protons, respectively, of compound **9**. The integration ratio of the first set of signals to the second set (4:1) indicates that the mixture consists of 80% of compound **10** and 20% of compound **9**. The alternative interpretation of the nmr spectrum as arising from a mixture of *cis–trans* isomers is not consistent with the chemical shifts observed for the C_7 and C_9 protons of compound **9**: the two isomeric alcohols **5** and **7** show vinylic proton signals at 6.92 and 6.98, respectively, and C_7 proton signals at 4.45 in each. Similarly the isomeric *p*-nitrobenzoates show vinylic proton signals at 6.95 and 7.12, respectively, and C_7 proton signals at 5.88 and 5.83, respectively.

The mixture of chlorides reacted very slowly with silver acetate in refluxing acetic acid to give, as the only products isolated, the alcohol **5** and the acetate **11**. This acetate was identical with that obtained from the reaction of alcohol **5** with acetic anhydride.

Catalytic hydrogenation of the mixture of chlorides **9** and **10** in alcoholic potassium hydroxide solution gave a mixture of products from which 6′-methoxyrubane (**12**) was isolated in low yield. The two antipodal forms



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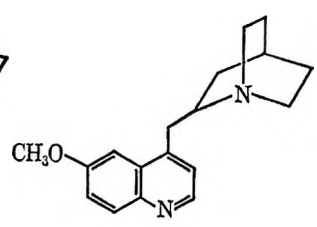
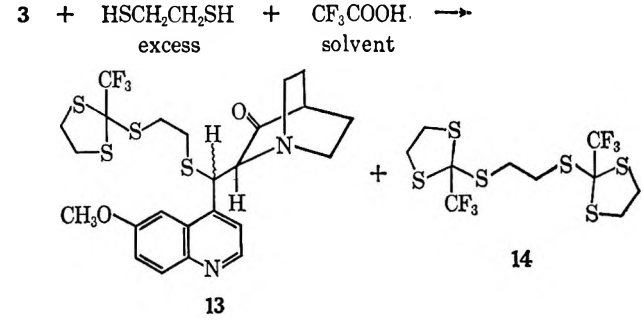


12

(20) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p 296.

of this compound have been synthesized previously by Rabe.[6b]

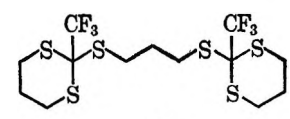
A more direct route to 6′-methoxyrubane (**12**) was anticipated in the thioketalization of the α,β-unsaturated ketone **3** followed by simultaneous hydrogenolysis and hydrogenation over Raney nickel. However, the ketone resisted all attempts to transform it into a thioketal. A reaction with 1,2-ethanedithiol takes place in refluxing trifluoroacetic acid, however the product, compound **13**, derives from sequential condensation with the dithiol, the solvent, and a second molecule of the dithiol.



13 **14**

A by-product of the reaction, compound **14**, was shown to result from a still more complex condensation in which five molecules in the reacting system combine into one.

The structure of the by-product **14** gave an essential hint in elucidating the structure of the main product **13**; hence the determination of this structure will be discussed first. The compound was obtained in 89% yield when 1,2-ethanedithiol and excess trifluoroacetic acid were heated under reflux. It is a colorless solid, readily recrystallized from ethanol without decomposition. The compound shows C–F bands at 1200 cm^{-1} in its infrared spectrum, two singlets at 3.19 and 3.52 ppm (ratio 1:2) in its proton nmr spectrum, and intense peaks at *m/e* 173 and 265 in its mass spectrum. These data, together with the analysis and observed molecular weight, can only be accommodated by structure **14**.[21] This direct condensation of a mercaptan with a carboxylic acid to form an ortho thiol ester is without precedent and is more or less unique for these two reactants. Acetic and formic acids do not condense with ethanedithiol in this manner although 1,3-propanedithiol gives, in much lower yield, the analogous product **15** with trifluoroacetic acid.[22]



15

Skeletal rearrangements attending the transformation of ketone **3** into compound **13** are precluded by the facile regeneration of **3** under a variety of conditions (heat, alumina, acetic anhydride). Compound **13** crystallizes as an ethanol solvate and this fact, combined with the thermal instability, required reduction to the alcohol **16** for molecular weight determination. The mass spectrum of compound **13** is that of the ketone

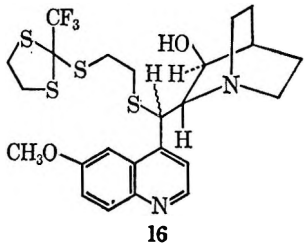
(21) A preliminary description of this reaction has been published: D. L. Coffen, *Chem. Commun.*, 1089 (1967).

(22) Compound **15** was first synthesized by Miss Patricia Garrett of our laboratory.

3. An infrared absorption band at 1730 cm^{-1} demonstrates that the ketone function is still present but no longer conjugated; new bands at 1150, 1175, and 1240 cm^{-1} are consistent with a compound containing C–F bonds. The nmr spectrum of a sample recrystallized from ethanol shows by a triplet at 1.20 and a quartet at 3.69 ppm (J = 7 cps) that crystalline compound **13** is a monoethanol solvate. A sample obtained by evaporating a benzene solution of **13** no longer contained these nmr bands nor an infrared band at 3300 cm^{-1}. The 100-Mc nmr spectrum of the ethanol-free sample, in comparison with the spectrum of its precursor **3**, shows the following changes: the vinyl proton singlet at 7.66 ppm has vanished; two new one-proton doublets appear at 3.71 and 5.02 ppm (J = 8 cps) and are assigned to protons at C_8 and C_9 (confirmed by spin decoupling); in addition to the methoxyl singlet at 3.89 ppm, a four-proton singlet appears at 3.20 which can be ascribed to the 1,3-dithiolane ring protons; signals from the exocyclic ethanedithiol residue are superimposed on the quinuclidine multiplets but probably give rise to triplets observed at 2.45 and 2.85 ppm (J = 8 cps).

Although compounds **13** and **16** have two and three centers of asymmetry, respectively, each of them is nevertheless obtained as a single racemate. Although it is not possible to assign stereochemistry to C_9 relative to C_8 in these compounds, the configuration indicated for C_7 in **16** can be assigned with confidence when the steric hindrance to borohydride ion attack from the upper side of **13** is considered.

The myriad products available from 1,3-dipolar addition reactions[23] suggested that numerous synthetic quinine analogs might be derivable from ketone **3** if 1,3-dipolar additions can be effected across the C_8–C_9 double bond. This possibility has been realized and demonstrated in the nearly quantitative formation of pyrazoline **17** in the reaction of ketone **3** with diazomethane. The spectroscopic properties of the adduct are in accord with structure **17**.



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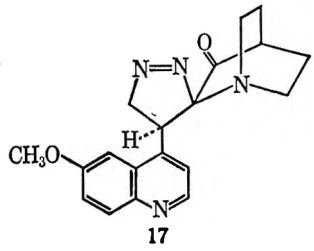
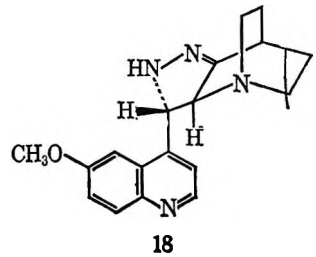


17

A second pyrazoline derivative, **18**, was obtained by warming the ketone **3** with alcoholic hydrazine. Mercuric acetate oxidation of compound **18** gave the corresponding pyrazole **19**. Structure **18**, rather than that of an α,β-unsaturated hydrazone, is assigned on the basis of the compound's nmr spectrum. The spectrum contains no vinyl proton singlet but does have two one-proton doublets at 3.11 and 4.75 ppm ($J_{8,9}$ = 4 cps). These two doublets vanish with the oxidation to pyrazole **19**. The low value of $J_{8,9}$ suggests the *trans* relationship[24] indicated for the protons at C_8 and C_9.



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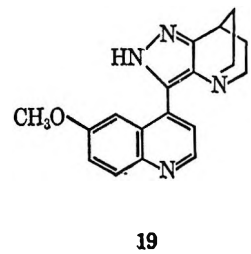

19

(23) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

Experimental Section[25]

6′-Methoxy-7-oxo-8-rubene.—Sodium (1.56 g, 0.068 g-atom) was dissolved in absolute ethanol (60 ml) and to the resulting solution 6-methoxyquinoline-4-carboxaldehyde[18] (9.64 g, 0.0515 mol) and 3-quinuclidinone hydrochloride[15] (8.35 g, 0.0515 mol) were added. The mixture was warmed to 35°, swirled for *ca.* 5 min, and then kept at room temperature for 2 hr. Crystallization of the product was completed by slowly adding water (150 ml). The product was filtered, washed with water, and dried in air giving 14.13 g (91%) of yellow crystals. An analytical sample, recrystallized from ethanol, had mp 155–156°; ν_{max} 1710, 1620, 1510, 1230, 1095, 1035, 928, 858, and 731 cm^{-1}; λ_{max} 228 (ϵ 43,000), 250 (sh, 17,000), 337, (7300) and 362 (7200); nmr ($CDCl_3$), 2.10 (4 H, multiplet, H_3 and H_5), 2.70 (1 H, multiplet, H_4), 3.10 (4 H, multiplet H_2 and H_6), 3.96 (3 H, singlet, methoxyl), 7.32 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.66 (1 H, singlet, H_9), 8.04 (2 H, two doublets, three lines, $H_{3'}$ and $H_{8'}$), and 8.80 (1 H, doublet, $H_{2'}$, $J_{2',3'}$ = 5 cps); and mol wt 294 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.65; H, 6.16; N, 9.52. Found: C, 73.62; H, 6.13; N, 9.29.

Equilibration of Ketone 3 with Ketone 4.—A sample of ketone **3** (200 mg) dissolved in 6 *N* sulfuric acid was kept at room temperature for 18 hr. The solution was neutralized with aqueous sodium bicarbonate and the ketones were extracted with methylene chloride. The product showed two yellow spots on a silica gel thin-layer chromatogram ($CHCl_3$–CH_3OH 10:1), the starting material and a new spot with a lower R_f value. When material from the lower spot was eluted directly into an ultraviolet cell with ethanol, it showed a maximum at 337 mμ. The remaining product was separated by preparative layer chromatography. The ketone from the lower yellow band (68 mg) was crystallized from ethanol. This material, mp 121–123°, showed by tlc and nmr that partial conversion back to ketone **3** had occured during purification. The infrared spectrum of this material showed only minor differences from that of pure ketone **3**. The nmr spectra were also very similar with slight differences in some chemical shifts: methoxyl protons at 3.89, vinyl proton at 7.17, and $H_{2'}$ at 8.76 ppm in ketone **4**.

6′-Methoxy-7-hydroxy-8-rubene (5).—Ketone **3** (4.57 g, 0.0153 mol) was partially dissolved in methanol (50 ml) with warming, then treated with sodium borohydride (1.00 g, 0.026 mol) in portions while swirling. The ketone dissolved completely and the yellow color disappeared. The solution was slowly diluted with cold water (250 ml) and stored in the cold overnight. The product was filtered, washed with water, and dried in air, giving 4.51 g (98%) of colorless, crystalline alcohol, mp 153–155°. The compound had ir bands at ν_{max} 3200, 1640, 1620, 1580, 1510, 1230, 1090, 1030, 845, and 720 cm^{-1}; the nmr spectrum ($CDCl_3$) showed peaks at 1.1–3.3 (9 H, multiplets, quinuclidine H), 3.78 (3 H, singlet, methoxyl), 4.49 (1 H, broad singlet, H_7), 4.60 (1 H, broad singlet, vanished when solution was shaken with D_2O, hydroxyl), 6.92 (1 H, doublet, H_9, $J_{7,9}$ = 1.5 cps), 7.25 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.83 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 4.5 cps), 8.00 (1 H, doublet, $H_{8'}$, $J_{7',8'}$ = 10 cps), and 8.64 (1 H, doublet, $H_{2'}$); and the molecular weight was 296 (mass spectrum).

6′-Methoxy-7-(*p*-nitrobenzoyloxy)-8-rubene (6).—A solution

(24) A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

(25) Melting points are uncorrected. Infrared spectra were measured as Nujol mulls on a Perkin-Elmer Infracord Model 137. Strong bands and those characteristic of the functional groups present are listed. Ultraviolet spectra (in 95% ethanol) and mass spectra were recorded on Cary 14 and CEC 21-103 instruments, respectively. Nmr spectra (ppm) were measured on Varian A-60A and HA-100 instruments using solvents indicated and tetramethylsilane as an internal standard. Analyses and molecular weight determinations were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Some of the compounds with strong molecular ion peaks in their mass spectra were not analyzed.

of alcohol **5** (400 mg, 1.35 mmol) and *p*-nitrobenzoyl chloride (500 mg, 2.70 mmol) in pyridine (5 ml) was kept overnight at room temperature. The resulting mixture was diluted with methylene chloride, washed with aqueous sodium bicarbonate, dried, and evaporated. The crude product (543 mg, 91%) was recrystallized from ethanol giving colorless crystals with mp 142–145° and ir bands at ν_{max} 1720, 1625, 1580, 1525, 1500, 1350, 1320, 1265, 1225, 1105, 1025, 850, and 724 cm^{-1}. The nmr spectrum ($CDCl_3$) was essentially the same as that of the alcohol between 1 and 4 ppm. H_7 appears as a poorly resolved doublet at 5.88 and a new, four-proton singlet appears at 8.26 (*p*-nitrobenzoyl group). The quinoline and vinyl proton signals are essentially unchanged.

Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43. Found: C, 66.19; H, 5.17; N, 9.18.

Isomerization of *p*-Nitrobenzoate 6 to *p*-Nitrobenzoate 8.—A solution of *p*-nitrobenzoate **6** (200 mg) and sodium acetate (800 mg) in acetic acid (8 ml) was heated under reflux for 6 hr. The solution was then diluted with water, neutralized with aqueous sodium bicarbonate, and extracted with methylene chloride. The dried extract was evaporated leaving 164 mg of partly crystalline, crude product, Recrystallization from ethanol gave 70 mg (35%) of pure, colorless crystals with mp 162–163° and ir bands at ν_{max} 1720, 1620, 1580, 1525, 1345, 1320, 1260, 1225, 1115, 1105, 1030, and 720 cm^{-1}. The nmr spectrum ($CDCl_3$) shows the quinuclidine protons as three multiplets between 1.0 and 3.6, the methoxyl singlet at 3.94, and H_7 at 5.83. The 7.0–8.6-ppm region of the spectrum contains at least 20 lines (10 H) of which only the $H_{2'}$ doublet at 8.48 can be assigned with confidence. The R_f value of ester **8** on tlc is distinctly lower than that of ester **6**.

Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43. Found: C, 66.35; H, 5.34; N, 9.21.

Alcohol 7. A. By Hydrolysis of *p*-Nitrobenzoate 8.—*p*-Nitrobenzoate **8** (65 mg) was taken up in methanolic KOH (two pellets in 2 ml) andkept at room temperature for 2 hr. The solution was diluted with water and extracted with methylene chloride. The extracts were dried and evaporated leaving 36 mg (82%) of crystalline residue. Recrystallization from ethanol gave colorless crystals: mp 166–167°; ν_{max} 3150, 1640, 1620, 1580, 1505, 1230, 1045, 1035, 905, 822, and 715 cm^{-1}; nmr ($CDCl_3$), 1.1–3.4 (9 H, multiplets, quinuclidine H), 3.6 (1 H, broad singlet, hydroxyl), 3.87 (3 H, singlet, methoxyl), 4.45 (1 H, broad singlet, H_7), 6.98 (1 H, singlet, H_9), 7.25 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.58 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 4.5 cps), 7.36 (1 H, doublet, $H_{8'}$, $J_{7',8'}$ = 9 cps), and 8.43 (1 H, doublet, $H_{2'}$). The molecular weight was 296 (mass spectrum); the mass spectra of alcohols **5** and **7** are nearly identical. Alcohol **7** has a distinctly lower R_f value on tlc than alcohol **5**.

B. By Reduction of Ketone 4.—The sample of ketone **4** from preparative layer chromatography (60 mg, contaminated with **3**) was repurified in the same manner. The lower yellow band was removed from the plate and added directly to a stirred solution of sodium borohydride (100 mg) in methanol (5 ml). The reaction mixture was diluted with methylene chloride, filtered through Celite to remove the silica gel, dried, and evaporated leaving 42 mg of colorless residue. The product was purified by preparative layer chromatography and recrystallization from ethanol giving 20 mg of colorless crystals, mp 163–165° (mmp 164–167°). The infrared spectrum and tlc behavior of this material are identical with those of the alcohol from method A.

6′-Methoxy-7-chloro-8-rubene (10) and 6′-Methoxy-9-chloro-7-rubene (9).—Alcohol **5** (200 mg, 0.66 mmol) was dissolved in thionyl chloride (5 ml) and the solution was refluxed for 45 min then kept at room temperature for 17 hr. Excess thionyl chloride was evaporated in a nitrogen stream. The residue was taken up in methylene chloride, washed with aqueous sodium bicarbonate, dried, and evaporated leaving 232 mg of viscous yellow oil. The product is a mixture of two compounds (tlc), crystalline in the cold but an oil at room temperature; ir bands were at ν_{max} (film) 1620, 1580, 1500, 1230, 1030, 845, 775 and 715 cm^{-1}. The nmr spectrum ($CDCl_3$) shows the quinuclidine and quinoline multiplets in the 1–3.3- and 7.2–8.8-ppm regions, respectively. Signals at 3.96 (singlet), 4.90 (quartet, $J_{4,7}$ = 3.5 cps and $J_{7,9}$ = 1.5 cps), and 6.98 (doublet, $J_{7,9}$ = 1.5 cps) in the ratio 3:1:1 are assigned to the methoxyl protons, H_7, and H_9 of chloride **10**. Signals with one-fourth of the intensity at 3.89 (singlet), 6.11 (broad singlet), and 6.48 (doublet, $J_{4,7}$ = 7 cps) in the ratio 3:1:1 are assigned to the methoxyl protons, H_9, and H_7 of chloride **9**.

6′-Methoxy-7-acetoxy-8-rubene (11). A. From Chlorides 9 and 10.—The crude chloride mixture from alcohol **5** (200 mg) was stirred with silver acetate (300 mg) in acetic acid (10 ml) for 3 days at room temperature. The mixture was diluted with aqueous sodium chloride, filtered, neutralized with aqueous sodium bicarbonate, and extracted with methylene chloride. The dried extracts were evaporated leaving 179 mg of yellow gum. Separation of the crude products by preparative layer chromatography afforded 29 mg (14%) of alcohol **5** (infrared, tlc) and 75 mg (33%) of acetate **11**. The acetate formed colorless crystals from ether: mp 136–137°; ν_{max} 1730, 1660, 1620, 1580, 1500, 1245, 1230, 1035, 870, 840, and 718 cm^{-1}. The nmr ($CDCl_3$) spectrum contains signals for the quinuclidine and methoxyquinoline protons similar to those in the spectrum of the alcohol **5**. There is a new three-proton singlet at 2.16 (acetyl), H_7 appears as a poorly resolved quartet at 5.58, and H_9 appears as a broad singlet at 6.80 ppm.

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.37; N, 8.47.

B. From Alcohol 5.—Alcohol **5** (500 mg, 1.69 mmol) was taken up in acetic anhydride and the solution was kept overnight at room temperature. The solution was then slowly poured into cold, aqueous sodium bicarbonate. The product was extracted with methylene chloride and, after drying and evaporating, recrystallized from ether to give 470 mg (82%) of colorless crystals, identical (melting point, tlc, infrared) with that obtained by method A.

6′-Methoxyrubane (12).—The crude chloride mixture from alcohol **5** (300 mg) was taken up in a solution of potassium hydroxide (2 g) in ethanol (15 ml) and shaken with Raney nickel (0.5 g) under hydrogen at 50 psi for 16 hr. The catalyst was filtered out and washed with ethanol. The filtrate and washings were poured into water and extracted with methylene chloride giving, when dried and evaporated, 260 mg of brown oil. The most polar component of this mixture was isolated by preparative layer chromatography (silica gel) and the dihydrochloride was recrystallized twice from methylene chloride–ether giving 16 mg of colorless crystals: mp 162–164°; ν_{max} 1670, 1620, 1590, 1510, 1225, 1125, 1030, 800, and 720 cm^{-1}; molecular weight of the free base, 282 (mass spectrum).

Anal. Calcd for $C_{18}H_{22}N_2O \cdot 2HCl$: C, 60.84; H, 6.80; N, 7.88. Found: C, 60.62; H, 6.40; N, 7.92.

Compound 13.—Ketone **3** (500 mg) and 1,2-ethanedithiol (1 ml) in trifluoroacetic acid (10 ml) were heated under reflux for 16 hr. Excess trifluoroacetic acid was evaporated off and the residue was taken up in methylene chloride. This solution was washed with aqueous sodium bicarbonate, dried, and evaporated. The residue was dissolved in ethanol (4 ml) and stored in the cold for 1 week. The crystals were filtered, washed with cold ethanol, and air dried giving 750 mg (73%) of crude crystalline **13** as an ethanol (mono) solvate. Two subsequent crops of crystals were nearly pure compound **14**. Recrystallization of the main product from ethanol gave 570 mg of pure **13** in large, colorless crystals: mp 89–92° dec; ν_{max} 3250 (ethanol), 1730, 1625, 1580, 1505, 1240, 1180, 1150, 1030, 845, and 720 cm^{-1}. The nmr spectrum ($CDCl_3$, ethanol-free sample) shows three multiplets at 2.00, 2.45, and 4.00 (13 H) assigned to the quinuclidine and exocyclic ethanedithiol moiety protons, 3.20 (4 H, singlet, dithiolane ring), 3.71 (1 H, doublet, H_8, $J_{8,9}$ = 8 cps), 3.89 (3 H, singlet, methoxyl), 5.02 (1 H, doublet, H_9), 7.35, (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.60 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 5 cps), 8.01 (1 H, doublet, $H_{8'}$, $J_{7',8'}$ = 9.5 cps), and 8.72 (1 H, doublet, $H_{2'}$).

Anal. Calcd for $C_{26}H_{33}F_3N_2O_3S_4$: C, 51.46; H, 5.48; N, 4.62; S, 21.14. Found: C, 51.40; H, 5.59; N, 4.45; S, 21.26.

Alcohol 16.—Compound **13** (50 mg) in methanol (1 ml) was treated with excess sodium borohydride and kept at room temperature for 1 hr. The solution was diluted with water and chilled and the product (42 mg, 84%) was filtered out. Recrystallization from methylene chloride–ether gave fine, colorless needles: mp 198°; ν_{max} 3200, 1620, 1580, 1240, 1170, 1145, 1070, 1030, and 829 cm^{-1}. The nmr spectrum ($CDCl_3$) shows a complex multiplet pattern in the 1.1–4.1-ppm region in which the dithiolane and methoxyl singlets appear at 3.28 and 4.00 ppm, and H_9 appears as a doublet at 5.34 ($J_{8,9}$ = 11 cps). The quinoline proton signals show only slight differences from those of compound **14**; $H_{8'}$ appears at 7.70 and $H_{2'}$ appears at 8.48 ppm.

Anal. Calcd for $C_{24}H_{29}F_3N_2O_2S_4$: C, 51.22; H, 5.19; N, 4.98; S, 22.79; mol wt, 562.78. Found: C, 51.39; H, 5.05; N, 4.60; S, 22.39; mol wt ($CHCl_3$), 564.

1,2-Bis-2(2-trifluoromethyl-1,3-dithiolanyl)thioethane (14).—A solution of 1,2-ethanedithiol (3 g, 32 mmol) in trifluoroacetic acid (20 ml) was heated under reflux for 20 hr. A second phase began to form after 3 hr. The mixture was chilled and the solid product was filtered and dried giving 4.12 g (89%) of colorless; crystals. A sample was recrystallized from ethanol: mp 85°; ν_{max} 1420, 1370, 1280, 1225, 1160, 980, 960, 890, 860, 835, 820, 708, and 693 cm^{-1}; nmr (CCl_4), 3.19 (4 H, singlet) and 3.52 ppm (8 H, singlet); mass spectrum, *m/e* 173 and 265 (no M^+ at 70 eV or at 14 eV).

Anal. Calcd for $C_{10}H_{12}F_6S_6$: C, 27.38; H, 2.76; S, 43.87; mol wt, 438.6. Found: C, 27.33; H, 2.72; S, 44.06; mol wt ($CHCl_3$), 429.

1,3-Bis-2(2-trifluoromethyl-1,3-dithianyl)thiopropane (15).—A solution of 1,3-propanedithiol (4 g, 37 mmol) in trifluoroacetic acid (20 ml) was heated under reflux for 20 hr. The solution was cooled and excess trifluoroacetic acid was evaporated under reduced pressure (0.5 mm at 60°) leaving a colorless oil which exhibits carbonyl absorption at 1710 cm^{-1}. This oil was taken up in ethanol (25 ml), seeded with a crystal of product (isolated by alumina chromatography), and stored in the cold for 2 weeks. The crystals were filtered and washed with cold ethanol giving 1.86 g (32%) of product. A sample was recrystallized from ethanol: mp 54–55°; ν_{max} 1420, 1400, 1275, 1225, 1170, 1010, 884, 858, 810, 770 and 703 cm^{-1}; nmr (CCl_4), 2.0 (6 H, multiplet) and 2.94 ppm (12 H, unsymmetrical triplet); mass spectrum, *m/e* 187 and 293 (no M^+ peak).

Anal. Calcd for $C_{13}H_{18}F_6S_6$: C, 32.48; H, 3.77; S, 40.03. Found: C, 32.69; H, 3.64; S, 40.08.

Spiro-4′-(6-methoxy-4-quinolyl)-1-pyrazoline[3′.2]quinuclidin-3-one (17).—A solution of ketone **3** (500 mg) in methylene chloride (10 ml) was treated with *ca.* 0.2 *M* diazomethane in ether (50 ml). Colorless needles began to separate after 10 min. The mixture was kept in the cold for 2 days and at room temperature for 2 days, then concentrated to *ca.* 10 ml, chilled, and filtered giving 500 mg (88%) of colorless needles, mp 235–245° dec. A sample recrystallized from methylene chloride–ether had the same melting point; ir bands were at ν_{max} 1725, 1625, 1580, 1505, 1230, 1140, 1030, 850, and 820 cm^{-1}. The nmr spectrum ($CDCl_3$) contains quinuclidine proton multiplets from 1.8 to 3.2 ppm and the methoxy singlet at 3.89. H_9 appears as a quartet (1 H) at 4.21. The methylene protons of the pyrazoline ring give a cleanly resolved eight-line pattern at 4.2 arising from the splitting of an AB quartet by H_9 (J_{AB} = 18 cps, J_{A9} = 8 cps, and J_{B9} = 4 cps, confirmed by spin decoupling). The five quinoline protons appear as doublets at 6.97 ($H_{3'}$), 8.00 ($H_{8'}$), and 8.62 ($H_{2'}$), and a two-proton multiplet at 7.30 ppm.

Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.79; H, 6.09; N, 16.47.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)-2-pyrazoline (18).—Ketone **3** (250 mg) was dissolved in ethanol (5 ml) with warming and treated with 95% hydrazine (0.5 ml). The yellow color faded with additional warming. Evaporation left 275 mg (100%) of crystalline white solid. The product crystallizes as a monohydrate. Crystals from dimethyl sulfoxide had mp 205–207° and ir bands at ν_{max} 3300, 1620, 1580, 1505, 1225, 1025, 852, and 718 cm^{-1}. The nmr spectrum (d_6-DMSO) differed from that of ketone **3** by the absence of a vinyl proton signal and the appearance of one-proton doublets at 3.11 (H_8) and 4.75 ppm (H_9, $J_{8,9}$ = 4 cps). The product had uv absorptions at λ_{max} 207 mμ (ε 34,000), 237 (43,000), and 335 (6400), and a molecular weight of 308 (mass spectrum).

Anal. Calcd for $C_{18}H_{20}N_4O \cdot H_2O$: C, 66.23; H, 6.79; N, 17.16. Found: C, 66.83; H, 6.63; N, 17.06.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)pyrazole (19).—The crude pyrazoline **18** from 1 mmol of ketone **3** (294 mg) in acetic acid (5 ml) was treated with a warm solution of mercuric acietate (350 mg, 1.10 mmol) in acetic acid (10 ml). The resulting mixture was stirred at room temperature for 2 days, then poured into dilute aqueous ammonia, and extracted with methylene chloride. The crude product from evaporating the dried extracts was purified by chromatography on alumina and recrystallized from methylene chloride–ether. The pure product (179 mg, 58%) was obtained as small, colorless crystals: mp 239–243°; ν_{max} 3100, 1620, 1575, 1550, 1500, 1240, 1155, 1135, 850, and 720 cm^{-1}; λ_{max} 206 mμ (ε 26,000), 233 (34,000), 302 (7000), and 338 (7400). The nmr spectrum ($CDCl_3$–d_6-DMSO) shows quinuclidine proton signals from 1.2 to 3.0, methoxyl at 3.94, and peaks at 7.41 (1 H, quartet, $H_{7'}$, $J_{7',8'}$ = 10 cps and $J_{7',5'}$ = 3 cps), 7.65 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 4 cps), 8.04 (2 H, two doublets, $H_{5'}$ and $H_{8'}$), and 8.82 ppm (1 H, doublet, $H_{2'}$).

Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29; mol wt, 306. Found: C, 69.61; H, 6.10; N, 17.85; mol wt 306 (mass spectrum).

Registry No.—**3,** 16526-29-7; **4,** 16526-45-7; **5,** 16526-30-0; **6,** 16526-31-1; **7,** 16526-32-2; **8,** 16526-33-3; **9,** 16526-34-4; **10,** 16526-35-5; **11,** 16526-36-6; **12,** 16526-44-6; **13,** 16526-37-7; **14,** 16526-38-8; **15,** 16526-39-9; **16,** 16526-40-2; **17,** 16526-41-3; **18,** 16526-42-4; **19,** 16526-43-5.

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Deamination of 5-Aminodecahydroisoquinolines. An Improved Synthesis of *cis*-5,9,10-H- and *trans*-9,10-*trans*-5-H-5-Hydroxydecahydroisoquinolines

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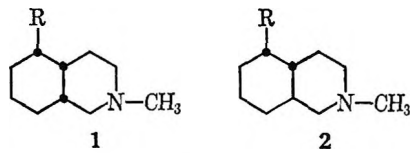
The stereochemistry of some previously unreported 5-amino-2-methyldecahydroisoquinolines, and their derivatives, has been elucidated by relation to the 5-hydroxy-2-methyldecahydroisoquinolines (**1a** and **2a**). The isomeric 5-amino-2-methyldecahydroisoquinolines were prepared by a one-step reduction of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate and converted into their acetamide derivatives which allowed convenient separation of the *cis*-9,10 (**1c**) and *trans*-9,10 (**2c**) isomers. Acid hydrolysis of these separated acetamides subsequently yielded pure *cis*-5,9,10-H- (**1b**) and *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**). The hydrolysis of **1c** proceeded at a faster rate than **2c**. Conversion of **1b** and **2b** by deamination with nitrous acid into the corresponding alcohols in high yield supports the equatorial nature of the 5 substituents. A small amount (2%) of inversion was observed during the deamination of **2b**.

An investigation of the effects on the cardiovascular system induced by various stereoisomers of substituted decahydroisoquinolines led us to develop an improved method of producing reduced isoquinolines of known stereochemistry at the ring junction, *i.e.*, *cis*-9,10 and *trans*-9,10. The stereochemistry of decahydroisoquinoline[1] and 5-hydroxy-2-methyldecahydroisoquinolines[2,3] has previously been studied. No previous work has been reported on the 5-amino-2-alkyldecahydroisoquinolines and their derivatives, the stereochemistry of which we have now related to the hydroxy analogs.



1 **2**

a, R = OH
b, R = NH_2
c, R = $NHCOCH_3$

Witkop[1] showed that direct, low pressure, platinum-catalyzed hydrogenation of isoquinoline in acidic media produced a 2:1 mixture of *cis*- and *trans*-decahydroisoquinolines. We have found, under similar conditions, the addition of a 5-hydroxy substituent to the isoquinoline nucleus does not significantly alter the 2:1 *cis* to *trans* ratio of 5-hydroxydecahydroisoquinolines produced, as demonstrated by vapor phase chromatography of the crude reaction products. Quaternization of 5-hydroxyisoquinoline with methyl *p*-toluenesulfonate and hydrogenation of the resulting product under identical acidic conditions to those previously reported[4] yielded 5-hydroxy-2-methyldecahydroisoquinolines; the *cis*/*trans* ratio is unaltered from that reported by Witkop[1] for isoquinoline. The yield, in our hands, approximated 25% alcohols [*cis* and *trans*, predominantly as the acetate ester(s) as shown by infrared spectra] and 25% decahydroisoquinolines, *cis* and *trans* in a 2:1 ratio, as shown by vapor phase chromatography.[5] Kimoto and Okamoto[2] report only *cis*-9,10-5-acetoxy-2-methyldecahydroisoquinoline and *cis*-9,10-2-methyldecahydroisoquinoline from the platinum-catalyzed reduction of 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. A similar reduction[3] of 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline did not produce the acetate (although the work-up may have obscured its presence) nor any hydrogenolysis products, but did yield two alcohols, the *cis* alcohol being the predominant isomer.

We have been able to avoid or minimize the problems of hydrogenolysis and ester formation and to improve the yield during hydrogenation, by reducing 5-nitro-2-methylisoquinolinium *p*-toluenesulfate, under the same acidic conditions, to the previously unreported *cis*-5,9,-10-H- (**1b**) and *trans*-9-10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**). Vapor phase chromatography of the crude reaction products indicated 85–90% 5-amino-2-methyldecahydroisoquinolines **1b**–**2b** (2:1) and only 10–12% hydrogenolysis products. The lower boiling hydrogenolysis products were separated from the 5-amino isomers by distillation, and vapor phase chromatography of the 5-amino isomers showed only two components. Efficient separation of these isomers was not possible by distillation on spinning-band columns. The 5-amino isomeric mixture was converted into a mixture of the corresponding acetamides. It is possible by differences in water solubility to separate the *cis*-5,9,10-H- (**1c**) and *trans*-9,10-*trans*-5-H-5 acetamido (**2c**) derivatives. Hydrolysis of the amides afforded pure *cis*-5,9,10-H- (**1b**) and pure *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**) in quantitative yield. Hydrolysis of the pure acetamide isomers proceeded at markedly different rates. The *cis* acetamide hydrolyzed readily on refluxing with 15% w/v sulfuric acid over 1 day; the *trans* isomer, however, required up to 6 days refluxing with 20% w/v sulfuric acid before complete hydrolysis was achieved—a rate difference of approximately six to ten. Examination of Dreiding molecular models of the equatorial isomers reveals little hindrance to the water molecule attacking the protonated amide function. We speculatively suggest that this marked difference in hydrolytic rates between the isomers to be due to the flexibility of the *cis* isomer as opposed to the rigidity of the *trans* isomer. The formation of the tetrahedral carbon intermediate required by the hydrolytic mechanism[6] may be more readily accommodated by the flexible *cis* ring system. We are unaware of any studies of comparable hydrol-

(1) B. Witkop, *J. Amer. Chem. Soc.*, **70**, 2617 (1948).

(2) S. Kimoto and M. Okamoto, *Yakugaku Zasshi*, **85**, 371 (1965).

(3) S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. Chim. Fr.*, 3424 (1966).

(4) I. W. Mathison, *J. Org. Chem.*, **30**, 3558 (1965).

(5) The stereochemistry in this hydrogenation is developed at the same point as hydrogenations outlined by Kimoto and Okamoto[2] and Durand-Henchoz and Moreau;[3] the experimental details are therefore not reported in this paper.

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 328, 329.

ysis differences in similar cyclic systems. These differences suggest the possibility of separating the *cis* and *trans* isomers by selective hydrolysis.

We have demonstrated the equatorial conformation of the 5-amino substituent of the separated 5-amino-2-methyldecahydroisoquinolines (and therefore their aceamides) by deamination with nitrous acid in high yield to the corresponding alcohols (see Experimental Section). These conclusions are based upon the work of Dauben, *et al.*,[7] who reported that in the decalylamines high conversions (100%) were obtained only with the equatorial conformers; axial amino substituents on deamination with nitrous acid yielded small amounts of alcohol (27%) and large amounts of olefins. The stereochemical assignments for the alcohols produced during our deaminations are based on the work of Durand-Henchoz and Moreau,[3] who related spectrally the decahydroisoquinolinols with the corresponding known decalols.[7]

Additionally, we observed some inversion during the deamination of the *trans*-9,10-*trans*-5-H-5-amino (2b) isomer. A small quantity of *trans*-9,10-*cis*-5-H-5-hydroxy-2-methyldecahydroisoquinoline (2%) was isolated from the deamination of *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline (2b). Dauben did not report any evidence for this type of inversion in the corresponding decalylamines. Hückel,[8] however, demonstrated the production of 13% inverted product from the deamination of the equatorial amino grouping in 4-*t*-butylcyclohexylamine.

The advantages of our above-noted procedure for the synthesis of the decahydroisoquinolinols are twofold, namely, increased over-all yield over previously reported procedures[2-4] and the elimination of time-consuming chromatographic techniques for purification of the various isomers, especially the *trans* isomer.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are corrected. Ir spectra were recorded on a Perkin-Elmer Model 137 B Infracord spectrophotometer and a Perkin-Elmer Model 421 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Varian Aerograph Model 700 Autoprep chromatograph. Nmr spectra were recorded on a Varian A-60 spectrometer. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England.

5-Nitro-2-methylisoquinolinium *p*-Toluenesulfonate.—Methyl *p*-toluenesulfonate (49.5 g) and 5-nitroisoquinoline[9] (46.1 g) were mixed in dimethylformamide (130 ml). After warming to get all the 5-nitroisoquinoline in solution, the mixture was allowed to stand 48 hr. The dimethylformamide was decanted and the crystalline cake was washed with EtAc. A second crop of crystals was obtained when the dimethylformamide decantate was diluted with EtAc. The two combined crops recrystallized from EtAc–EtOH gave 76.6 g, mp 145–146°. An analytical sample melted at 146.5–147.5°.

Anal. Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.65; H, 4.48; N, 7.78; S, 8.90. Found: C, 56.58; H, 4.62; N, 7.92; S, 8.98.

5-Amino-2-methyldecahydroisoquinoline.—5-Nitro-2-methylisoquinolinium *p*-toluenesulfonate (25 g) was dissolved in glacial acetic acid (150 ml), concentrated H_2SO_4 (0.6 ml) was added, and the mixture was hydrogenated over platinum oxide (4 g) at 50 psi. In 25 min the color changed from yellow-brown to colorless, and the rate of hydrogen uptake dropped markedly; during this stage the temperature rose to approximately 60–70°. After 120 hr, the uptake of hydrogen was very slow though only 90–95% of the theoretical amount had been absorbed. After removal, *in vacuo*, of most of the acetic acid, the residue was made alkaline with aqueous base and the free amine extracted with ether. The weight of recovered material after removal of the ether was 95% of the calculated amount based on 5-amino-2-methyldecahydroisoquinoline. Vapor phase chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) showed two 5-amino products, 29% *trans* 9,10-*trans*-5-H- (2b) and 59% *cis*-5,9,10-H (1b) (shown by hydrolysis of acetamides), and two products of shorter retention time, presumably (see Okomato and Kimoto[2]) *trans*- and *cis*-2-methyldecahydroisoquinoline, 4% and 8%, respectively. The 5-amino-2-methyldecahydroisoquinoline isomeric mixture distils at 50–57° (0.2 mm). Exposure of this amine to air causes rapid formation of a solid carbonate.

***cis*-5,9,10-H- and *trans*-9,10-*trans*-5-H-5-Acetamido-2-methyldecahydroisoquinoline.**—Freshly distilled 5-amino-2-methyldecahydroisoquinoline (29.7 g) was dissolved in dried, distilled dimethylformamide (240 ml). To this solution, cooled to 0°, was added acetic anhydride (18.0 g) in benzene (75 ml) during 1.5 hr. The mixture was allowed to warm and stand at room temperature overnight. The benzene and dimethylformamide were removed at reduced pressure by rotary evaporation. The residue was dissolved in water (55 ml), cooled, and made basic (solution A). Scratching and stirring caused the insoluble viscous oil to crystallize. The crystalline product (1) was collected by filtration, washed with cold water, and allowed to dry over $CaCl_2$ in a vacuum desiccator (weight 16.0 g), mp 163–165°. When 1 was recrystallized from EtOH (30 ml) and H_2O (60 ml), and dried, 12.3 g of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (1c) was obtained, mp 168–169°. An analytical sample melted at 169–170°.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.69; H, 10.65; N, 13.00.

The basic filtrate (solution A) was extracted with eight 100-ml portions of ether. The ether solution was dried over Na_2SO_4 overnight. A light precipitate was decanted and collected by filtration to yield 1.0 g of II, mp 199.3–200.3°. The filtrate was concentrated to a residue of 9.4 g (II) which was recrystallized from EtAc–benzene several times to yield 1.0 g of product, mp 197.3–198.3°. The basic, aqueous solution A (after ether extraction) was then concentrated to a slightly tacky solid. This solid was extracted four times with EtAc to yield 4.7 g solid when dry. Two recrystallizations from EtAc–benzene afforded 2.5 g, white crystals of analytical *trans*-9,10-*trans*-5-H-5-acetamido-2-methyldecahydroisoquinoline (2c), mp 199.5–200.5°. Further work-up of the various mother liquors provided more 2c.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.48; H, 10.50; N, 13.20.

Hydrolysis of *cis*-5,9,10-H-5-Acetamido-2-methyldecahydroisoquinoline to *cis*-5,9,10-H-5-Amino-2-methyldecahydroisoquinoline.—A solution of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (1c, 8.0 g), and concentrated H_2SO_4 (8 ml) in water (100 ml) was refluxed 20 hr. The acid solution was concentrated *in vacuo* to a small volume and made basic with NaOH pellets. The basic solution was extracted with ether. The ether solution was dried over K_2CO_3 and concentrated to yield 6.14 g of a straw-colored oil. The product was shown to be a single component by gas chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) and corresponded in retention time to the larger peak of the gas chromatogram for the mixture produced by the hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate, *i.e.*, *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline (1b). A dipicrate of the amine melted at 237.8–238.8°.

Anal. Calcd for $C_{22}H_{26}N_8O_{14}$: C, 42.17; H, 4.18; N, 17.89. Found: C, 42.24; H, 4.30; N, 18.11.

Hydrolysis of *trans*-9,10-*trans*-5-H-5-Acetamido-2-methyldecahydroisoquinoline to *trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline.—A solution of *trans*-9,10-*trans*-5-H-5-acetamido-2-methyldecahydroisoquinoline (2c, 8.7 g) and concentrated H_2SO_4 (22 ml) in water (200 ml) was refluxed for 144 hr. The solution was concentrated and made alkaline with NaOH pellets, extracted with ether, dried over K_2CO_3, and concentrated to yield 6.3 g of oily product. A vapor phase chromatogram showed a single component having the same retention time as the smaller peak for the chromatogram of the mixture produced from the

(7) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(8) W. Hückel and K. Heyder, *Chem. Ber.*, **96**, 220 (1963).

(9) The 5-nitroisoquinoline, mp 109.5–110.5° (from EtOH–H_2O), was prepared by the method of Claus and Hoffman [*J. Prakt. Chem.*, **47**, 252 (1893)] as modified by C. Lé Fevre and R. Lé Fevre [*J. Chem. Soc.*, 1475 (1935)]. Material from Aldrich Chemical Co., mp 106–109°, gave similar results.

hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate, *i.e.*, *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline (**2b**). A dipicrate of the amine melted at 261.8–263.8°.

Anal. Calcd for $C_{22}H_{26}N_8O_{14}$: C, 42.17; H, 4.18; N, 17.89. Found: C, 42.23; H, 4.34; N, 17.90.

Deamination with Nitrous Acid[10] of *cis*-5,9,10-H-5-Amino-2-methyldecahydroisoquinoline to *cis*-5,9,10-H-5-Hydroxy-2-methyl decahydroisoquinoline.—To a solution of sodium nitrite (5.0 g) in water (4.0 ml) was added *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline (**1b**, 6.1 g) and acetic acid (8.0 g). The mixture was heated with stirring to 60° and acetic acid (0.87 g) in water (4 ml) was added over a period of 30 min. The mixture was heated with stirring for 13 hr at 55–65°. Then NaOH pellets (5.0 g) were added; the mixture was heated near reflux for 4 hr. More NaOH pellets were added, and the mixture was cooled and extracted with ether in a continuous extractor for 48 hr. The ether solution was dried over K_2CO_3 and concentrated to yield 5.5 g of viscous oil. Vapor phase chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) of the crude oily product prior to distillation showed 2% olefins, 92% *cis*-5,9,10-H-5-hydroxy-2-methyldecahydroisoquinoline (**1a**), and 6% unidentified product. This oil crystallized on standing and was distilled to yield *cis*-5,9,10-H-5-hydroxy-2-methyldecahydroisoquinoline (**1a**, 4.4 g), mp 94–95°. Examination of the ir and nmr spectra of this alcohol showed them to be consistent with the proposed structure. An nmr ($CDCl_3$) peak appeared at 3.75 ppm (half-band width of 15 cps), >CH–OH.

Deamination with Nitrous Acid[10] of *trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline to *trans*-9,10-*trans*-5-H-5-Hydroxy-2-methyldecahydroisoquinoline.—*trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline (**2b**, 6 g) was deaminated in a procedure identical with that described above for the *cis* isomer. A viscous oil (5.8 g) was recovered from the continuous ether extraction and was shown by vapor phase chromatography to contain 87% *trans*-9,10-*trans*-5-H-5-hydroxy-2-methyldecahydroisoquinoline (**2a**), 7% olefins, and 6% unidentified product. Distillation of this material yielded 4.7 g of **2a**, bp 120–124° (0.3 mm). The ir and nmr spectra of this alcohol were consistent with the proposed structure. An nmr ($CDCl_3$) peak appeared at 3.75 ppm (half-band width of 16 cps), >CH–OH.

It was found that seeding of the above oil with a crystal of *trans*-9,10-*cis*-5-H-5-hydroxy-2-methyldecahydroisoquinoline[11] caused crystallization of 90 mg (2%) of this isomer, mp 131–132°. An nmr ($CDCl_3$) peak appeared at 3.8 ppm (half-band width of 6 cps), >CH–OH.

Registry No.—**1b**, 16336-19-9; dipicrate of **1b**, 16336-20-2; **1c**, 16336-21-3; **2b**, 16336-22-4; dipicrate of **2b**, 16336-23-5; **2c**, 16336-24-6.

Acknowledgment.—The authors are indebted to Marion Laboratories, Inc., Kansas City, Mo., for their financial assistance in the support of this project and also to Drs. F. C. Chang and J. G. Beasley for useful discussions during the course of this work and to Mrs. M. Petrie for recording the nmr spectra.

(10) W. Hückel and M. Hanack, *Angew. Chem. Intern. Ed. Engl.*, **6**, 534 (1967).

(11) Prepared from 5-hydroxy-2-methylisoquinolinium *p*-toluenesulfonate and isolated by the chromatographic procedure of Kimoto and Okamoto.[2]

Photoreactions. V. Mechanism of the Photorearrangement of Alkyl-*p*-benzoquinones[1]

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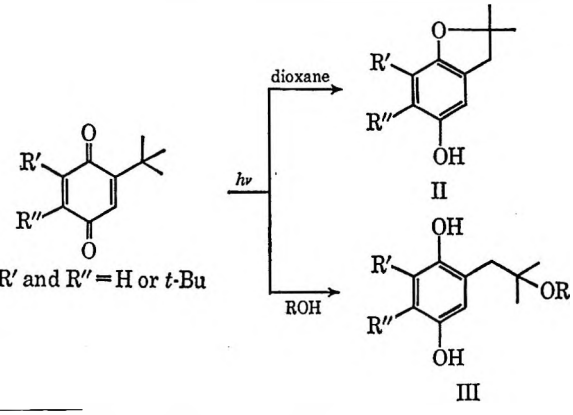
Photolysis of *p*-benzoquinones with various side chains have been studied in alcoholic solution. The identical ether was obtained by the photorearrangement of *t*-butyl- and isobutyl-*p*-benzoquinone. The rearranged side chain was the same from *n*-propyl- and isopropyl-substituted *p*-benzoquinones. Since light of wavelength longer than 400 mμ is capable of initiating the photolysis, it is assumed that the n → π* transition of the quinone system is involved. A spirocyclopropyl intermediate has been postulated to account for the observations on the photorearrangement of the side chain.

Previous investigations[1] in our laboratories have uncovered the photorearrangement of the side chain of mono- and di-*t*-butyl-*p*-benzoquinones (I) in various solvents. In nonalcoholic media, the *t*-butyl group undergoes rearrangement to generate the 2,2-dimethyl-5-hydroxycoumaran system (II), while in alcoholic solvents an analogous rearrangement leads to the formation of the 2-alkoxy-2-methyl-1-propyl side chain (III). We have now examined the effect of the side chain on the course of the photorearrangement and attempted to formulate a mechanism to account for the observations.



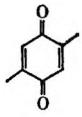
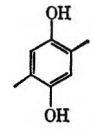
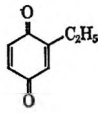
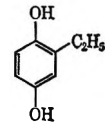
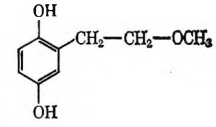
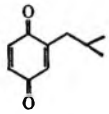
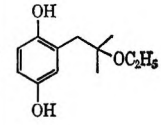
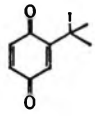
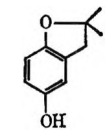
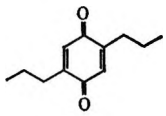
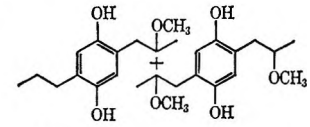
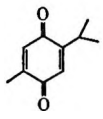
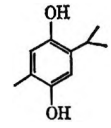
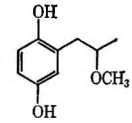
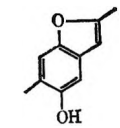
Results

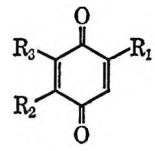
The photolysis of dilute solutions of various alkyl-substituted *p*-benzoquinones (IV) was carried out under a sun lamp. For completeness of sequence, the following side chains were studied: methyl, ethyl, isopropyl, *n*-propyl, and isobutyl. The reaction mixtures were treated with alkaline dimethyl sulfate to convert the phenolic components into methyl ethers which were easily separated by gas chromatography. In general, spectral data (nmr, mass, ir, uv) were ade-

(1) For part IV, see C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Amer. Chem. Soc.*, **89**, 6527 (1967).

(2) (a) Kay-Fries Chemicals, Inc.; (b) General Electric Research and Development Center, Schenectady, N. Y. 12301; (c) Stevens Institute of Technology.

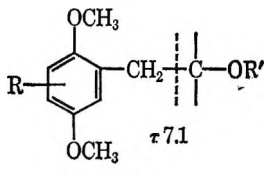
TABLE I

Quinone	Alcohol	Hydroquinone	Ether	Benzofuran derivative
	C_2H_5OH			
	CH_3OH			
	C_2H_5OH			
	C_2H_5OH			
	CH_3OH			
	CH_3OH			

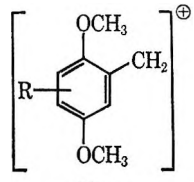


IVa, $R_1 = R_2 = CH_3$; $R_3 = H$
b, $R_1 = C_2H_5$; $R_2 = R_3 = H$
c, $R_1 = i\text{-}C_4H_9$; $R_2 = R_3 = H$
d, $R_1 = t\text{-}C_4H_9$; $R_2 = R_3 = H$
e, $R_1 = R_2 = n\text{-}C_3H_7$; $R_3 = H$
f, $R_1 = i\text{-}C_3H_7$; $R_2 = CH_3$; $R_3 = H$

quate for deducing the structure of the products. Advantage was taken of the earlier observation[1,3] that the benzylic methylene protons in a hydroquinone derivative of type V resonate at about τ 7.1 and the major mode of fragmentation of V under electron impact leads to the ion VI. The phenolic products



V



VI

from the photolysis of substituted quinones are listed in Table I. No information was collected at this stage on the nonphenolic products.

All the photolyses in this and the previous[1] study were carried out in Pyrex vessels using either a 275-W G.E. sun lamp or sunlight. Therefore, in these experiments light of wavelength greater than 295 mμ was responsible for the phototransformations. In one experiment a filter[4] was employed to eliminate wavelengths lower than 400 mμ while irradiating an ethanol solution of 2,6-di-*t*-butyl-*p*-benzoquinone (I, R′ = *t*-Bu; R″ = H). Even under these conditions the usual photorearrangement product III (R′ = *t*-Bu; R″ = H; R = C_2H_5) was obtained.

Discussion

The ultraviolet spectra of benzoquinone and alkyl-*p*-benzoquinones[5] possess four distinct absorption regions: λ_{max}, mμ (ϵ), 540 (0.2), 400–500 (20–30), 300 (320), 250 (20,000). The higher intensity absorptions at 300 and 250 mμ have been ascribed to $\pi \rightarrow \pi^*$ transitions.[5b] Further analyses of the weak absorptions at 400–500 and 540 mμ have established them as $n \rightarrow \pi^*$ transitions.[5a,6] The former transition has been attributed to a $n \rightarrow \pi^*$ singlet[5b,7] and the latter to an $n \rightarrow \pi^*$ triplet.[5-7] The ultraviolet spectra of all the alkyl-*p*-benzoquinones employed in our study displayed the characteristic *p*-benzoquinone absorptions as discussed above (see Experimental Section).

Since photorearrangement was observed using wavelengths longer than 400 mμ, the $n \rightarrow \pi^*$ excitation of the quinone system appears to be involved. We have not established whether the singlet state is formed initially; however, it has been reported[8] that, for quinones, the singlet–triplet intersystem crossing is relatively frequent. If $n \rightarrow \pi^*$ carbonyl excitation is the

(3) C. M. Orlando, Jr., H. Mark, A. K. Bose, and M. S. Manhas, *Chem. Commun.*, 714 (1966).

(4) The filter solution employed was an aqueous sodium hydrogen phthalate–sodium nitrite solution which did not transmit light below 400 mμ. Information describing the preparation of this filter solution was kindly supplied by Professor A. Gilbert of the University of Reading, U. K.

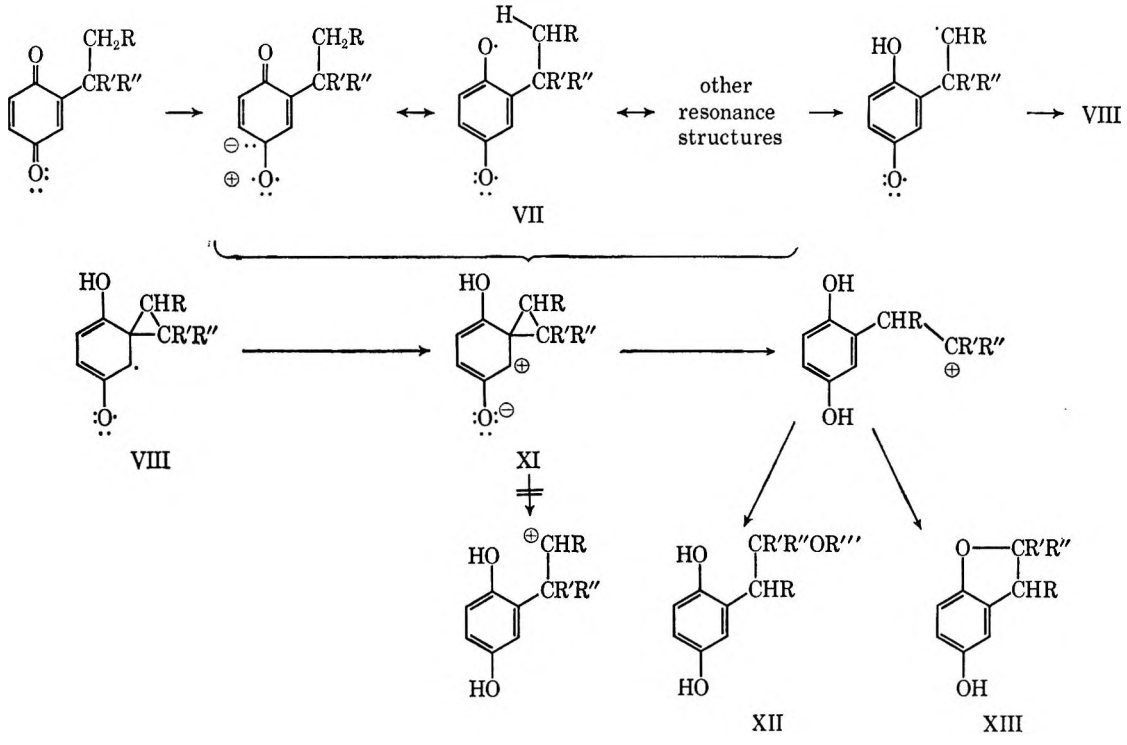
(5) (a) A. Kuboyama, *Bull. Chem. Soc. Jap.*, **35**, 295 (1962); (b) J. W. Sidman, *J. Amer. Chem. Soc.*, **78**, 2363 (1956).

(6) H. McConnell, *J. Chem. Phys.*, **20**, 700 (1952).

(7) J. A. Barltrop and B. Hesp, *J. Chem. Soc.*, 5182 (1965).

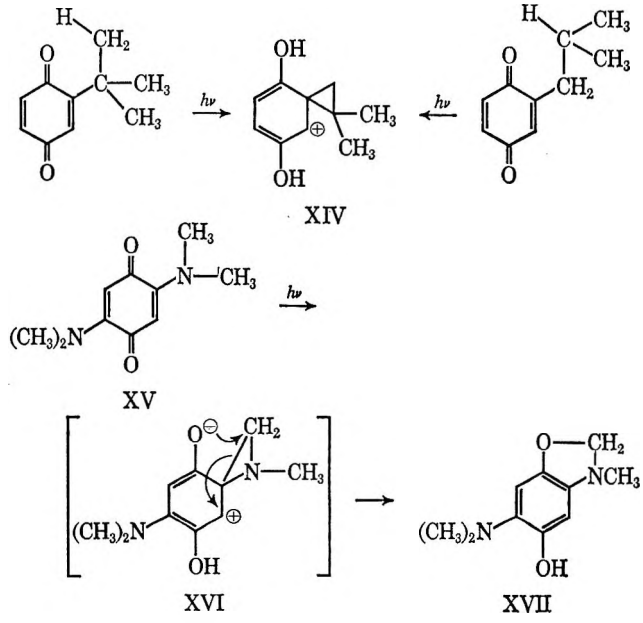
(8) J. W. Sidman, *Chem. Rev.*, **58**, 689 (1958).

CHART I



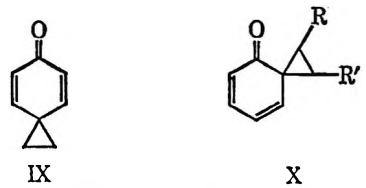
first step in the photolysis of quinones, some of the subsequent steps should be analogous to those postulated by Zimmerman and Schuster[9] for dienone photochemistry. The presence of a suitable 2-alkyl group could easily lead to intramolecular hydrogen abstraction. An examination of Table I reveals that a six-membered transition state appears to be essential for such hydrogen abstraction. For example, in thymoquinone the methyl group is unaffected while the isopropyl group participates in hydrogen abstraction.

The intramolecular hydrogen abstraction leads to the diradical VII and its resonance forms (see Chart I). All the data in Table I can be rationalized by postulating that a spirocyclopropyl intermediate[10] VIII is formed at this stage. Electron demotion would then afford an ionic intermediate XI which would have a strong tendency for aromatization. Interaction of the spirocyclopropyl group with an alcohol would cleave the three-membered ring and bond isomerization will eventually yield a rearranged hydroquinone (XII). Alternatively, one of the cyclopropyl bonds could also be ruptured by intramolecular interaction with the adjacent oxygen and lead to a coumaran (XIII). Of the two alternative modes of cleavage of the spirocyclopropyl group, the one leading to the more substituted ether will be favored because this involves the formation of more stable tertiary carbonium ion as the intermediate. This postulate fully accounts for the same photoproduct from isobutyl-*p*-benzoquinone (IVc) and *t*-butyl-*p*-benzoquinone (I, R′ = R″ = H) as the same cyclopropyl intermediate (XIV) would be involved in both cases. This postulate also explains why there is no rearrangement of the side chain when *n*-propyl-*p*-benzoquinone is photolyzed. The lack of rearrangement[13] of the side chain during the photolysis of XV can be explained by invoking the formation of a spiroaziridine intermediate, XVI, which undergoes selective cleavage ($^{\oplus}CH_2$–N– favored over $CH_3N^{\oplus}$–CH_2–) leading to the formation of XVII.



(9) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, **83**, 4486 (1961), and other papers in this series.

(10) The analogous compound, spiro[2.5]octa-2,5-dien-1-one (IX), has been synthesized.[11] Evidence has been presented[12] for the intermediacy of the isomeric spiro compound X in the abnormal Claisen rearrangement.



(11) R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 567 (1963); **79**, 4238 (1957).

(12) E. N. Marvell and B. Schatz, *Tetrahedron Lett.*, 67 (1967).

(13) D. W. Cameron and R. G. F. Giles, *Chem. Commun.*, 573 (1965).

It is desirable to have more direct evidence for the spirocyclopropyl intermediate postulated above. Work is in progress for gathering further information on this type of photorearrangement.

Experimental Section

Infrared, nmr, and mass spectra were recorded on a Perkin-Elmer Model 21 spectrometer, a Varian A-60A spectrometer and a C.E.C. 21-103 mass spectrometer, respectively. Ultraviolet absorption spectra were determined in methanol using a Cary Model 14 spectrophotometer. Gas chromatographic analyses were carried out on an F & M Model 500 vapor fractometer with a 2-ft silicone rubber column (10% on Chromosorb W). Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Photolyses were carried out in water-cooled Pyrex reactors equipped with magnetic stirring. Sunlight or a G.E. 275-W sun lamp were used as light sources. For nmr signals the following data are reported in sequence: chemical shift of the center of the signal, the multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet) of the signal, the area under the peaks, and coupling constant (J). The ultraviolet absorption data were recorded in methyl alcohol unless otherwise stated and are reported in the form λ_{max}, mμ (ϵ).

Materials.—Thymoquinone [mp 43–45°; λ_{max} 253 (18,687), 260 sh (17,187), 312 (287), 428 (27)] and 2,5-dimethyl p-benzoquinone [mp 124–125°; λ_{max} 253 (15,789), 260 sh (14,474), 313 (244), 425 (24.2)] were obtained from City Chemical Corp., New York, N. Y. Ethyl-p-benzoquinone [mp 34–37°, lit.[14] mp 38.5–39.5°; λ_{max} 246 (13,953), 308 (531), 425 (50.6), 447 (50.9)] and isobutyl-p-benzoquinone [mp 35–36°;[15] λ_{max} 248 (16,235), 313 (692), 425 (65.9), 447 (82.3)] were prepared by silver oxide oxidation of the corresponding ethyl-[16a] and isobutylhydroquinone.[16b]

Preparation of 2,5-Di-n-propyl-p-benzoquinone (IVe).—2,5-Diallyl-p-benzoquinone[17] was catalytically hydrogenated (5% Pd–C) to 2,5-di-n-propylhydroquinone (mp 150–152°). A solution of 2,5-di-n-propylhydroquinone (3.0 g, 0.015 mol) in 100 ml of ether was stirred for 4 hr at 25° with silver oxide (10 g, 0.043 mol). The solid was filtered and the filtrate evaporated to an orange liquid, 2.2 g (76%), which was the title compound: λ_{max} 255 (18,367), 315 (363), 431 (39).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.80; H, 8.3.

Preparation of the Filter Solution.[4]—A saturated solution (250 ml) of sodium nitrite in distilled water was added to a solution of 5 g of sodium hydrogen phthalate in 1 l. of distilled water with uniform stirring. This solution was brought to pH 12 by dilute sodium hydroxide and then used as a filter for all light below 400 mμ.

Photolysis of 2,5-Dimethyl-p-benzoquinone (IVa) in Ethanol.—A solution of 2.0 g (0.015 mol) of 2,5-dimethyl-p-benzoquinone in 200 ml of absolute ethanol was irradiated for 49 hr with a 275-W G.E. sun lamp. Evaporation of the solvent gave a solid which upon crystallization from ethyl acetate–benzene gave 0.56 g (29%) of 2,5-dimethylhydroquinone, mp 212–217°.

Photolysis of Ethyl-p-benzoquinone (IVb) in Methanol.—A solution of 1.6 g of IVb in 160 ml of methanol was irradiated 19 hr at 25° with a 275-W G.E. sun lamp. After solvent evaporation 2.08 g of an oil was isolated. This reaction product was methylated with 3.15 g of dimethyl sulfate in 10 ml of water containing 1 g of sodium hydroxide for 1 hr at 25°. Extraction of this reaction mixture with ether provided 2.32 g of product. Vacuum distillation of this liquid at 140° (0.1 mm) gave 0.683 g of a yellow distillate. Gas chromatographic separation of the distillate on a silicone rubber column at 150° gave two products: (1) **ethylhydroquinone dimethyl ether** [0.549 g (30%); mass spectrum, molecular ion m/e 166 (M, calcd for $C_{10}H_{14}O_2$); uv λ_{max}^{THF} 290 mμ (ϵ 3520); nmr ($CDCl_3$) τ 8.8 (t, 3 H), 7.4 (q, 2 H), 6.27 (s, 3 H), 3.27 (m, 3 H)] and (2) **β-methoxyethylhydroquinone dimethyl ether** [6.134 g (6.2%); mass spectrum, molecular ion m/e 196 (M, calcd for $C_{11}H_{16}O_3$); λ_{max}^{THF} 291 mμ (ϵ 3100); nmr ($CDCl_3$) τ 7.12 (t, 2 H), 6.67 (s, 3 H), 6.41 (t, 2 H), 6.25 (s, 3 H), 3.25 (s, 3 H)].

Photolysis of Isobutyl-p-benzoquinone (IVc) in Ethanol.—A solution of 1.0 g of isobutyl-p-benzoquinone in 100 ml of absolute ethanol was irradiated with a 275-W G.E. sun lamp for 25 hr. The solvent was evaporated to 1.14 g of dark brown oil. Trituration of this oil with hexane gave 0.293 g (23%) of 2-ethoxy-2-methyl-n-propylhydroquinone, mp 142–145°, identical with the product isolated from the irradiation of t-butyl-p-benzoquinone in ethanol.

Photolysis of 2,5-Di-n-propyl-p-benzoquinone (IVe) in Methanol.—A solution of 1 g of 2,5-di-n-propyl-p-benzoquinone in 100 ml of methanol was irradiated with a G.E. sunlamp for 75 hr. Evaporation of the solvent gave 1 g of an oil. Methylation of this oil with 1.26 g of dimethyl sulfate and 0.5 g of sodium hydroxide in 10 ml of water gave 0.226 g of distilled product. Gas chromatographic separation of this reaction product on a 2-ft silicone rubber column (10% on Chromosorb W) at 160° gave three products: (1) **dimethyl-2-(2-methoxy-1-propyl)-5-n-propylhydroquinone** [0.105 g (8.0%); nmr ($CDCl_3$) τ 8.75 (m), 8.20 (m), 7.20 (m), 6.55 (s), 6.05 (s), 3.15 (broad s)], (2) **dimethylbis-2,5-(2-methoxy-1-propyl)hydroquinone** [0.045 g (3.0%); nmr ($CDCl_3$) τ 8.88 (d, 6 H), 7.30 (m, 4 H), 6.50 (s, 6 H), 5.50 (m, 2 H), 6.22 (s, 6 H), 3.35 (s, 2 H)], and (3) **methyl-2-(2-methoxy-1-propyl)-5-n-propylhydroquinone** [0.045 g (3.6%); nmr ($CDCl_3$) τ 9.00 (m), 7.4 (m), 6.65 (s), 6.25 (s), 3.55 (s), 3.32 (s), 2.15 (s)].

Photolysis of Thymoquinone (IVf) in Methanol. A. Gas Chromatographic Product Isolation.—A solution of 11.5 g of thymoquinone in 1150 ml of anhydrous methanol was irradiated in sunlight for 12 days.[18] Evaporation of the solvent provided 14.7 g of a crude oil. A suspension of 14.7 g of this oil in 100 ml of water containing 23.2 g of dimethyl sulfate and 7.4 g of sodium hydroxide was stirred at room temperature for 24 hr. The reaction mixture was extracted with 150 ml of ethyl acetate, and the extract was dried over anhydrous magnesium sulfate after washing with water to neutrality. Removal of the solvent and vacuum distillation of the product afforded 7.4 g of distillate. Gas chromatographic separation of this distillate on a 2-ft silicone rubber column at 150° gave four components: (1) **dimethyl-2-(2-methoxy-1-propyl)-5-methylhydroquinone** [3.83 g (20%); mass spectrum, molecular ion m/e 224 (M, calcd for $C_{13}H_{20}O_3$), base peak, m/e 165 [M − $CH(OCH_3)CH_3$]$^{\oplus}$; nmr ($CDCl_3$) τ 8.91 (d, 3 H), 7.88 (s, 3 H), 7.38 (m, 2 H), 6.78 (s, 3 H), 6.52 (m, 1 H), 6.35 (s, 6 H), 3.55 (s, 2 H)], (2) **methyl-2-(2-methoxy-1-propyl)-5-methylhydroquinone** [0.154 g (10%); mass spectrum, molecular ion m/e 209 (M, calcd for $C_{12}H_{18}O_3$); nmr pattern similar to that for other derivatives in this series], (3) **2,6-dimethyl-5-methoxybenzofuran** [1.58 g (13%); mass spectrum, molecular ion m/e 176 (M, calcd for $C_{11}H_{12}O_2$); nmr[19] ($CDCl_3$) τ 7.70 (s, 3 H), 7.55 (s, 3 H), 6.18 (s, 3 H), 3.75 (s, 1 H), 2.85, s.14 (d, 2 H)], and (4) **dimethylthymohydroquinone** [2.01 g (15%), identical with an authentic sample].

B. Column Chromatographic Product Isolation.—A solution of 4.0 g of thymoquinone in 400 ml of methanol was irradiated for 53 hr with a 275-W G.E. sun lamp. Evaporation of the solvent gave an oil (5.5 g) which upon chromatography on 150 g of silica gel (100–200 mesh) gave three products (eluted with 1:1 carbon tetrachloride–chloroform): (1) **2-(2-methoxy-1-propyl)-5-methylhydroquinone** [0.36 g (7.8%); mp 97.9–98.3° (hexane–benzene); λ_{max} 294 mμ (ϵ 4500); nmr (CD_3COCD_3) τ 8.90 (d, 3 H), 7.85 (s, 3 H), 7.35 (m, 2 H), 6.67 (s, 3 H), 6.35 (m, 1 H), 3.67 (s, 2 H) (*Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.34; H, 8.16. Found: C, 67.38; H, 8.02)], (2) **2,6-dimethyl-5-hydroxybenzofuran** [0.091 g (2.1%); mp 98–99.6° (hexane); λ_{max}^{THF} 250 mμ (ϵ 10,634), 257 sh (8730), 297 (5238), 305 (4603); nmr (CD_3COCD_3) τ 7.75 (s, 3 H), 7.65 (s, 3 H), 3.75 (s, 1 H), 3.15 (s, 1 H), 2.90 (s, 1 H), 2.2 (s, 1 H) (*Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.02; H, 6.17. Found: C, 74.20; H, 5.80)], and (3) **thymohydroquinone** [0.096 g (2.4%); mp 141–144° (hexane–benzene); lit.[20] mp 142–142.5°; λ_{max} 293 mμ (ϵ 4357)].

Photolysis of 2,6-Di-t-butyl-p-benzoquinone in Ethanol Using

(14) R. K. Ladisch, *Chem. Abstr.*, **52**, 20061*d* (1958); U. S. Patent 2,840,571.

(15) M. F. Hawthorne and M. Reintjes, *J. Amer. Chem. Soc.*, **86**, 951 (1964).

(16) (a) Prepared according to the method described by T. B. Johnson and W. W. Hodge, *ibid.*, **35**, 1014 (1913); (b) Prepared by the catalytic reduction of β-methallylhydroquinone.

(17) L. F. Fieser, W. P. Campbell, and E. M. Fry, *ibid.*, **61**, 2206 (1939).

(18) Comparable results were obtained when a 1% solution of thymoquinone in methanol was irradiated with a 275-W G.E. sun lamp for 53 hr.

(19) For the chemical shifts of protons in the furan ring system, see A. R. Katritzky, "Physical Method of Heterocyclic Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, p 124.

(20) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20**, 82 (1955).

Sodium Nitrite–Sodium Hydrogen Phthalate Filter Solution.—A solution of 1 g of 2,6-di-*t*-butyl-*p*-benzoquinone in 100 ml of ethanol was irradiated through a sodium nitrite–sodium hydrogen phthalate filter solution (λ >400 mμ) for 48 hr with a 275-W G.E. sun lamp. Evaporation of the solvent gave an orange oil which when triturated with hexane afforded a solid. This solid upon recrystallization from benzene–hexane gave 2-(2-ethoxy-2-methyl-1-propyl)-6-*t*-butylhydroquinone,[1] 0.277 g (23%), mp 125–127°.

Registry No.—IVa, 137-18-8; IVb, 4754-26-1; ethylhydroquinone dimethyl ether, 1199-08-2; β-methoxyhydroquinone dimethyl ether, 16162-59-7; IVc, 4197-79-9; IVe, 16162-61-1; dimethyl-2-(2-methoxy-1-propyl)-5-*n*-propylhydroquinone, 16162-62-2; dimethylbis-2,5-(2-methoxy-1-propylhydroquinone, 16203-63-7; IVf, 490-91-5; dimethyl-2-(2-methoxy-1-propyl)-5-methylhydroquinone, 14753-10-7; 2,6-dimethyl-5-methoxybenzofuran, 14753-09-4; 2-(2-methoxy-1-propyl)5-methylhydroquinone, 16162-65-5; 2,6-dimethyl-5-hydroxybenzofuran, 16162-66-6; 2,6-di-*t*-butyl-*p*-benzoquinone, 719-22-2.

Notes

The Cuprous Chloride–Amine Catalyzed Oxidation of 2,6-Di-*t*-butyl-*p*-cresol with Oxygen

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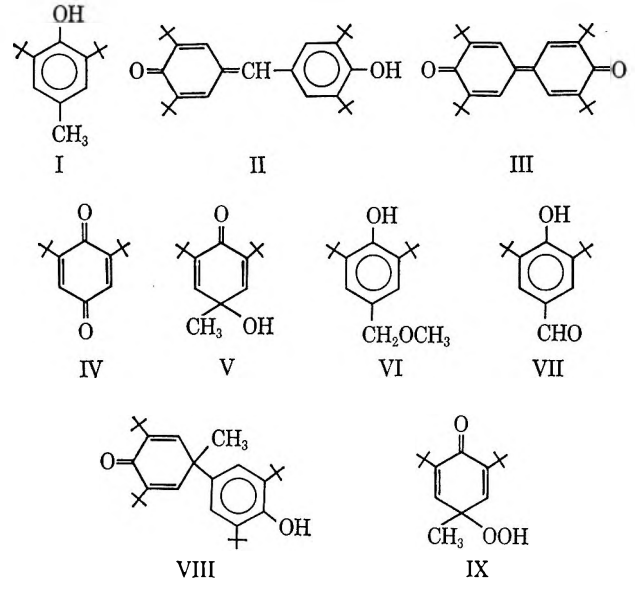
General Electric Research and Development Center, Schenectady, New York

Received February 2, 1968

Recently, the air oxidation of 2,6-di-*t*-butyl-*p*-cresol (I) in alkaline ethanol was reported to give the demethylated dimers 2,6-di-*t*-butyl-4-(4-hydroxy-3,5-di-*t*-butylbenzylidene)-2,5-cyclohexadien-1-one (II) and 3,5,3′,5′-tetra-*t*-butyldiphenoquinone (III) (Chart I).[1] We now describe the formation of III and a different demethylated dimer, 2,6-di-*t*-butyl-4-methyl-4-(3,5-di-*t*-butyl-4-hydroxyphenyl)-2,5-cyclohexadien-1-one (VIII), among six identifiable products in the cuprous chloride–amine catalyzed reaction of I with oxygen.[2a] Based upon the earlier work of Kharasch and Joshi[2b] and the data obtained in the present investigation, a reasonable mechanism has been proposed to account for the over-all oxidation reaction.

The oxygenation of I in methanol solution using a cuprous chloride–amine catalyst gave six identifiable products which constituted 73% (weight) of the total reaction mixture. These products were (1) 3,5,3′,5′-tetra-*t*-butyldiphenoquinone (III, 5%); (2) 2,6-di-*t*-butyl-*p*-benzoquinone (IV, 27%); (3) 2,6-di-*t*-butyl-4-methyl-4-hydroxy-2,5-cyclohexadien-1-one (V, 14%); (4) 3,5-di-*t*-butyl-4-hydroxybenzylmethyl ether (VI, 14%); (5) 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (VII, 12%); (6) 2,6-di-*t*-butyl-4-methyl-4-(3,5-di-*t*-butyl-4-hydroxyphenyl)-2,5-cyclohexadien-1-one (VIII, 2%) (see Chart I). All of these compounds have been previously described as low-yield oxidation products of I under varied conditions.[1,3] The hydroperoxide IX which was isolated in the reaction of I with oxygen in ethanolic potassium hydroxide was observed to decompose to V (45%) and an unknown compound, mp 159–160° (20%).[2] This latter compound was identical with the product VIII (mp 154–156°) isolated from the oxygenation described herein, based upon the identity of the infrared, ultraviolet, and nmr spectra.

CHART I



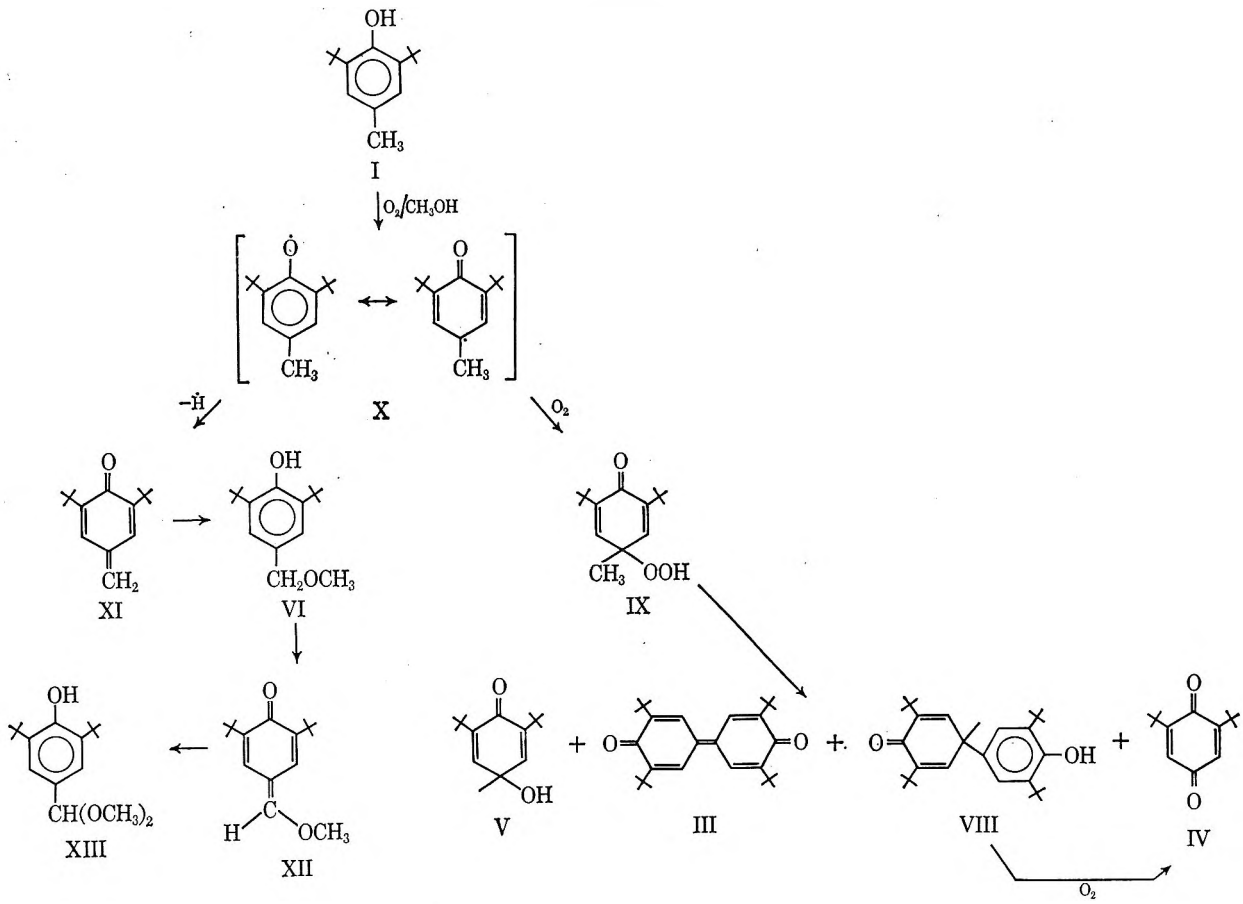
Conclusive evidence for the structural assignment VIII to the compound, mp 154–156°, was provided by several spectroscopic methods. The dimeric structure of VIII was evident on the basis of molecular weight determination [Calcd for $C_{29}H_{44}O_2$: mol wt, 424. Found: mol wt, 424 (mass spectrometry)]. The infrared spectrum possessed both a nonbonded hydroxyl absorption at 3640 cm^{-1} and a cross-conjugated dienone absorption at 1660 and 1640 cm^{-1}. The ultraviolet spectrum had absorption maxima at 237 mμ (ϵ 21,188) and 274 (2510) and is consistent

(1) C. H. Brieskorn and K. Ullmann, *Chem. Ber.*, **100**, 618 (1967).

(2) (a) For a recent review of the cuprous chloride–amine–oxygen system in phenol oxidation see, A. S. Hay, *Adv. Polymer Sci.*, **4**, 496 (1967); (b) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).

(3) (a) L. V. Gorbunova, N. S. Vasileiskaya, M. L. Khidekel, and B. A. Razuvaev, *J. Org. Chem. USSR*, **2**, No. 7, 1227 (1967); (b) J. I. Wasson and W. M. Smith, *Ind. Eng. Chem.*, **45**, 197 (1953); (c) S. J. Metro, *J. Amer. Chem. Soc.*, **77**, 2901 (1955); (d) E. Muller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Ber.*, **92**, 2278 (1959); (e) J. Sugita, *Nippon Kagaku Zasshi*, **87**, 1082 (1966) [*Chem. Abstr.*, **66**, 9477*w* (1967)].

CHART II



with a 4,4-arylalkylcyclohexadienone structure.[4] The evidence thus far indicates the compound to be a dimeric phenol-substituted cyclohexadienone. More conclusive data which indicated VIII to be the correct structure was obtained from nmr analysis[3e] ($CDCl_3$, τ): 8.77 (18 H, *t*-Bu quinoid ring), 8.60 (18 H, *t*-Bu aromatic ring), 8.41 (3 H, CH_3), 4.88 (1 H, -OH), 3.45 (2 H, quinoid ring H), and 2.95 (2 H, aromatic H).

The mechanism of the reactions of oxygen and hydroperoxides with I have been examined by several groups.[2,5,6] The products formed in these reactions have been explained on the basis of the intermediacy of corresponding resonance stabilized phenoxycyclohexadienone radical (X)[2,6,7] of I. The phenoxy radical of I has been demonstrated to decay to I and the corresponding quinone methide XI and the latter in turn formed the 1,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane and 3,3′,5,5′-tetra-*t*-butyl-4-4′-stilbenequinone.[7]

Formation of the products that we have obtained can be explained *via* the intermediacy of both the quinone methide XI and the cyclohexadienone radical (X) (see Chart II). The initially formed phenoxy radical could produce the quinone methide XI which in methanolic solution would lead to the benzyl methyl ether (VI) by a rapid 1,6 addition. Further oxidation of VI to the methoxyquinone methide XII and methanol addition to the latter would give the acetal (XIII).[8] The conditions under which the reaction was quenched would hydrolytically convert the acetal into the aldehyde VII. The absence of the stilbenequinone-type dimer in this reaction does not preclude the intermediacy of the quinone methide XI since the latter has been observed to undergo 1,6-type additions more rapidly than dimerization.[9]

The initially formed phenoxy radical can also react as the cyclohexadienone radical leading to the formation of the hydroperoxide IX. This hydroperoxide has been established as the source of the other products isolated. When IX was oxygenated under the same conditions as I, the following products were observed: (1) III, 5%; (2), IV, 2%; (3) V, 58%; (4) VIII, 2%. While a small yield of the *p*-benzoquinone IV was obtained from the oxygenation of the hydroperoxide, we have found that the quinone was also formed from the dimer VIII upon oxygenation with the cuprous chloride–amine system (22%). There was no evidence for the formation of the diphenoquinone III in the latter reaction. The oxygenation of V under the standard conditions resulted in a quantitative recovery of starting material. The demethylation of I to produce the dimers III and VIII presumably occurred *via* the loss of formaldehyde as has been observed previously in this system.[1]

Experimental Section

Melting points were taken on a Mel-Temp apparatus and were uncorrected. Infrared, ultraviolet, nmr, and mass spectra were

(4) N. P. Neureiter, *J. Org. Chem.*, **28**, 3486 (1963).
(5) C. D. Cook, *ibid.*, **18**, 261 (1953).
(6) T. W. Campbell and G. M. Coppinger, *J. Amer. Chem. Soc.*, **74**, 1469 (1952).
(7) R. H. Bauer and G. M. Coppinger, *Tetrahedron Lett.*, **19**, 1201 (1963).
(8) Recent investigations in this laboratory have established the oxidative methoxylation of I under a variety of conditions to involve quinone methide intermediates. See also H. D. Becker, *J. Org. Chem.*, **30**, 982 (1965).
(9) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).

recorded on a Perkin-Elmer Model 337 spectrophotometer, a Cary Model 14 spectrophotometer, a Varian Model A-60 spectrometer, and a GE Monopole mass spectrometer (mass range 600), respectively. Gas chromatographic analyses were carried out on an F & M Model 700 vapor fractometer with a 4-ft 10% Apiezon L on Chromosorb W column.

Oxidation of 2,6-Di-*t*-butyl-*p*-cresol (I) in Methanol with Cuprous Chloride–Amine Catalyst. A. Conditions for the Isolation of III, IV, VII, and VIII.—A suspension of 0.544 g (0.0055 mol) of cuprous chloride and 6 g of anhydrous magnesium sulfate in a solution of 0.646 g (0.0055 mol) of tetramethylethylenediamine (TMEDA) and 0.59 g (0.01 mol, 7.5 ml of a solution of trimethylamine in toluene −0.078 g/ml) of trimethylamine in 125 ml of anhydrous methanol was prepared. A stream of oxygen (flow rate, 1 ft³/hr) was bubbled through the stirred suspension for 10 min. While oxygen was continuously bubbled through the blue suspension, a solution of 22 g (0.1 mol) of I in 125 ml of methanol was then added to this mixture over a 0.5-hr period. The temperature of the reaction mixture was kept at 25° with cold-water bath. The reaction was continued for an additional 3.83 hr. The yellow-green reaction mixture was filtered and the filtrate evaporated to an oil. The oil was extracted with 200 ml of hot hexane and the hexane extract decanted from the residue. The volume of the extract was reduced to 50 ml and refrigeration of the resulting solution at 0° for 12 hr provided 0.66 g (3%) of VIII: mp 154–156°; $\lambda_{max}^{CCl_4}$ (cm^{-1}), 3640, 1660, and 1640; $\lambda_{max}^{C_2H_5OH}$ ($m\mu$) 237 (ϵ 21,188), 274 (2150); nmr, τ (CCl_4) 8.77 (18 H), 8.60 (18 H), 8.41 (3 H), 4.88 (1 H, exchanged in D_2O), 3.45 (2 H), and 2.95 (2 H); mass spectrum, *m/e* 424 $(M)^+$.

A second crop of crystals was obtained upon cooling the filtrate, 0.012 g (0.05%) of III, mp 246° (lit.[2b] mp 246°). The infrared spectrum of this product was identical with that of authentic 3,5,3′,5′-tetra-*t*-butyl-4,4′-diphenoquinone.

Preparative thin layer chromatography of the filtrate from III on 1-mm thickness silica gel (Stahl GF 254) 8 × 8 in. plates using benzene–carbon tetrachloride (1.7:1) as solvent provided two isolable crystalline fractions: (1) 2,6-di-*t*-butyl-*p*-benzoquinone (IV), mp 55–58° (lit.[2b] mp 67°), and (2) 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (VII), mp 180–183° (lit.[2b] mp 187°). The infrared spectra of both of these products were identical with those of authentic samples.

B. Conditions for Quantitative Analysis of Products.—A suspension of 0.544 g (0.0054 mol) of cuprous chloride and 6 g of magnesium sulfate in 125 ml of methanol containing 0.646 g (0.0055 mol) of TMEDA and 0.59 g (0.01 mol) of trimethylamine (7.5 ml of a solution of trimethylamine in toluene, 0.078 g/ml) was stirred at 25° while a stream of oxygen was bubbled through the mixture (flow rate, 1 ft³/hr) for 10 min. A solution of 22 g (0.1 mol) of I in 125 ml of methanol was then added dropwise during a 0.5-hr period to the blue reaction mixture maintaining the same oxygen flow rate. After the addition was complete, the mixture was oxygenated for an additional 3.83 hr. During the reaction, the temperature rose to 45° and gradually returned to 25°. The yellow-green reaction mixture was filtered and evaporated to a dark oil. This oil was dissolved in 250 ml of ethyl acetate and this solution was washed with 150 ml of cold 3% aqueous hydrochloric acid. The ethyl acetate layer was washed with water several times until the washings were neutral. The organic layer was dried ($MgSO_4$), filtered, and evaporated to a liquid which contained some solid. Filtration of the mixture gave 1.79 g of a solid, mp 180–183°, which was identical with 3,5-di-*t*-butyl-4-hydroxybenzaldehyde. The filtrate (21.2 g) was then analyzed by gas chromatography. This analysis provided the following percentage composition of this mixture: (1) III (5%); (2) IV (27%); (3) V (14%); (4) VI (14%); (5) VII (12%);[10] and (6) VIII (2%).

Oxidation of VIII in Methanol with Cuprous Chloride–Amine Catalyst.—A mixture of 0.490 g (0.0011 mol) of VIII, 0.0059 g (5.9×10^{-5} mol) of cuprous chloride, 0.0071 g (6×10^{-5} mol) of TMEDA, 0.0065 g (1.1×10^{-4} mol) of trimethylamine, and 0.066 g of magnesium sulfate in 12 ml of methanol was oxygenated for 4.5 hr and worked up as previously described for I (part B). Gas chromatographic analysis of the reaction product (0.383 g) showed the following components: (1) VIII, 0.333 g (67% recovered); (2) 2,6-di-*t*-butyl-*p*-benzoquinone, (IV, 22%);[11] (3) 2,6-di-*t*-butyl-4-methyl-4-hydroxy-2,5-cyclohexadien-1-one (V, 0.9%).[11]

(10) This per cent yield includes the 1.79 g of VII which was isolated.

(11) Yield based upon the number of moles of VIII which reacted (3.7×10^{-4}).

Oxidation of IX[12] in Methanol with Cuprous Chloride–Amine Catalyst.—A mixture of 1.0 g (0.004 mol) of IX, 0.022 g (2.2×10^{-4} mol) of cuprous chloride, 0.24 g of magnesium sulfate, 0.025 g (2.2×10^{-4} mol) of TMEDA, and 0.0236 g (4×10^{-4} mol) of trimethylamine was oxygenated for 4.5 hr and worked up as previously described. Gas chromatographic analysis of the reaction product (0.743 g) indicated the following components: (1) III, 5%; (2) IV, 2%; (3) V, 58%; (4) VIII, 2%.

Oxidation of V in Methanol with Cuprous Chloride–Amine Catalyst.—A mixture of 2.0 g (0.0084 mol) of V, 0.045 g (4.5×10^{-4} mol) of cuprous chloride, 0.054 g (4.6×10^{-4} mol) of TMEDA, and 0.049 g (8×10^{-4} mol) of trimethylamine in 21 ml of methanol was oxygenated for 4.5 hr and worked up as previously described. A quantitative recovery of V was obtained.

Registry No.—I, 128-37-0; VIII, 14387-13-4; oxygen, 7782-44-7.

(12) Prepared according to the method described in ref 2.

The Photolysis of Perfluoro-2,3-diazabuta-1,3-diene and Perfluoroacyl Fluorides

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The generation of the difluoromethylenimino radical from the photolysis of perfluoro-2,3-diazabuta-1,3-diene has been reported recently.[1] The apparent stability of this radical and the ease with which it adds to fluoro olefins[2] suggested that the photolysis of perfluoro-2,3-diazabuta-1,3-diene in the presence of photolytic sources of fluoroalkyl radicals would be a convenient route to the synthesis of azomethines. Heretofore, the only method of preparing these compounds was from the pyrolysis of oxazetidines[3] since it has recently been shown that the pyrolysis of tertiary perfluoroamines produces isomers of azomethines.[4,5]

Although several photolytic sources of fluoroalkyl radicals are available it was decided to use perfluoroacyl fluorides in this study. These materials were readily available and have been shown to produce both fluoroalkyl and fluoroformyl radicals upon photolysis.[6] Few reactions of the fluoroformyl radical have been described previously although the formation of difluoramino carbonyl fluoride, $NF_2C(O)F$, from the photolysis of tetrafluorohydrazine and carbon monoxide, is thought to involve a combination of difluoramino and fluoroformyl radicals.[7]

Results and Discussion

The photolysis of monofunctional perfluoroacyl fluorides in the presence of perfluoro-2,3-diazabuta-1,3-

(1) R. A. Mitsch and P. H. Ogden, *Chem. Commun.*, 59 (1967).

(2) P. H. Ogden and R. A. Mitsch, *J. Amer. Chem. Soc.*, **89**, 3868 (1967).

(3) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 1881 (1955); 3461 (1955). D. A. Barr, R. N. Haszeldine, and C. J. Willis, *ibid.*, 1351 (1961).

(4) W. H. Pearlson and L. J. Hals, U. S. Patent 2,643,267.

(5) R. E. Banks, M. G. Barlow, R. N. Haszeldine, and M. K. McCreath, *J. Chem. Soc.*, 7203 (1965).

(6) J. F. Harris, *J. Org. Chem.*, **30**, 2182 (1965).

(7) G. W. Fraser and J. M. Shreeve, *Inorg. Chem.*, **4**, 1497 (1965).

diene produces trifluoromethyl isocyanate and the predicted azomethine together with carbonyl fluoride and some noncondensable material. The noncondensable, which was not characterized, is presumably carbon monoxide and/or nitrogen, since these are known products from the photolytic decomposition of the above compounds.[1,6]

The products obtained may be rationalized using the reaction scheme in eq 1–5.

$$CF_2{=}NN{=}CF_2 \xrightarrow{h\nu} 2CF_2{=}N\cdot \quad (1)$$

$$R_FC(O)F \xrightarrow{h\nu} R_F\cdot + FC(O)\cdot \quad (2)$$

$$R_F\cdot + CF_2{=}N\cdot \longrightarrow R_FN{=}CF_2 \quad (3)$$

$$CF_2{=}N\cdot + FC(O)\cdot \longrightarrow CF_2{=}NC(O)F \quad (4)$$

$$CF_2{=}NC(O)F \longrightarrow CF_3N{=}C{=}O \quad (5)$$

That N-difluoromethylene carbamyl fluoride, $CF_2{=}NC(O)F$, should rearrange is not surprising since such compounds have been postulated as intermediates which isomerize in the presence of fluoride ion. Fawcett and his coworkers[8] suggest that the formation of pentafluoroethyl isocyanate from the addition of carbonyl fluoride to trifluoroacetonitrile involves such a rearrangement (eq 6).

$$COF_2 + CF_3C{\equiv}N \longrightarrow [CF_3CF{=}NC(O)F] \longrightarrow CF_3CF_2N{=}C{=}O \quad (6)$$

In addition, Banks and his coworkers[5] suggest that isomerization of this type of intermediate is responsible for the formation of pentafluoropropionitrile and carbonyl fluoride from heptafluoro-*n*-propyl isocyanate during the pyrolysis of trisheptafluoro-*n*-propylhydroxylamine (eq 7).

$$C_2F_5CF_2N{=}C{=}O \longrightarrow [C_2F_5CF{=}NC(O)F] \longrightarrow C_2F_5C{\equiv}N + COF_2 \quad (7)$$

The mechanism of isomerization (eq 5) has not been investigated but it is probably initiated by nucleophilic attack at the terminal azomethine group by fluoride ion (eq 8), trace quantities of which could be generated by

$$F^- \curvearrowright CF_2{=}N{-}C(O){-}F \xrightarrow{-F^-} CF_3N{=}C{=}O \quad (8)$$

the presence of adventitious moisture on the glass. That the carbamyl fluoride should isomerize under conditions which do not cause the azomethine to isomerize also is not surprising since the nature of the groups adjacent to the azomethine moiety affects the ease with which isomerization of the C=N bond occurs, as will be shown later.

Yields of azomethine and trifluoromethyl isocyanate after purification by gas–liquid partition chromatography are summarized in Table I.

The data contained in Table I indicates that the photolysis of perfluoro-2,3-diazabuta-1,3-diene in the presence of a photolytic source of fluoroalkyl radicals is a potentially useful route to azomethines. The detrimental affect on the yield of azomethine caused by the formation of isocyanate could be avoided by using an alternative source of fluoroalkyl radicals, *i.e.*, azo compounds, etc.

(8) F. S. Fawcett, C. W. Tullock, and D. D. Coffman, *J. Amer. Chem. Soc.*, **84**, 4275 (1962).

TABLE I

YIELD OF PRODUCTS FROM THE PHOTOLYSIS OF $CF_2{=}NN{=}CF_2$ WITH VARIOUS PERFLUOROACYL FLUORIDES

Acyl fluoride	Ratio of acyl fluoride to azine	Product	% yield	T_r[a]
$C_3F_7C(O)F$	5:1	$CF_3N{=}C{=}O$	36	
		$C_3F_7N{=}CF_2$	24	46
$(CF_3)_2CFC(O)F$	5:1	$CF_3N{=}C{=}O$	20	
		$(CF_3)_2CFN{=}CF_2$	35	40
$C_4F_9C(O)F$	3:1	$CF_3N{=}C{=}O$	25	
		$C_4F_9N{=}CF_2$	25	145

[a] T_r = relative retention time = $(T_{compd} - T_{air})/(T_{CFCl_3} - T_{air}) \times 100$.

Isomerization of Azomethines.—Perfluoro-2-azapentene-1 has been shown to isomerize at 250° in the presence of anhydrous potassium fluoride producing perfluoro-2-azapentene-2 in 55% yield.[5] In the presence of cesium fluoride, both perfluoro-2-azapentene-1 ($C_3F_7N{=}CF_2$) and perfluoro-2-azahexene-1 ($C_4F_9N{=}CF_2$) isomerize quantitatively at room temperature; however, the isomeric azomethine, perfluoro-3-methyl-2-azabutene-1 [$(CF_3)_2CFN{=}CF_2$] did not, even when heated to 200°. This observation is in agreement with the relative rates with which the $CF_2{=}N$ moiety isomerizes in perfluoro α,ω-bisazomethines.[9]

Spectral Properties.—The spectral properties of the materials described above are summarized in Table II.

TABLE II

SPECTRAL DATA

Compd	Registry no.	Infrared, μ (>C=N—)	F^{19} nmr ϕ*[a]	F^{19} nmr Group
$(CF_3)_2CFN{=}CF_2$	16200-40-1	5.51	33.7	$CF_2{=}N$[b]
			42.7	
			80.7	CF_3[c]
			155.5	CF[d]
2 1 $CF_3CF_2CF_2N{=}CF_2$	378-00-7	5.55[e]	28.9	$CF_2{=}N$[f]
			44.7	
			93.7	$CF_2(1)$[d]
			129.7	$CF_2(2)$[d]
			81.5	CF_3[g]
3 2 1 $CF_3CF_2CF_2CF_2N{=}CF_2$	424-32-8	5.56	28.4	$CF_2{=}N$[h]
			44.5	
			92.7	$CF_2(1)$[d]
			ca. 126.2	$CF_2(2)$[d]
			ca. 126.4	$CF_2(3)$[d]
			81.8	CF_3[i]
$CF_3CF_2CF{=}NCF_3$	680-23-9	5.61	2.64	CF[d]
			57.7	CF_3N[j]
			121.4	CF_2[k]
			83.5	CF_3C[l]
2 1 $CF_3CF_2CF_2CF{=}NCF_3$	559-93-3	5.63[m]	23.0	CF[d]
			57.8	$CF_3{-}N$[n]
			119.0	$CF_2(1)$[n]
			127.0	$CF_2(2)$[n]
			81.7	$CF_3{-}C$[n]

[a] G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959). [b] Broad AB. [c] Doublet (J = 4.1 cps) of triplets (J = 1.5 cps). [d] Complex. [e] Lit.[3a] 5.51. [f] AB pattern (J = 80 cps). [g] Triplet (J = 8.9 cps). [h] AB pattern (J = 86 cps). [i] Triplet (J = 9.0 cps) of triplets (J = 1.8 cps). [j] Doublet (J = 13.4 cps). [k] Doublet (J = 13.3 cps). [l] Doublet (J = 5.0 cps). [m] R. E. Banks, W. M. Cheng, and R. N. Haszeldine [*J. Chem. Soc.*, 3407 (1962)] report 5.63. [n] For J values see ref *m*.

All of the azomethines show a characteristic infrared absorption at about 5.5 μ corresponding to the C=N bond. Isomerization to the internal azaalkene causes a small shift to longer wavelength; however, the shift is

(9) P. H. Ogden and R. A. Mitsch, *ibid.*, **87**, 5007 (1967).

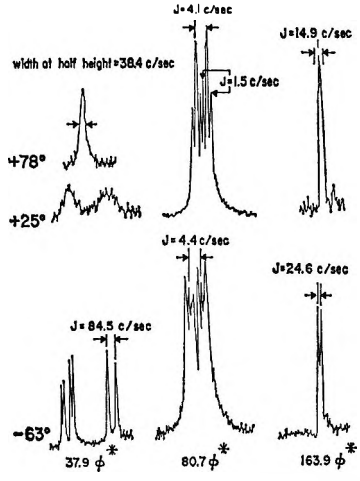

Figure 1.—F^{19} nmr spectrum of $(CF_3)_2CFN{=}CF_2$ at +78, +25, and −63°.

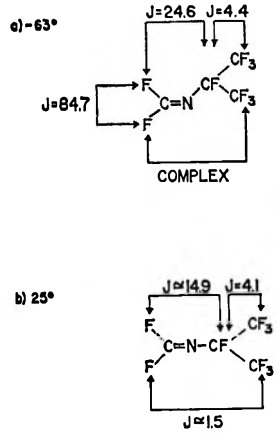

Figure 2.—Structures assigned to $(CF_3)_2CFN{=}CF_2$ at −63 and +25°

not so large as that observed previously when perfluorobisazomethines isomerize.[9]

The F^{19} nmr spectra show an AB pattern characteristic of the $CF_2{=}N{-}$ group. In the case of $(CF_3)_2CFN{=}CF_2$, the pattern is broadened into two humps. F^{19} nmr measurements at various temperatures show that this effect, which appears to be characteristic of the $CF_2{=}N{-}$ group when adjacent to a branched fluorocarbon chain, *i. e.*, $CF_2{=}NCF(CF_3)_2$, $CF_2{=}NCF(CF_3)CF_2N{=}CF_2$, or $CF_2{=}N(CFCF_3)_2N{=}CF_2$,[2] is caused by stereoisomerization about the C=N bond.[10] The F^{19} nmr spectrum of $(CF_3)_2CFN{=}CF_2$ at different temperatures is summarized in Figures 1 and 2.

Experimental Section

Infrared spectra were measured on a Perkin-Elmer Model 21 double-beam instrument using a 2.5-cm gas cell fitted with NaCl windows. Nuclear magnetic resonance measurements were made with a Varian V-4300-2 instrument operating at 40.0 Mc and utilizing an internal standard of $CFCl_3$ for the determination of chemical shifts. The values reported are ϕ^* values[11] at a dilution of 10–25%. Trifluoroacetic acid is ϕ^* 76.5 on this scale. Mass spectra were measured utilizing a C.E.C. 21-103c instrument with an inlet temperature of 30°, ion chamber temperature of 250°, ion voltage of 70 V, and ion current of 10 μA. Molecular weights where quoted were determined by effusion. Peaks reported are the most significant ones and are described by *m/e* (relative intensity) assigned ion. Vapor phase chromatographic separations were made using a 2 m × 0.5 in. Kel-F 8126 column, and by condensing the products from the effluent gas at −196° in a trap filled with glass beads. The recovery of products from the vpc apparatus was unfortunately rather low and the actual yields obtained are probably considerably higher.

Perfluorobutyryl Fluoride.—Perfluoro-2,3-diazabuta-1,3-diene (5.5 mmol) and perfluorobutyryl fluoride (22.0 mmol, 4 molar excess) were condensed at −196° into a silica tube of 200-cc capacity fitted with a Fischer & Porter polytetrafluoroethylene valve. After warming to room temperature, the tube was irradiated with ultraviolet light from a water-cooled Hanovia 450-W lamp for 24 hr. Trifluoromethylisocyanate (4.0 mmol, 36% conversion of $CF_2{=}NN{=}CF_2$) and perfluoro-2-azapentene-1 (2.7 mmol, 24% conversion of $CF_2{=}NN{=}CF_2$) were then separated from unreacted starting material and by-products by vapor phase chromatography. They were identified by comparison of their infrared spectra with those of authentic samples. The spectral properties of $C_3F_7N{=}CF_2$ are summarized in Table II. The mass spectral pattern is summarized as follows: 31(29.9) CF, 43(2.4) C_2F, 50(19.7) CF_2, 69(91.2) CF_3, 76(5.2) C_2F_2N, 95(4.6) C_2F_3N, 100(6.7) C_2F_4, 114(100) C_7F_4N, 119(6.3) C_2F_5, 164(16.7) C_3F_6N, 169(5.9) C_3F_7, and 214(13.7) C_4F_8N.

Calcd for C_4F_9N: mol wt, 233. Found: mol wt, 232.

Perfluorovaleryl fluoride was prepared from perfluorovaleric acid by treatment with phosphorus pentachloride followed by potassium fluoride. Tetrafluoro-2,3-diazabuta-1,3-diene (3.1 mmol) and perfluorovaleryl fluoride (9.0 mmol, 3 molar excess) were photolyzed together in the manner described previously. Trifluoromethyl isocyanate (1.6 mmol, 25% conversion of $CF_2{=}NN{=}CF_2$) and perfluoro-2-azahexene-1 (1.6 mmol, 25% conversion of $CF_2{=}NN{=}CF_2$) were isolated by vapor phase chromatography. Perfluoro-2-azahexene-1, $CF_3CF_2CF_2CF_2N{=}CF_2$, was characterized by its molecular weight and infrared, F^{19} nmr, (see Table II), and mass spectra. The mass spectrum is summarized as follows: 31(20.3) CF, 50(12.6) CF_2, 69(100) CF_3, 76(3.7) C_2F_2N, 95(3.9) C_2F_3N, 100(9.5) C_2F_4, 114(67.9) C_2F_4N, 119(9.9) C_2F_5, 126(2.5) C_3F_4N, 131(3.3) C_3F_5, 145(3.0) C_3F_6N, 164(4.3) C_3F_6N, 176(3.1) C_4F_6N, 214(5.8) C_4F_8N, and 264(9.9) $C_5F_{10}N$.

Calcd for $C_5F_{11}N$: mol wt, 283. Found: mol wt, 289.

Perfluoroisobutyryl Fluoride.—Tetrafluoro-2,3-diazabuta-1,3-diene (5.5 mmol) and perfluoroisobutyryl fluoride (25 mmol, 4.5 molar excess) were photolyzed together in the manner described previously. Trifluoromethyl isocyanate (2.2 mmol, 20% conversion of $CF_2{=}NN{=}CF_2$) and perfluoro-3-methyl-2-azabutene-1 (3.8 mmol, 35% conversion of $CF_2{=}NN{=}CF_2$) were isolated by vapor phase chromatography. Perfluoro-3-methyl-2-azabutene-1, $(CF_3)_2CFN{=}CF_2$, was characterized by its infrared, mass, and F^{19} nmr spectra. The mass spectrum is summarized as follows: 31(34.1) CF, 50(26.0) CF_2, 69(95.0) CF_3, 76(12.6) C_2F_2N, 95(7.8) C_2F_3N, 100(4.4) C_2F_4, 114(84.0) C_2F_4N, 119(3.6) C_2F_5, 164(100) C_3F_6N, and 214(22.6) C_4F_8N. The F^{19} nmr spectrum is described in Figures 1 and 2.

Anal. Calcd for C_4F_9N: C, 20.6; N, 6.0; F, 71.4; mol wt, 233. Found: C, 20.6; N, 5.8; F, 72.3; mol wt, 232.

Isomerization of Azomethines.—Perfluoro-2-azapentene-1 (2.0 mmol) and trichlorofluoromethane (8.0 mmol) were condensed under vacuum at −196° into an nmr tube containing dried cesium fluoride (0.2 g). The cesium fluoride was dried immediately before use by heating it at 250° for 5 min under vacuum. The F^{19} nmr spectrum of the sample, which is summarized in Table II, indicated that isomerization was complete almost immediately. After removal of $CFCl_3$, the infrared spectrum of the product, perfluoro-2-azapentene-2, was shown to be identical with that of the major product from the pyrolysis of perfluoro tertiary *n*-propylamine.[4]

Perfluoro-2-azahexene-1 (2.0 mmol) and trichlorofluoromethane (8.0 mmol) were condensed under vacuum into a tube containing dried ferric fluoride (0.1 g). After heating at 100° for 30 min, no evidence of isomerization was observed from infrared measurements. The volatile material was then transferred to an nmr tube containing dried cesium fluoride (0.1 g). Infrared and F^{19} nmr spectral observations indicated that isomerization occurred almost immediately. The F^{19} nmr spectrum was shown to be identical with that reported by Banks, *et al.*,[12] for perfluoro-2-azahexene-2, $CF_3CF_2CF_2CF{=}NCF_3$. After removal of $CFCl_3$,

(10) P. H. Ogden and G. V. D. Tiers, *Chem. Commun.*, 5217 (1967).

(11) See Table II, ref *a*.

(12) See Table II, footnote *m*.

the infrared spectrum was also shown to be identical with that of an authentic sample of $CF_3CF_2CF_2CF{=}NCF_3$.

Perfluoro-3-methyl-2-azabutene-1 did not isomerize when heated at 200° in the presence of dried cesium fluoride for 12 hr.

Registry No.—Perfluoro-2,3-diazabuta-1,3-diene, 692-73-9.

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The Synthesis of Saturated and Unsaturated α-Difluoramino Ethers

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In recent years, the syntheses of a variety of organic compounds containing the difluoramino grouping have been reported. Included are acyl difluoramines,[1] alkyl difluoramines,[2] perfluoroalkyldifluoramines,[3] and difluorourea.[4] In addition, the properties of a *vic*-difluoramino compound, 1,2-bisdifluoramino-4-methylpentane,[5] have been reported. Several review articles[6] emphasizing inorganic difluoramino compounds have also appeared.

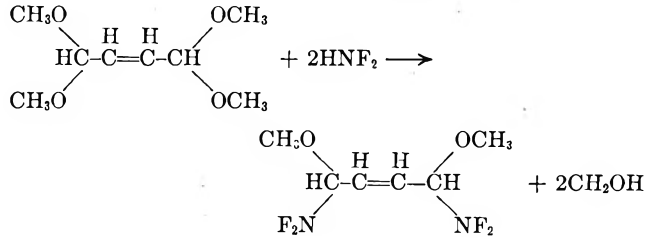
For the most part the synthesis of difluoramino-containing molecules had been accomplished *via* fluorination of amines and thermal or photochemical reactions of tetrafluorohydrazine. A more recent publication[7] has disclosed the alkylation of difluoramine by various carbonium ions. As one of several reactions, Graham and Freeman reported the preparation of α-difluoraminopyran by reaction of dihydropyran and HNF_2 at room temperature. This appears to be the first indication that HNF_2 had any synthetically useful nucleophilic properties.

We now wish to report an additional synthetic utility of difluoramine. The reaction of acetals with HNF_2 now provides a new method for preparing α-difluoramino ethers. This reaction probably represents a fairly general mode of attack in that it occurs with saturated and unsaturated mono- and diacetals such as dimethyl acetal, acrolein acetal, tetra-

$$RCH(OR)_2 + HNF_2 \longrightarrow RCH(OR)NF_2 + ROH$$

methoxypropane, tetramethoxybutene-2, and tetraethoxybutyne-2.[8] The only acetals tried that failed to react were two ketene acetals, specifically, the parent compound and dicyano ketene acetal. In all other examples, one alkoxide from each acetal grouping was replaced by $-NF_2$.

The reaction conditions varied according to the starting material used. All reactions were carried out under an excess pressure of HNF_2 at temperatures ranging from ambient to 100° using standard vacuum line techniques. The appropriate alcohol (1 molar equiv) was isolated in each case and identified *via* infrared and gc. Tetramethoxypropane and tetraethoxybutyne-2 reacted similarly in that under the milder reaction conditions a mixture of the mono- and bisdifluoramino ether was isolated. On recycling this material with additional HNF_2 at a higher temperature the corresponding 1,3 or 1,4 product formed. On the other hand, tetramethoxybutene-2 reacted at room temperature in CCl_4 to give a nearly quantitative yield of high purity (92%) 1,4-bisdifluoramino ether. The



integrated area ratio of 3:1:1 for methoxy, vinyl, and tertiary hydrogens and the nmr results listed in Table I are consistent with the proposed difluoramino ether. The reaction was also run in the absence of solvent (excess NHF_2) without affecting either the yield or purity of the bis ether. The work-up of the reaction mixture was greatly facilitated in the latter case.

TABLE I

F^{19}	H^1
ϕ −25.5 (d) [-CH(OR)NF_2]	τ 3.91 (m) (-CH=C)
$J_{HF} \sim 18.5$ cps	τ 5.21 (dt) (tertiary H)
	$J_{HF} \sim 18.5$ cps
	τ 6.43 (s) ($-OCH_3$)

Experimental Section

Caution: Difluoramine should be handled with care. Explosions have occurred when HNF_2 was condensed at −196°.

Apparatus.—A heavy-wall glass pressure reactor[9] (15-ml capacity) fitted with a Teflon[10] valve was used in this experiment.

1,4-Bisdifluoramino-1,4-dimethoxybutene-2.—Tetramethoxybutene-2 (0.5 g, 0.0029 mol) was dissolved in 0.5 ml of CCl_4 and charged *via* a drawn-out medicine dropper to the bulb of the reactor. The reactor was then degassed three times and 0.700 g (0.013 mol) of HNF_2 was condensed in using a −126° bath (Freon-21 and liquid N_2). The reactor was allowed to warm to room temperature. Stirring (*via* magnetic stirrer) was continued for 24 hr. The volatile products were passed through a −78° (trichloroethylene–Dry Ice) and a −126° trap. The desired product remained behind as a colorless liquid. Bulb-to-bulb distillation of this liquid at 75° (0.5 mm) gave 0.607 g (98%) of the bis-α-difluoramino ether.

Anal. Calcd for $C_6H_{10}O_2N_2F_4$: C, 33.0; N, 12.85; F, 34.9; mol wt, 218. Found: C, 32.85; N, 13.02; F, 34.6; mol wt, 214.

1,4-Bisdifluoramino-1,4-diethoxybutyne-2.—The tetraethoxybutyne-2 (0.59 g, 0.0026 mol) was charged neat into a glass pressure reactor. The reactor was then degassed three times. The HNF_2 (0.50 g, 0.009 mol) was condensed in using a −126° bath. After reaching room temperature the reaction was stirred for 24 hr. Work-up in the usual manner (see reaction above)

(1) R. Petry and J. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).
(2) J. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960).
(3) R. Haszeldine, *J. Amer. Chem. Soc.*, **72**, 1638 (1950); R. Pearson and R. Dresdner, *ibid.*, **84**, 4743 (1962).
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(5) W. Good, D. Douslin, and J. McCullough, *J. Phys. Chem.*, **67**, 1312 (1963).
(6) A. V. Pankratov, *Russ, Chem. Rev.*, **32**, 157 (1963); C. Hoffman and R. Neville, *Chem. Rev.*, **62**, 1 (1962).
(7) W. Graham and J. Freeman, *J. Amer. Chem. Soc.*, **89**, 716 (1967).
(8) D. D. Rosenfeld, *J. Org. Chem.*, **28**, 2900 (1963).
(9) R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).
(10) Available from Fischer & Porter, Warminster, Pa., Catalog No. 795-609.

gave 0.61 g of a product which was composed of 70% mono- and 30% bisdifluoramino ether *via* nmr spectroscopy. Fresh HNF_2 was condensed into the reactor, and it was heated (oil bath) to 70° for 16 hr. Work-up gave 0.61 g of the bisdifluoramino ether as a colorless liquid.

Anal. Calcd for $C_5H_{12}O_2N_2F_4$: C, 39.67; N, 11.57; F, 31.40. Found: C, 39.4; N, 11.37; F, 30.8.

1,3-Bisdifluoramino-1,3-dimethoxypropane.—Tetramethoxypropane (0.500 g, 0.003 mol) was allowed to react with 0.420 g (0.008 mol) of HNF_2 in a glass pressure reactor at 50° for 3 days. The resulting liquid product was fractionated to give 0.53 g of a colorless liquid product.

Anal. Calcd for $C_5H_{10}O_2N_2F_4$: C, 29.12; N, 13.6; F, 36.9. Found: C, 29.3; N, 14.0; F, 36.6.

3-Ethoxy-3-difluoraminopropene-1.—Acrolein diethyl acetal (0.34 g, 0.0026 mol) and 0.35 g (0.006 mol) of HNF_2 were allowed to react in a glass pressure vessel and worked up as above to give 0.3 g of the title compound.

Anal. Calcd for $C_5H_9ONF_2$: C, 45.11; N, 10.2; F, 27.7. Found: C, 45.5; N, 10.13; F, 27.9.

Registry No.—1,4-Bisdifluoramino-1,4-dimethoxybutene-2, 16452-20-3; 1,4-bisdifluoramino-1,4-diethoxybutene-2, 16452-21-4; 1,3-bisdifluoramino-1,3-dimethoxypropane, 16462-48-9; 3-ethoxy-3-difluoramino-1-propene, 16452-22-5.

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Direct Fluorination of Sodium Dicyanamide and Cyanoguanidine

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Ruff and Giese[1] have reported that silver cyanide when diluted with fluorspar could be fluorinated with elemental fluorine to yield numerous products. Subsequently, we found that by using alkali metal fluorides as the diluent in place of fluorspar, guanidine could be fluorinated to pentafluoroguanidine.[2] In this Note, we report the extension of this technique to the direct fluorination of sodium dicyanamide and cyanoguanidine.

Sodium dicyanamide, $NaN(CN)_2$, mixed with a large amount of magnesium fluoride as diluent was fluorinated with 50% fluorine diluted with nitrogen. The low boiling product was collected in a Dry Ice trap. Fractionation of the light yellow liquid using codistillation indicated that it contained about 20 minor impurity components and a major component, $F_2NCF_2NFC{\equiv}N$ (I), representing about 90–95% of the over-all material.

The molecular weight of I determined by gas density measurements was 157 and 159 (calcd 161). The boiling point was 18.4° determined from vapor pressure–temperature measurements.

The infrared absorption spectrum of I in the gas phase showed a sharp, weak intensity band at 4.45 μ assigned to C≡N stretch, strong bands at 6.7, 8.1, and 8.3 μ assigned to the CF_2 group, a strong broad band at 10.4–10.8 μ assigned to the NF bands, a medium strong band at 9.85 μ, and medium weak bands at 9.2, 12.45, and 14.2 μ.

The ^{19}F nmr spectrum ($CFCl_3$ as reference) showed a CF_2 doublet at 101.0 ppm due to coupling (J = 22.8 cps) with the –NF group, resulting in a NF triplet at 54.1 ppm and a NF_2 broad single peak at −20.55 ppm.

The fluorination of 5 g of cyanoguanidine diluted with a large amount of sodium fluoride resulted in 1.5 ml of material collected in a Dry Ice–acetone cooled trap. This crude liquid product contained five major components, three of which were identified by infrared and mass spectroscopy as the previously reported compounds $(F_2N)_2C{=}NF$[2], $(F_2N)_3CF$[3], and $F_2NCF_2NFC{\equiv}N$. The two higher boiling products were identified as $F_2NC(=NF)NFCF_2NF_2$ and $(F_2N)_2CFNFCF_2NF_2$, both of which have the skeletal cyanoguanidine structure intact. Thus, the over-all reaction and the relative amounts of products obtained from the fluorination of cyanoguanidine may be illustrated as in Table I. 1-[(Difluoramino)-difluoromethyl]-1,2,3,3-tetrafluoroguanidine, $F_2NC(=NF)NFCF_2NF_2$, is an explosive, colorless liquid below its boiling point, 55°, obtained by extrapolation from vapor pressure–temperature measurements. The molecular weight found by gas density measurements was 229 (calcd 232). The mass spectrum showed no parent peak, which is common for many nitrogen–fluorine compounds. The largest mass peak at m/e 180 was assigned to $C_2N_3F_6^+$ which results from loss of NF_2 from the parent molecule. Other major peaks were at m/e of 161, 142, 128, 114, 109, 102, 97, 90, 83, 78, 69, and 64.

TABLE I

	Relative amounts
$H_2NCNHC{\equiv}N \xrightarrow[NaF]{F_2/N_2}$ $(F_2N)_2C{=}NF$	1
$(F_2N)_3CF$	4.7
$F_2NCF_2NFC{\equiv}N$	Trace
$F_2NC(=NF)NFCF_2NF_2$	3.5
$(F_2N)_2CFNFCF_2NF_2$	7

The infrared absorption spectrum of $F_2NC(=NF)NFCF_2NF_2$ in the gas phase showed a weak intensity band at 6.15 μ assigned to C=N stretch, strong bands in the CF region at 7.70, 7.95, 8.15, and 8.50 μ, and strong bands in the NF region at 10.00, 10.50, and 11.20 μ. The 10.00-μ band had shoulders at 9.6 and 9.85 μ. In addition, a medium strong band at 11.65 μ and medium bands at 12.55 and 14.00 μ were observed. The ^{19}F nmr spectrum ($CFCl_3$ as reference) showed a NF_2 band at −41.0 ppm and the =NF band at −33.8 ppm. These are reasonable for the $-C(=NF)NF_2$ portion of the molecule since it has been previously shown[1] that in the compound $(F_2N)_2C{=}NF$ the NF_2 groups came at −42.3 and −46.9 ppm and the =NF at −20.2 ppm. The NF_2 band at −19.7 ppm and the

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(3) R. J. Koshar, D. R. Husted, and C. D. Wright, 4th International Symposium on Fluorine Chemistry, Estes Park, Colo., July, 1967.

$-CF_2-$ doublet at +100.5 ppm coupled by 22.8 cps to the -NF- at +48.4 ppm are very reasonable for the F_2NCF_2NF- portion of the molecule and in good agreement for the same assignments made for F_2NCF_2-NFCN.

The highest boiling product obtained from the fluorination, N[(difluoroamino)difluoromethyl]-N,N′,N′,-N″,N″-1-hexafluoromethanetriamine, $(F_2N)_2CFNFC-F_2NF_2$, is an explosive, colorless liquid boiling at 60°, extrapolated from vapor pressure–temperature measurements. The molecular weight found by gas density measurements was 267 (calcd 270).

The infrared absorption spectrum in the gas phase showed strong intensity bands in the CF region at 7.85, 8.10, and 8.32 μ. The 7.85-μ band had a shoulder at 7.65 μ. Strong bands at 10.45 and 10.95 μ, usually attributed to NF bonds, and weak bands at 9.45, 9.70, 9.95, 11.50, 11.75, 12.60, and 13.20 μ were also observed. The mass spectrum of $(F_2N)_2CFNFCF_2NF_2$ showed no parent peak. A peak observed at m/e of 218 was assigned to $C_2N_3F_8^+$ which results from loss of NF_2 from the parent molecule. Other major peaks observed which can be accounted for by the structure were at m/e of 147, 128, 135, 116, 102, 83, 69, and 64. The ^{19}F nmr spectrum ($CFCl_3$ as reference) showed five lines consistent with the structure as follows (peak, assignment, relation area): −23.5 ppm, $C(NF_2)_2$, 4; −19.2 ppm, CNF_2, 2; +90.0 ppm, -NF-, 1; +100.4 ppm, $-CF_2-$, 2; and 131.2 ppm, CF, 1.

Experimental Section

Caution! The products and various unidentified by-products from the fluorination of sodium dicyanamide and cyanoguanidine are extremely explosive in the gas, liquid, and solid state. They have been manipulated routinely in a mercury-free vacuum line with CF_2Cl_2 slush baths at −130 to −145°. It was standard practice to use adequate shielding and protective equipment and to keep the sample size below 0.5 g.

Fluorination of Cyanoguanidine.—Cyanoguanidine (5 g, 60 mmol) was mixed with 50 g of sodium fluoride which had been dried at 110°. The mixture was charged into a three-necked, 1-l. monel flask fitted with a stirrer and gas inlet and outlet. The flask was immersed in an ice bath and stirred while 20–40% fluorine diluted with nitrogen was introduced into the flask at a total gas flow rate of 200–400 ml/min for 60 min. The crude product was collected from the effluent stream in a glass U-trap cooled in a Dry Ice bath. When approximately 0.5 ml of crude product was collected in the U-trap, the trap was removed and additional product was collected in a second and third trap, etc.

Purification of the products was achieved by repeated codistillation[4] using a 10-mm copper column packed with fluorine-treated 40–60 mesh magnesium beads.

Fluorination of $NaN(CN)_2$.—Sodium dicyanamide (2 g, 20 mmol) and 20 g of magnesium fluoride were put into a 500-ml flask fitted with a stirrer, a fluorine inlet, and a gas outlet connected to a Dry Ice cooled trap. The rapidly stirred mixture was cooled in an ice bath and a 50:50 mixture of F_2–N_2 was passed through the flask at 200 cc/min for 60 min. During this time, about 1 cc of liquid was collected in the Dry Ice trap. The product was purified by codistillation.

The infrared data were obtained with a Perkin-Elmer Model 137B spectrophotometer. The cell had a 2.5-cm path length and NaCl windows. The vapor pressure was measured in a mercury-free system from −80 to −2°. The nuclear magnetic resonance spectrum was obtained on an instrument described by Baker and Burd.[5]

Registry No.—Sodium dicyanamide, 4615-74-1; cyanoguanidine, 461-58-5; $(F_2N)_2CFNFCF_2NF_2$, 16408-92-7; $F_2NC(=NF)NFCF_2NF_2$, 16408-93-8; I, 16408-94-9.

Acknowledgment.—This work was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by the Air Force Rocket Propulsion Laboratory, under Contact Nr. AF 33-(616)-6149.

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Effect of Fluorine on Photoelimination Reactions in Ketones

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Considerable interest has been shown recently in the type II photolytic process in ketones. Wagner and Hammond[1] and Dougherty[2] have shown that both excited singlet and triplet species can be involved in solution while the work of Coulson and Yang[3] and Wagner[4] indicates that biradical species may also play a role. Earlier, it had been shown by Srinivasan,[5] by means of deuterium substitution, that the γ hydrogen is transferred to the carbonyl oxygen. The over-all process may be represented as

$$RC(=O)CH_2CH_2CHR' \xrightarrow{h\nu} CH_2{=}CHR' + RC(OH'){=}CH_2 \longrightarrow RC(=O)CH_2H'$$

Nicol and Calvert[6] have carried out an extensive study of the effect of alkyl substitution on the vapor phase photolysis of a series of n-propyl ketones. Under these conditions the type I process is also important. Es-

$$RC(=O)R' \xrightarrow{h\nu} R + R'CO + R' + RCO$$

sentially no work has been carried out on the effect of substituents other than alkyl at the γ-carbon atom. For this reason we examined the effect of fluorine on the photolysis of 4,6,8,8,8-pentafluoro-3-octanone, $CF_3-CH_2CHFCH_2CHFC(=O)CH_2CH_3$.

When irradiated either neat or in hydrocarbon solvents (0.2 M) four products could be detected by glpc. Only two of these could be separated in sufficient amount and purity for identification. 1-Fluoro-2-butanone was identified by comparison with a sample prepared independently from fluoroacetonitrile (Experimental Section). Glpc retention times, infrared, and H^1 and F^{19} nmr spectra were identical. 1,1,1,3,5-Pentafluoropentane was identified by comparison with a sample prepared from the 2:1 telomer of vinyl fluoride and trifluoromethyl iodide (Experimental Section).

(1) P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.*, **88**, 1245 (1966).

(2) T. J. Dougherty, *ibid.*, **87**, 4011 (1965).

(3) D. R. Coulson and N. C. Yang, *ibid.*, **88**, 4511 (1966).

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(6) C. H. Nicol and J. G. Calvert, *ibid.*, **89**, 1790 (1967).

Chromatographic and spectral characteristics were identical for the samples. A third material, trapped as a gas from the chromatograph and analyzed by infrared spectroscopy, showed it to contain a fluoro-substituted double bond (1690 cm^{-1}) and a trifluoromethyl group (1280 cm^{-1}). Vinyl-type fluorine was also detected in the photolyzed solution of the fluoro ketone by F^{19} nmr spectroscopy. This compound is tentatively identified as 1,1,1,3-tetrafluoro-3-butene. Its rate of formation by glpc is identical with that of 1-fluoro-2-butanone. The fourth product which could not be separated completely from the starting ketone exhibited a strong OH absorption in the infrared spectrum at 3200 cm^{-1}. This material could be a cyclobutanol derivative, compounds which are often found in low yields in these reactions or a reduction product of the starting material. Yields as measured by glpc are 1-fluoro-2-butanone, 1,1,1,3-tetrafluoro-3-butene, 32%; 1,1,1,3,5,-pentafluoropentane, 16%; alcohol, 21.4%. The material balance leaves 31.6% unaccounted for. That hydrogen fluoride is produced during photolysis is evident by the slow etching of the quartz photolysis cells. It is not known if this derives from starting material or products or both.

The quantum yield at 2537 Å for disappearance of fluoro ketone in heptane solution was determined to be 0.39 by comparison with 2-hexanone which is reported to have a quantum yield of 0.327 at 3130 Å in pentane.[3] An indication of the amount of singlet and triplet reaction involved in the type II process producing 1-fluoro-2-butanone and 1,1,1,3-tetrafluoro-3-butene was obtained by carrying out quenching experiments with piperylene and *cis*-dichloroethylene.[1,2] In each case only 93% of the reaction to form type II products could be quenched, indicating this fraction of triplet reaction. Both pieces of quantitative data are subject to the uncertainties of less than total material balance. This amount of triplet reaction, however, may be compared with 60% for 2-hexanone and 2-octanone under similar conditions. The larger fraction of triplet reaction may be due to the increased energy required for abstraction, by the excited carbonyl group, of a γ hydrogen at a position of low electron density thus allowing for intersystem crossing from excited singlet to excited triplet to compete more effectively. Formation of the type I product, 1,1,1,3,5-pentafluoropentane, in 16% yield is unusual in solution photolyses. In unsubstituted ketones, *e.g.*, 2-hexanone this product generally accounts for less than 3% of the total.[7] (In vapor phase photolysis, on the other hand, type I products generally run well over 50% of the total.) The increased tendency for type I reactions may simply reflect the slower rate of type II reactions with which they compete. However, some increased stability of the intermediate fluoro-substituted radical is also to be expected, *i.e.*

$$CF_3CH_2CHFCH_2\dot{C}HF \longleftrightarrow CF_2CH_2CHFCH_2CH{=}F\cdot$$

Experimental Section

Synthesis of 4,6,8,8,8-Pentafluoro-3-octanone.—3,5,7,7,7-Pentafluoro-2-heptene available from a previous study[8] was oxidized in a typical experiment as follows. To a slurry of olefin (5.0 g, 0.024 mol) in 100 ml of water was added dropwise a solution of potassium permanganate (17 g) and sodium hydroxide (2.0 g) in water (400 ml). After stirring overnight, sodium bisulfite and dilute sulfuric acid were added alternately until the solution became clear. The mixture was then extracted with three 100-ml portions of ether which were dried ($MgSO_4$) and evaporated to yield a white solid (3.8 g, 75%). Separation into two isomers, mp 88–91 and 68–71°, could be achieved by fractional crystallization from a chloroform–petroleum ether (bp 30–50°) solution. Each gave the same average analysis (samples from several runs) and neutral equivalent.

Anal. Calcd for $C_6H_7F_6O_2$: C, 34.9; H, 3.4; F, 46.1; neut equiv, 206. Found: C, 35.3; H, 3.5; F, 45.8; neut equiv, 210.

The mixture of diastereoisomeric acids was converted into the acid chlorides, bp 73–79° (22 mm), in 70% yield by thionyl chloride. The ketone was prepared typically as follows. Diethylcadmium was prepared from ethylmagnesium bromide [from 3.56 g (0.149 g-atom) of Mg, 17.6 g (0.161 mol) of ethyl bromide, and 125 ml of dry ether] and cadmium chloride (13.4 g, 0.073 mol) at ice-bath temperature. After refluxing about 1 hr the slurry was cooled in an ice–salt bath to about −10° and the acid chlorides (20 g, 0.096 mol) in ether (15 ml) were added dropwise over 30 min. The reaction mixture was stirred overnight and cooled and 10% sulfuric acid added slowly until clear. The ether layer was washed with dilute sodium carbonate solution and dried. Evaporation of the ether yielded 14.6 g (92%) of crude product. The oily residue was distilled under reduced pressure, 29–34° (0.05 mm), and purified as follows. The distilled mixture was solidified by cooling in Dry Ice and then partially melted by slowly warming to room temperature. When about one-half of the material had melted, the slurry was rapidly filtered under suction and the solid sucked dry with a rubber dam. The material which remained solid at room temperature was further purified by a combination of recrystallization (ethanol–water) and sublimation, mp 40–41°. The mother liquor could be recycled several times to obtain more solid material. Separation into a liquid and solid form could also be carried out by preparative gas chromatography. These materials had identical infrared spectra (carbonyl at 1730 cm^{-1}) with the exception of the intensity of a peak at 943 cm^{-1}. The fluorine nmr spectrum (60 Mc) showed CF_3 as a complex multiplet at 65.0 ppm (relative to CCl_3F), relative area = 3; –CHF– as a broad unresolved peak centered at 186.3 ppm, relative area = 1; and –C(=O)CHF– as a septet at 193 ppm, relative area = 1. The proton nmr spectrum indicated CH_3 as a triplet (J = 7 cps) at τ 8.96, relative area = 3; the $-CH_2$ group of the ethyl group as a quartet (J = 7 cps) centered at τ 7.46 on top of the remaining methylene groups which occur as a broad unresolved peak centered at approximately τ 7.5, total relative area = 6; and –CHF– as two broad, unresolved doublets (J = 53.4 cps) at τ 5.1, relative area = 2. The ultraviolet spectrum of the solid isomer showed a maximum at 2825 Å (ϵ 26.9) and formed a 2,4-dinitrophenylhydrazone, mp 85–87.5°. Elemental analyses tended to be erratic even with a single sample.

Synthesis of 1-Fluoro-2-butanone.—Fluoroacetamide (Peninsular ChemResearch) was converted in 65% yield into fluoroacetonitrile by reaction with phosphorous pentoxide.[9] To a cold (−15°) ethereal solution of ethylmagnesium bromide prepared from 9.8 g (0.42 g-atom) of magnesium, 45.8 g (0.42 mol) of ethyl bromide, and 125 ml of ether, was added dropwise a solution of fluoroacetonitrile (24.8 g, 0.42 mol) in ether (125 ml). The mixture was stirred overnight and cooled and 10% sulfuric acid slowly added. The ether layer was dried and evaporated to yield a dark oil which was distilled at atmospheric pressure resulting in extensive decomposition. A fraction boiling at 60–120° was purified by gas chromatography. The proton nmr spectrum showed the ethyl group and a fluoromethylene group in 1:1 ratio. The fluorine nmr spectrum indicated a single CH_2F type of fluorine at 228.5 ppm (relative to CCl_3F). The ketone formed a 2,4-dinitrophenylhydrazone, mp 89–90.5°.

Anal. (2,4-DNPh). Calcd for $C_{10}H_{11}N_4O_4F$: C, 44.5; H, 4.07; N, 20.8. Found: C, 43.5; H, 4.3; N, 20.7.

Preparation of 1,1,1,3,5-Pentafluoropentane.—1,1,1,3,5-Pentafluoroamyl iodide[10] (55.7 g, 0.193 mol) dissolved in ethanol (100 ml) was added over 6 hr to a mixture of zinc (38.6 g, 0.59 g-atom) in absolute ethanol (900 ml) saturated with hydrogen

(7) P. Ausloos and R. E. Rebbert, *J. Amer. Chem Soc.*, **83**, 4897 (1961).
(8) T. J. Dougherty, *ibid.*, **86**, 460 (1964).
(9) R. E. Kent and S. M. McElvain, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 493.
(10) T. J. Dougherty, *J. Amer. Chem. Soc.*, **86**, 2236 (1964).

chloride at 70–80°. Hydrogen chloride was added periodically to maintain saturation. After standing overnight, the mixture was filtered and mixed with water (3000 ml) containing $NaHCO_3$ and extracted with four 100-ml portions of ether. The ether solution was separated, dried ($MgSO_4$), and distilled. After removal of ether and a low-boiling (54–103°) fraction, the pentafluoropentane was collected at 103–105° to yield 6.3 g (19%). The infrared spectrum showed the CH stretch at 2960 cm^{-1} and C-F at 1265 and 1170 cm^{-1}. Unsaturation was absent. The proton nmr spectrum showed the $-CH_2-$ groups as a complex multiplet centered at τ 5.4, relative area = 4; $-CHF-$ as two quintets (J = 6.0 cps) separated by 50 cps, relative area = 1; and $-CH_2F$ at τ 4.5 as two triplets (J = 5.8 cps) separated by 48 cps, relative area = 2.

Anal. Calcd for $C_5F_5H_7$: C, 37.1; F, 58.6; H, 4.3. Found: C, 37.3; F, 58.6; H, 4.4.

Photolysis Procedure.—Photolysis cells of approximately 1.8-ml capacity (1.5 cm long) were filled with a 0.2 *M* solution of the ketone in heptane (spectroquality), immersed in a quartz circulating water bath at 35 ± 0.5° and exposed to either a low-pressure mercury lamp (>90% uv output at 2537 Å) or a medium-pressure mercury lamp (25% uv output at 3100–3300 Å, 75% at 3300–3700 Å). Degassing (freeze–thaw technique) had no effect on quantum yields. Distilled quencher was added directly from a microliter syringe. Samples of 1 or 2 μl were taken every 20–60 min, depending on the lamp employed, over a period of several hours and analyzed by gas chromatography on a Carbowax 1500 column operated at 140° with a helium flow of 50 cc/min. Runs were carried to approximately 5–25% completion in the case of the quenching experiments utilizing the medium-pressure lamp and up to 75% completion when the 2537-Å lamp was used.

Four photolysis products were detected at retention times of 1.0, 2.2, 3.0, and 15.5 min. The first of these products was gaseous and was collected from the chromatograph in an evacuated infrared gas cell. The infrared spectrum bore a strong resemblance to that of 2,3,5,7,7,7-hexafluoro-1-heptene[10] exhibiting a =CF absorption at 1690 cm^{-1} and a CF_3 absorption at 1280 cm^{-1}. Insufficient material was obtained for further examination. The second eluted product had a retention time and ir spectrum identical with those of 1,1,1,3,5-pentafluoropentane obtained by reduction of the corresponding iodide (see above). The product eluted at 3.0 min proved to be 1-fluoro-2-butanone by comparison with the sample prepared as described above. These materials agreed in retention times as well as infrared and nmr spectra (H^1 and F^{19}). The last eluted product was obtained in only trace amounts and highly contaminated with the starting ketone. However, the presence of a hydroxyl group was apparent in the infrared spectrum at 3200 cm^{-1}.

Registry No.—4,6,8,8,8-Pentafluoro-3-octanone, 16408-87-0; 4,6,8,8,8-pentafluoro-3-octanone 2,4-dinitrophenylhydrazone, 16408-88-1; 1-fluoro-2-butanone, 453-10-1; 1-fluoro-2-butanone 2,4-dinitrophenylhydrazone, 580-05-2; 1,1,1,3,5-pentafluoropentane, 16408-89-2; fluorine, 7782-41-4.

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The Oxidation of Aldehydes in Alcoholic Media with the Caro Acid

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The Caro acid (peroxymonosulfuric acid) has often been used as a characteristic oxidizing agent in the field of organic synthesis. It was early observed that the Baeyer–Villiger reaction occurred in the oxidation of carbonyl compounds with this oxidant as follows.[1]

$$R-CO-R' + H_2SO_5 \longrightarrow R-O-CO-R' + H_2O + H_2SO_4$$

Oxidation of acrolein in alcoholic media with hydrogen peroxide in the presence of selenium dioxide as catalyst was reported to give acrylates in 15–40% yield.[2] This method was investigated further in oxidation of other aldehydes in methanol or ethanol.[3] Methyl methacrylate was obtained also by the oxidation of methacrolein in methanol with *t*-butyl hydroperoxide in the presence of metal salt catalysts, such as $FeCl_2$ and $FeCl_3$.[4]

We wish to report that when aldehydes were oxidized with the Caro acid in the presence of alcohols the esters of corresponding acids could be obtained in high yield according to the equation

$$R-CHO + H_2SO_5 \xrightarrow{R''OH} RCOOR'' + H_2O + H_2SO_4$$

The results of these oxidations are summarized in Table I.

TABLE I
OXIDATION OF ALDEHYDES IN ALCOHOLS WITH THE CARO ACID

Aldehyde	Alcohol	Product	Conversion, %[a]	Selectivity, %[b]
Methacrolein	Methanol	Methyl methacrylate	94	91[c]
Methacrolein	Methanol	Methyl methacrylate	90	97[d]
Methacrolein	[e]	Methacrylic acid	65	29[d]
Methacrolein	Ethanol	Ethyl methacrylate	100	88[d]
Methacrolein	Isopropyl alcohol	Isopropyl methacrylate	83	55[d]
Acrolein	Methanol	Methyl acrylate	100	85[d]
Crotonaldehyde	Methanol	Methyl crotonate	100	63[d]
Propionaldehyde	Methanol	Methyl propionate	90	97[d]
Benzaldehyde	Methanol	Methyl benzoate	100	100[d]

[a] Conversion (%) = 100 (moles of aldehyde reacted/moles of aldehyde charged). [b] Selectivity (%) = 100 (moles of product/moles of aldehyde reacted). [c] The Caro acid was prepared from $(NH_4)_2S_2O_8$. [d] The Caro acid was prepared from H_2O_2 and H_2SO_4. [e] Ethyl ether was used instead of alcohol.

Mechanistically, it seems plausible that the Baeyer–Villiger reaction occurs first and esterification follows. Thus, the aldehyde is oxidized with the Caro acid to the corresponding carboxylic acid, which is esterified immediately with alcohol. However, when methacrolein was oxidized in ethyl ether instead of in methanol, the conversion of methacrolein and the selectivity of the main oxidation product (methacrylic acid) decreased remarkably. On the other hand, the rate of esterification of methacrylic acid with methanol in the presence of H_2SO_4 is much slower than that of oxidation of methacrolein in methanol with the Caro acid under the same condition of reaction (Figure 1). From these results, the above-mentioned mechanism involving intermediate formation of methacrylic acid followed by esterification could be excluded.

The direct formation of esters by the oxidation of primary alcohols with chromic acid was reported to occur by the reaction sequence, alcohol → aldehyde ⇌ hemiacetal → ester, rather than by the commonly ac-

(1) C. H. Hassall, *Org. Reactions*, **9**, 73 (1959).
(2) C. W. Smith and R. T. Holm, *J. Org. Chem.*, **22**, 746 (1957).
(3) M. Kitahara, T. Mitsui, and T. Hirayama, *Rika Gaku Kenkyusho Hokoku*, **38**, 81 (1962); *Chem. Abstr.*, **58**, 13788*a* (1963).
(4) Halcon International, Inc., Netherlands Patent Application, 6,412,904 (1965); *Chem. Abstr.*, **63**, 13085*e* (1965).

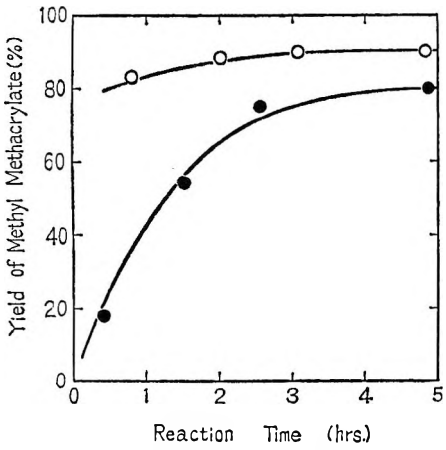

Figure 1.—Variation of yield of methyl methacrylate with reaction time in oxidation of methacrolein with the Caro acid in methanol (○) and in esterification of methacrylic acid with methanol in the presence of sulfuric acid (●); yield (%) = 100(moles of product/moles of aldehyde charged).

cepted path, alcohol → aldehyde → acid → ester.[5] It is most probable that this oxidation of aldehyde in alcoholic medium proceeds also through a hemiacetal peroxymonosulfate as Heywood, *et al.*, suggested in the oxidation of acetals with peracetic acid (Scheme I).[6]

SCHEME I

$$\mathrm{R{-}CHO + R''OH \xrightarrow{H^+} RCH(OH){-}OR''}$$

(I)

$$\mathrm{I + H_2SO_5 \longrightarrow R{-}CH(OOSO_2OH){-}OR'' + H_2O}$$

(II)

$$\mathrm{II \longrightarrow R{-}COOR'' + H_2SO_4}$$

Experimental Section

Materials.—Methacrolein was prepared from propionaldehyde and paraformaldehyde in the manner described by Mitsui, *et al.*,[7] and purified by distillation (bp 66–68°). Propionaldehyde, acrolein, crotonaldehyde, and benzaldehyde were obtained commercially and used after distillation [bp 48–49, 52–53, 104–105, 74–76° (20 mm), respectively]. Methacrolein, crotonaldehyde, and acrolein were kept under refrigeration after the addition of 0.5 wt % hydroquinone. Other reagents were commercial materials used without further purification.

Preparation of the Caro Acid. A.—Ammonium persulfate (23.0 g) was added in small portions to 29.0 g of 85% H_2SO_4 maintained below 15° with stirring.

B.—H_2O_2 (3.9 g, 90%) was added dropwise to 25.0 g of concentrated H_2SO_4 maintained below 15° with stirring. The mixture was kept at room temperature for 2 hr.

Oxidation of Methacrolein in Methanol. A.—To a well-stirred mixture of 0.76 g of methacrolein and 12.9 g of methanol cooled to 10°, 5.6 g of the Caro acid prepared according to procedure A was added dropwise over a period of 2 min. During this addition, the internal temperature was kept below 10°. After stirring for 4 hr at 15°, the reaction mixture was diluted with water and extracted with ether. Methacrolein and methyl methacrylate in the combined ether extracts were analyzed quantitatively by gas chromatography. Benzene was used as the internal standard. The analysis was performed on a Yanagimoto GCG-220 at 80° with a helium flow rate of 50 ml/min and a 2.5-m column packed with 30% dioctyl phthalate on Celite 545. The conversion of methacrolein was 94% and the selectivity of methyl methacrylate was 91%. The gas chromatographic retention time of the methyl methacrylate agreed with that of an authentic sample.

B.—To a stirred mixture of 3.04 g of methacrolein and 79.5 g of methanol cooled to 15°, 12.2 g (equimolar to methacrolein) of the Caro acid prepared according to procedure B was added over a period of 10 min. During this addition, the internal temperature was kept below 15°. Stirring was continued at 15° and a 15-ml portion of the solution was sampled out at intervals. The aliquot parts were treated as described above and analyzed quantitatively by gas chromatography. The conversion of methacrolein after 3 hr was 90% and the selectivity of methyl methacrylate was 97%. The results obtained are shown in Figure 1 together with the results in the esterification reaction of methacrylic acid described below.

Methyl methacrylate isolated by gas chromatography with a Varian Aerograph 1525-B was identified by comparison of its infrared spectrum with that of an authentic sample, $n^{20}D$ 1.414.

Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.70; H, 8.02.

The other oxidations were carried out virtually as described above.

Esterification of Methacrylic Acid with Methanol.—To a stirred solution of 3.74 g of methacrylic acid and 79.5 g of methanol cooled to 15°, 10.6 g of concentrated H_2SO_4 was added over a period of 10 min. During the addition, the internal temperature was kept below 15°. Stirring was continued at 15° and a 15-ml portion of the solution was sampled out at intervals. The aliquot parts were treated as in the preceding experiment and yield of methyl methacrylate were determined by gas chromatographic analysis.

Oxidation of Methacrolein in Ethyl Ether.—A stirred mixture of 0.78 g of methacrolein and 21.6 g of ethyl ether was treated at 15° with 3.10 g of the Caro acid (prepared from H_2O_2 and H_2SO_4) over 3 hr. The solution was subjected to ether extraction and methacrylic acid in the ether extract was gas chromatographed at 135° on a 3-m column packed with 10% dioctyl sebacate on Diasolid S. Cyclohexanol was used as the internal standard. The conversion of methacrolein was 65% and the selectivity of methacrylic acid was 29%. Other products were not identified.

Oxidation of Benzaldehyde in Methanol.—To a stirred mixture of 10.6 g of benzaldehyde and 155 g of methanol cooled to 15°, 28.1 g of the Caro acid (equimolar to aldehyde) prepared according to procedure B was added dropwise over a period of 10 min. During the addition, the internal temperature was kept below 15°. After stirring for 3 hr at 15°, the mixture was treated as usual. The ethereal solution was analyzed by gas chromatography at 150° on a 3-m column packed with 10% dioctyl sebacate on Diasolid S. Cyclohexanol was used as the internal standard. The yield of methyl benzoate was quantitative. Methyl benzoate collected by gas chromatography was identified by comparison of its infrared spectrum with that of an authentic sample.

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.78; H, 5.98.

Registry No.—Peroxymonosulfuric acid, 7722-86-3; methacrolein, 78-85-3; acrolein, 107-02-8; crotonaldehyde, 123-73-9; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7.

(5) J. Cymerman Craig and E. C. Horning, *J. Org. Chem.*, **25**, 2098 (1960).
(6) D. L. Heywood and B. Phillips, *ibid.*, **25**, 1699 (1960).
(7) T. Mitsui, M. Kitahara, and Y. Miyatake, *Rika Gaku Kenkyusho Hokoku*, **38**, 205 (1962); *Chem. Abstr.*, **59**, 3762*d* (1963).

Reduction of Some Sulfonium Salts with Lithium Aluminum Hydride

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Since Schmid and Karrer[1] performed the first reduction of some cyclic ammonium salts with lithium

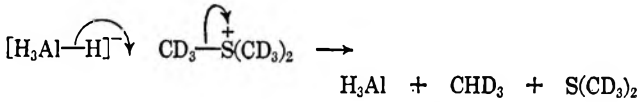
(1) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).

aluminum hydride, the reductions of phosphonium,[2] aliphatic ammonium,[3] and stibonium salts[4] have also been reported. Surprisingly enough, sulfonium salts have not been investigated. We previously observed[5] that a liquid reduction product mixture obtained by the reduction of 2-phenylethyldimethylsulfonium bromide with lithium aluminum hydride contained mainly methyl-2-phenylethyl sulfide.

A more thorough investigation of lithium aluminum hydride reductions of some sulfonium salts is now reported.

Reduction of Trimethylsulfonium Bromide.—The sulfonium salt suspended in diethylene glycol diethyl ether was reduced with lithium aluminum hydride at 45° for 2.5 hr, and at 60° for 4.5 hr, respectively. The analysis of the gaseous products by gas chromatography and the analysis of the reaction solution showed methane and dimethyl sulfide to be the only reduction products.

The deuterated sulfonium salt was also reduced with $LiAlH_4$. From the gaseous products, methane was isolated and analyzed by mass spectrometry. The mass spectrum contained an intensive mass of 19 mass units corresponding to CHD_3. The undeuterated sulfonium salt was also reduced with $LiAlD_4$. The methane had the main mass of 17 mass units, corresponding to CH_3D. No methane of the formula CH_2D_2 with mass 18 could be detected. This suggests that a simple displacement takes place, *e.g.*, in case of the deuterated salt



$$[H_3Al{-}H]^- \quad CD_3{-}\overset{+}{S}(CD_3)_2 \longrightarrow H_3Al + CHD_3 + S(CD_3)_2$$

(in the equation H_3Al is written only formally)

It is known[6] that sulfonium salts exchange hydrogens very rapidly, while ammonium salts exchange hydrogens extremely slowly, which has been explained in terms of d-orbital resonance occurring at the sulfonium salts. Since sulfonium salts are more easily reduced with lithium aluminum hydride than are ammonium salts, one could assume that the reduction occurs at the intermediate zwitterion in which a partial neutralization of charge by electron drift from the carbon atom into the d-orbital of the sulfur atom takes place, giving the carbon–sulfur bond considerable double-bond character. If it were so, the reduction of deuterated trimethylsulfonium salt would most probably yield methane of the formula CH_2D_2 with simultaneous evolution of an equivalent quantity of hydrogen (HD). This is not the case.

Reduction of 2-Phenylethyldimethylsulfonium Bromide.—The reductions were carried out in diethyl ether at 35° for 2.5 hr and overnight at room temperature, and also in tetrahydrofuran at 65° for 2.5 hr. The salt was again in suspension. The main reduction products were methyl-2-phenylethyl sulfide and methane. Small quantities of ethylbenzene and dimethyl sulfide (less than 5%) were also detected by gas chromatography and by mass spectrometry. The products are most probably formed by analogous hydride ion attack as suggested above.

In solvents dried with no special precautions, containing the usual amount of moisture of about 0.05%, the base-catalyzed elimination occurred during reduction, which yielded up to 40% of styrene. When the solvent was very carefully dried by several distillations over sodium and subsequently dried over Molecular Sieves 4A, no styrene could be detected in the reduction products.

In order to check the drying procedure, water containing tritium was added to the dry solvent and the drying procedure repeated. The specific activity of the solvent indicated that it contained about 0.0001% of water.

Cram found[7] that the reduction of *p*-toluenesulfonate of 3-phenyl-2-butanol with lithium aluminum hydride in diethyl ether yielded 2-phenylbutane, but elimination also occurred giving 2-phenyl-2-butene. We have carried out the same reaction applying the drying procedure of the solvent mentioned above (which practically excludes the base catalysis) and have found that the elimination still takes place. Gas chromatography shows that the ratio of 2-phenylbutane to 2-phenyl-2-butene is 3:1.

On the other hand, in the reduction of 2-phenylethyl *p*-toluenesulfonate (primary α carbon) with lithium aluminum hydride in dry diethyl ether, we could not find any elimination products.

It was interesting to see whether sulfonium salts of a similar type, having sulfur bonded to the secondary α-carbon atom, would also undergo elimination during the reduction with lithium aluminum hydride. It was found that the only products of the reduction of 3-phenyl-2-butyldimethylsulfonium bromide were methane and the corresponding sulfide. 2-Phenyl-2-butene was not detected.[8]

Cram suggested[7] that, in the reaction of 3-phenyl-2-butyl *p*-toluenesulfonate with lithium aluminum hydride, olefin is formed by a bimolecular mechanism. However, the fact that the mentioned tosylate yields olefin with lithium aluminum hydride and the corresponding sulfonium salt does not could be better explained by assuming that *p*-toluenesulfonate reacts *via* a salt-promoted ionization[9] and olefin is formed *via* a carbonium ion process, while sulfonium salt reacts by a displacement process.

2-Phenylethyltrimethylammonium iodide was also reduced with lithium aluminum hydride in tetrahydrofuran at 65° for 60 hr. Dimethyl-2-phenylethylamine and methane were the main products (about 95%). Ethylbenzene and trimethylamine were also detected (about 5%). Again, in very dry tetrahydrofuran, no elimination could be observed, but, in tetrahydrofuran containing about 0.05% of water, 23% of styrene was found.

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(7) D. J. Cram, *ibid.*, **74**, 2149 (1952).

(8) D. Stefanović, private communication from this laboratory.

(9) S. Winstein, S. Smith, and D. Darwish, *J. Amer. Chem. Soc.*, **81**, 5511 (1959).

Experimental Section

A Nier-type mass spectrometer with a resolution of 1:300, produced at the Institute "Jožef Stefan," Ljubljana, Yugoslavia, was used. Gas–liquid partition chromatographic analyses were performed using a Perkin-Elmer 154D instrument, and a Wilkens Instrument and Research A-90-C machine, respectively.

Materials.—Trimethylsulfonium bromide was prepared as described by Cooper, Hughes, Ingold, and Mac Nulty,[10] 2-phenylethyldimethylsulfonium bromide by the procedure of Saunders and Ašperger,[11] 2-phenylethyltrimethylammonium iodide by the procedure of von Braun and Neumann,[12] 2-phenylethyl-*p*-toluenesulfonate as described by Klamann,[13] and 2-phenyl-3-butyl-*p*-toluenesulfonate and 2-phenyl-2-butene by the procedures of Cram.[7,14] 2-Phenylbutane was prepared from 2-phenyl-2-butene by catalytic hydrogenation using palladium on activated charcoal (10%) as catalyst.

Deuterated Materials.—Deuterated trimethylsulfonium bromide was prepared by direct hydrogen exchange in 7.5 *M* sodium deuteroxide solution, following the procedure of Doering and Hoffmann.[6] The exchange is practically complete.

Drying of the Solvent.—Diethyl ether and tetrahydrofuran were dried over sodium, distilled, dried over Molecular Sieves 4A (activated during 8 hr at 300° and 1-torr pressure), and distilled. Drying over molecular sieves was repeated several times. This drying procedure was tested by the addition of known amount of water containing tritium (200 mCi/ml) to the dry solvent. After the drying procedure was repeated, the specific activity of the solvent showed that there was only about 0.0001% of water in the solvent.

Reduction with Lithium Aluminum Hydride.—The solution of lithium aluminum hydride was prepared by shaking of 6.0 g of $LiAlH_4$ with 50 ml of dry solvent for 4 hr. The solid was allowed to settle and the liquid was decanted. The concentration of lithium aluminum hydride in ethereal solution was estimated by the method of Felkin.[15]

A mixture consisting of lithium aluminum hydride in large excess to the substance was stirred in dry solvent at the appropriate temperature. Aqueous sodium hydroxide solution (10%) was then added. The products of the reduction were isolated by extraction with pentane and the organic layer was washed, dried, and concentrated.

Analysis of Products.—The gaseous products of the reduction were collected in a liquid air trap, purified on a vacuum line, and analyzed by mass spectrometry. By this method the following reaction products were estimated: methane, deuterated methane (CH_3D), dimethyl sulfide, and trimethylamine.

Gas–liquid partition chromatography was used for the analysis of concentrated pentane extract. The following reaction products were estimated (by comparison with the pure substances): methane (on 0.25 in. × 2 m stainless steel column packed with silica gel + 2% di-2-ethylhexyl sebacate using flame ionization detector), dimethyl sulfide, ethylbenzene, styrene, methyl-2-phenylethyl sulfide, 2-phenylbutane, and 2-phenyl-2-butene (on 0.25 in. × 1.5 m stainless steel column packed with 15% silicone GE SF-96 on 60–80 mesh firebrick using thermal conductivity detector), trimethylamine, and dimethyl-2-phenylethylamine (on 0.25 in. × 2 m stainless steel column packed with 10% silicone oil DC-200 on 60–80 mesh Chromosorb W using thermal conductivity detector).

Registry No.—Lithium aluminum hydride, 1302-30-3; trimethylsulfonium bromide, 676-84-6; 2-phenylethyldimethylsulfonium bromide, 16315-48-3.

Acknowledgment.—The authors thank Professor W. H. Saunders and Professor S. Borčić for helpful discussion.

(10) K. A. Cooper, E. D. Hughes, C. K. Ingold, and B. J. Mac Nulty, *J. Chem. Soc.*, 2038 (1948).

(11) W. H. Saunders, Jr., and S. Ašperger, *J. Amer. Chem. Soc.*, **79**, 1612 (1957).

(12) J. von Braun and L. Neumann, *Chem. Ber.*, **49**, 1286 (1916).

(13) D. Klamann, *Monatsh. Chem.*, **84**, 54 (1953).

(14) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949).

(15) H. Felkin, *Bull. Soc. Chim. Fr.*, **18**, 347 (1951).

Heterogeneous Photosensitization

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Received February 9, 1967

Recently Leermakers and James[1] described the use of a solid, polyvinylphenyl ketone, to photosensitize piperylene, norbornadiene, and myrcene in the liquid phase. As pointed out by these authors, liquid–solid or gas–solid cross phase photosensitization has the particular advantage that there are no problems of separation of the sensitizer from the products or reactants.

We have been investigating the cross phase photosensitization of the piperylenes and 1,3-cyclohexadiene in the vapor phase by thin polymeric films deposited on the walls of quartz or Pyrex photolysis reactors.

The photosensitizer films are produced by the *in situ* photolysis of suitable monomers in the gas or vapor phase. For example, the photolysis of 5 torr of benzaldehyde in a Pyrex reactor with the filtered light (0.5 cm of 1 *M* $CuSO_4$) of a Philips HP 125 medium-pressure Hg lamp for 30 min produces a polymeric film which was still active as a photosensitizer after more than 50 hr of service. This film does not have the same photochemical properties as benzaldehyde (*vide infra*) in sharp contrast to the polyvinylphenyl ketone sensitizer described by Leermakers and James[1] which seems to have approximately the same photochemical properties as the parent phenylvinyl ketone.

Control experiments performed before deposition of the polymeric film in the reactor showed that the dienes were totally unaffected by the light entering the cell; further blank experiments at 50° in the presence of the film for 24 hr indicated the total absence of dark reactions. Photodimerization of 1,3-cyclohexadiene, slower photodimerization of piperylene, and rapid *cis–trans* isomerization of the piperylenes were observed in the presence of the polymeric film. With either *cis*- or *trans*-1,3-pentadiene as starting material a photostationary *trans/cis* ratio of 4:1 was obtained after several hours irradiation. This ratio, much larger than that obtained in the liquid phase photosensitization of piperylene by benzaldehyde (triplet energy = 72 kcal/mol, ratio = 1.23),[2] suggests from the correlation of Hammond, Turro, and Leermakers[2] that the triplet energy of the polymeric films is 55 ± 5 kcal/mol. This latter result is substantiated by the fact that the polymeric film does not sensitize dimerization of *cis–trans* isomerization of 1,2-dichloroethylene[3] where the triplet energy is ~70 kcal/mol.[4]

The present results clearly indicate the practicability of photosensitization of molecules in the vapor phase

(1) P. A. Leermakers and F. C. James, *J. Org. Chem.*, **32**, 2898 (1967).

(2) G. S. Hammond, N. J. Turro, and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962).

(3) Two sets of experiments were carried out with initial *cis/trans* ratios of 2.5:1 and 7:1, respectively. These starting ratios are similar to the photostationary states found by Hammond, *et al.*,[2] for acetophenone (E triplet = 74 kcal/mol, *cis/trans* ratio = 3.1:1) and for benzophenone (E triplet = 70 kcal/mol, *cis/trans* ratio = 4.5:1) photosensitizations of the dichloroethylenes in the liquid phase. The use of two different *cis/trans* ratios eliminates the possibility that one may be the photostationary state.

(4) G. N. Lewis and M. Kasha, *J. Amer. Chem. Soc.*, **66**, 2100 (1944).

by thin polymeric films. The formation and properties of such films are under investigation.[5]

Registry No.—1,3-Cyclohexadiene, 592-57-4; *cis*-1,3-pentadiene, 1574-41-0; *trans*-1,3-pentadiene, 2004-70-8.

Acknowledgments.—The authors thank Dr. G. H. Huybrechts for helpful discussions and thank the "Fonds de la Recherche Fondamentale Collective" for financial aid.

(5) (a) D. Fuld, P. Goldfinger, G. Huybrechts, and M. Toth, "Seventh Informal Photochemistry Conference," Rensselaer Polytechnic Institute, Troy, N. Y., June 1966. (b) E. Jonas, Thesis, University of Brussels, to be presented. (c) G. R. De Maré, M. C. Fontaine, P. Goldfinger, G. H. Huybrachts, E. Jonas, and M. Toth, submitted for publication.

Dibenzopentalenoquinone and a Radical-Anionic Salt of Its Tetracyanodimethan Derivative

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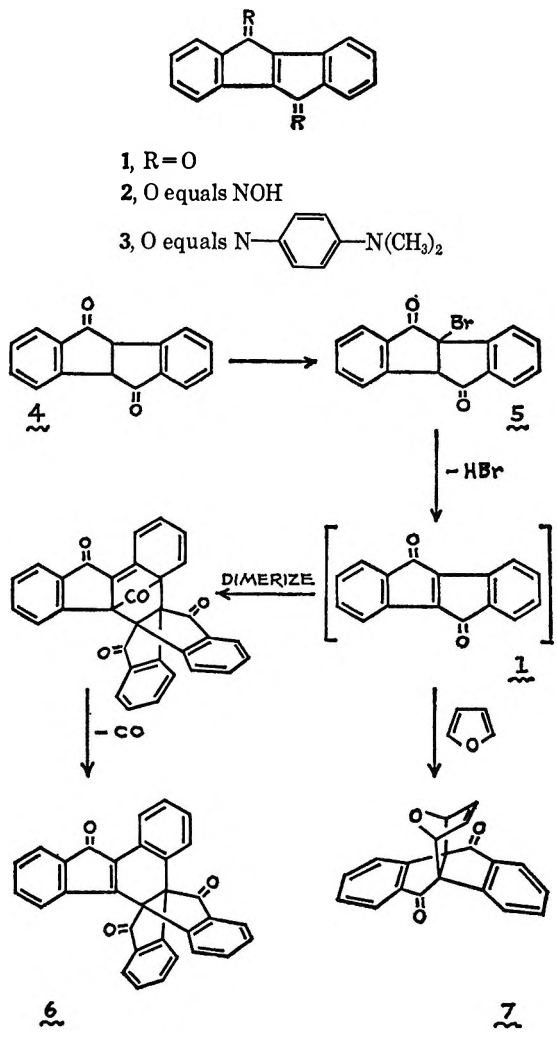
During the course of work directed toward the synthesis of pentalene derivatives, we undertook the investigation of dibenzopentalenoquinone, **1**. Brand[2] has previously described attempts to prepare **1** *via* hydrolysis of the derivatives **2** and **3**, oxidation of **4** with selenium dioxide, and dehydrobromination of **5** (Scheme I). In each case a good yield of the red trione **6** was obtained. This multicyclic trione appears to arise from a self-condensation (Diels–Alder) of **1** followed by aromatization by ejection of carbon monoxide, a product identified by Brand.[2] This sequence of steps is typical of the self-condensation reactions which cyclopentadienones undergo.[3]

Of special interest is the dehydrobromination of the bromodione **5** with pyridine. In this reaction a transient violet color is observed[2] which we find is due to a broad visible absorption peak centering at 550–560 mμ. This absorption is replaced in about 10 min by that of **6** at 457 mμ. If the absorption at 550–560 mμ is due to the presence of **1** then it should be possible to prevent its buildup by trapping **1** with a reactive diene before the formation of the self-Diels–Alder product. This has proven to be the case. No violet color was observed when the dehydrobromination of **5** was carried out in the presence of excess furan. From the pale yellow reaction mixture was isolated a new compound, $C_{20}H_{12}O_3$, plus a trace of the trione **6**. To $C_{20}H_{12}O_3$ the structure **7**, a Diels–Alder adduct of **1** and furan, has been assigned on the basis of elemental analysis, molecular weight, and spectroscopic properties. The infrared spectrum of **7** exhibits a conjugated carbonyl at 1701 cm^{-1} and an aromatic C=C at 1592 cm^{-1}. The nmr spectrum consists of a complex multiplet at τ 1.9–2.8 (8 H, aromatic), an AB quartet centered at τ 3.71 (J = 6 cps), each member of

SCHEME I



which is further split by 1.8 cps (2 H, olefinic), and two singlets at τ 4.85 and 4.55, each member being split into an unsymmetrical quartet (J = 1.8 and 0.3 cps).

A few degrees above its melting point **7** undergoes rapid decomposition accompanied by vigorous evolution of gases to form pure trione **6**. Presumably, a retro-Diels–Alder reaction takes place with the formation of gaseous furan and **1**. The latter instantly dimerizes cleaving carbon monoxide to form **6**. The generation of **1** in the presence of thiophene gave only high yields of **6**.

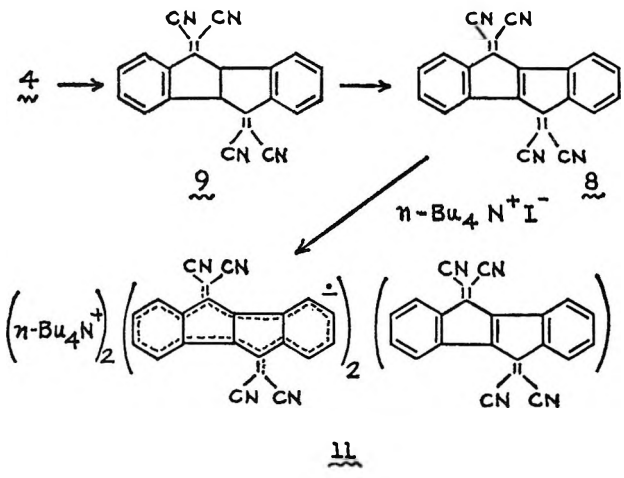
Although dibenzopentalenoquinone itself cannot be isolated, two simple derivatives of it, the bisoxime, **2**, and the bis(dimethylaminoanil), **3**, have been reported.[2] We have now found that the tetracyanodimethan derivative, **8**, is also stable showing no tendency to undergo either dimerization or polymerization. The preparation of **8** involves first the formation of the dihydro derivative **9** by condensing the readily prepared dione **4** with malononitrile (Scheme II). Then oxidation of **9** with N-bromosuccinimide afforded **8**, a nearly black, sparsely soluble crystalline solid. The infrared spectrum of **8** verified the presence of C≡N (2225 cm^{-1}), aromatic C=C (1592 cm^{-1}), conjugated C=C (1570 cm^{-1}), and 1,2-disubstituted benzene (768 cm^{-1}). The electronic absorption spectrum has two bands in the visible, one at 705 mμ which tails extensively into the near-infrared region, and one at 420 mμ.

(1) To whom inquires may be addressed: Department of Chemistry, Michigan State University.

(2) K. Brand, *Chem. Ber.*, **69**, 2504 (1936).

(3) C. F. H. Allen, *Chem. Rev.*, **62**, 653 (1962); M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *ibid.*, **65**, 261 (1965).

SCHEME II



In addition there are four absorption bands in the ultraviolet region at 343, 302, 291, and 273 mμ. Polarographic reduction of **8** in acetonitrile showed three half-wave potentials at +0.099, and −0.3 V corresponding to two one-electron reductions and +0.9 V corresponding to a two-electron reduction. The first step apparently gives a radical anion, while the second step gives the dianion. The third step requires the uptake of four electrons to give the tetraanion. This tetraanion would be somewhat more stable than expected for a molecule containing four extra electrons since two electrons would be delocalized in the two dicyanomethyl substituents and the other two electrons would convert the dibenzopentalene moiety into an 18 π-electron aromatic system. If the first reduction potential is a measure of π acidity, then **8** is a slightly weaker π acid then tetracyanoquinodimethan (+0.127 V).[4]

As anticipated from its high oxidation–reduction potential, **8** readily undergoes chemical reduction by mild reducing agents such as iodide to given radical-anionic salts. These reactions are quite like those found for a large number of dicyanomethylene compounds.[5] While these radical-anionic salts can be made in solution the limited solubility of **8** has prevented isolation of pure salts using procedures previously described.[5] However, it has been possible to prepare a tetrabutylammonium radical-anionic salt **11** by fusing together n-$Bu_4N^+I^-$ and **8**. The resulting purple-black solid analyzes for $(Bu_4N)_2(C_{22}H_8N_4)_3$.[6] The esr spectrum of solid **11** show a single sharp line (g = 2.00357) indicating the radical nature of the anion in this salt. The solution esr spectra have been somewhat anomolous and thus a detailed structural assignment cannot yet be made.

The infrared spectrum of **11** showed a weak C≡N at 2180 cm^{-1}, an aromatic C=C at 1942 cm^{-1}, and 1,2-disubstituted benzene at 736 cm^{-1}. However, the most unusual aspect of the infrared spectrum of **11** is the rather strong, broad band with a maximum centering at about 3.5 μ. This appears to be a very low energy *electronic absorption*. Electronic absorption bands in this region of the spectrum have previously been observed for the complex tetracyanoquinodimethan salt of the type $(M)^{2+}(TCNQ\cdot^-)_2(TCNQ)$.[5b] The remaining *electronic absorptions* occur at 1130 and 820 mμ in the near-infrared region, at 740, 594, 553, 433, and 409 mμ in the visible region, and at 340, 327, 292, and 274 mμ in the ultraviolet region. Such low-energy electronic transitions suggest that **11** may possess some unusual properties such as semiconductivity. However, the very limited quantities of **11** have so far prevented investigations along these lines.

Experimental Section

Melting points were made with a calibrated thermometer. Analyses were carried out by Mellon Institute's microanalytical laboratory and various commercial laboratories. Infrared spectra were obtained on a PE-21 or PE-237, electronic spectra on a Cary 14, and nmr spectra on an A-60 spectrometer using $DCCl_3$ as solvent and TMS as internal standard.

4b-Bromo-4b,5,9b,10-tetrahydroindeno[2.1-*a*]indenedione (5).—A mixture of 7.0 g of 4,[7] 5.4 g of N-bromosuccinimide, and 180 ml of CCl_4 was refluxed for 2 hr. A catalytic amount of benzoyl peroxide was then added and refluxing continued for 20 hr. The succinimide was filtered off and the CCl_4 evaporated. The residue was crystallized from methanol, affording 6.1 g (65%) of **5**, a white crystalline solid, mp 139–141°. Recrystallization from methanol gave a purer product, mp 142–144° (lit.[2] mp 147°).

Adduct of I and Furan (7).—To a stirred mixture of 3.0 g of **5**, 13 ml of furan, and 25 ml of absolute ethanol was added, over 75 min, 2 g of pyridine. After 3 hr the reaction mixture was freed of excess furan (rotary evaporator). The remaining solution deposited 2.43 g of a white solid, mp 163–165°. Recrystallization from 95% ethanol gave 2.15 g (84%) of **7**: mp 166–167°; ir (KBr) 1701 cm^{-1} (C=O), 1592 (C=C).

Anal. Calcd for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found: C, 79.92; H, 3.95.

From reaction mixture mother liquor, 40 mg (1.7%) of a bright red crystalline solid was isolated. This material is identical with the red crystalline product obtained in 74% yield from the SeO_2 oxidation of **4** and in 86% yield from the dehydrobromination of **5** with pyridine using Brand's[2] procedure. Recrystallization gave large, deep red prisms: mp 294–295° (lit.[2] mp 284°); uv and visible λ_{max} (95% ETOH) 252 mμ (ε 3160), 270 (2690), 279 (2510), 457 (145); ir ($HCCl_3$) 1715 cm^{-1} (C=O), 1600 (C=C).

Anal. Calcd for $C_{31}H_{16}O_3$: C, 85.31; H, 3.70; O, 11.00; mol wt, 436.4. Found: C, 85.23; H, 3.76; O, 11.50 mol wt, 438 (osmometric).

5,10-Bis(dicyanomethylene)-4b,5,9b,10-tetrahydroindeno-[2,1-*a*]indene (9).—A powdered mixture of 1 g of **4**, 1 g of malononitrile, and 25 mg of β-alanine was heated at 140° for 1 hr. The resulting semisolid was washed twice with water and twice with ether. The residue was dissolved in acetone and clarified with charcoal. Addition of water to this solution induced 0.325 g (28%) of crude **9** (mp 310–315°) to crystallize out. Recrystallization from acetone–water gave a white, analytical sample: mp 318–320°; uv λ_{max} (dioxane) shoulder 337 mμ (ε 12,600), 324 (15,900), shoulder 316 (15,500), shoulder 297 (12,100), 234 (11,000), shoulder 230 (10,600); ir (KBr) 2220 cm^{-1} (C≡N), 1560 (C=C), 765 (*o*-benzo).

Anal. Calcd for $C_{22}H_{10}N_4$: C, 79.99; H, 3.05; N, 16.96. Found: C, 80.17; H, 2.98; N, 17.02.

5,10-Bis(dicyanomethylene)-5,10-dihydroindeno[2,1-*a*]indene (8).—To a chilled (−20°) mixture of 500 mg of **9** and 670 mg of N-bromosuccinimide in 10 ml of acetonitrile was added over 0.5 hr a solution of 320 mg of pyridine in 5 ml of ether. After stirring for 72 hr at 25° the mixture was filtered, affording 360 mg (72%) of crude **8**, mp 317–320°. Recrystallization from chlorobenzene results in the recovery of about 60% of analytically pure **8** as nearly black crystals: mp 333–335° (evacuated tube); electronic spectrum λ_{max} (dichloroethane) 273 mμ (ε 68,600), 291 (23,400),

(4) D. S. Acker and W. R. Hertler, *J. Amer. Chem. Soc.*, **84**, 3370 (1962).

(5) (a) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *ibid.*, **84**, 3374 (1962); (b) J. Diekman, W. R. Hertler, and R. E. Benson, *J. Org. Chem.*, **28**, 2719 (1963); (c) T. K. Mukherjee and L. A. Levasseur, *ibid.*, **30**, 644 (1965); (d) S. Chatterjee, *J. Chem. Soc., Sect. B*, 1170 (1967).

(6) This same stoichiometry (cation)$_2$(radical anion)$_3$·(neutral molecule) was previously observed in the cesium and morpholinium radical salts of tetracyanoquinodimethan.[5b]

(7) A. C. Cope and S. W. Fenton, *J. Amer. Chem. Soc.*, **73**, 1672 (1951).

302 (24,400), 343 (15,900), 420 (17,200), 706 (61); ir (Nujol) 2230 cm^{-1} (C≡N), 1595, 1572 (C=C), 760 (*o*-benzo).

Anal. Calcd for $C_{22}H_8N_4$: C, 80.48; H, 2.46; N, 17.05. Found: C, 80.33; H, 2.43; N, 17.03.

The polaragraph was carried out in a 0.1 *M* $LiClO_4$ solution of acetonitrile and was measured against a saturated calomel electrode.

Synthesis of the Radical Salt 11.—Under an atmosphere of N_2 a mixture of 50 mg of **8** and 250 mg of tetra-*n*-butylammonium iodide were fused at 115°. After 10 min the melt was cooled and was extracted with four 15-ml portions of benzene. The residue was dissolved in tetrahydrofuran. After filtering of this solution, ether was added giving 40 mg of a purplish black precipitate. This precipitate was recrystallized from tetrahydrofuran–ether affording 7 mg of analytically pure purple-black powder, **11**, mp 197–199°. The original benzene extract afforded, after concentration and fractional crystallization, another 8 mg of less pure **11**: mp 196–200°; electronic spectrum, λ_{max} (chloroform) 274 mμ (ε 134,200), 292 (109,200), 328 (37,500), 341 (39,260), 409 (22,380), 433 (19,820), 553 (28,150), 594 (55,200), 740 (15,520), 820 (22,500), 1130 (2520), and about 3.5 μ (in KBr); ir (KBr) 2180 (C≡N), 1580 (C=C), 736 cm^{-1}.

Anal. Calcd for $C_{98}H_{96}N_{14}$: C, 80.08; H, 6.58; N, 13.34. Found: C, 79.62; H, 6.31; N, 13.58.

Registry No.—**1**, 16408-95-0; **6**, 16408-96-1; **7**, 16408-97-2; **8**, 16408-98-3; **9**, 16408-99-4; **11**, 12259-94-8.

Acknowledgment.—We wish to thank Dr. R. Nicholson (Michigan State University) for the polarographic determination and Dr. P. Manoharan (Michigan State University) for the esr results.

Reactions of the Cyclobutylcarbinyl Radical

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The occurrence of a 1,2-alkyl shift in a hydrocarbon monoradical has not been demonstrated.[1] We have unsuccessfully approached this problem by attempting to use the relief of ring strain accompanying ring expansion of the cyclobutylcarbinyl to the cyclopentyl radical as a driving force for such a rearrangement. The exothermicity of this reaction, estimated[2] to be about 25 kcal/mol, is very much larger than the 7 kcal/mol available in previously studied neopentyl systems. Also, if products resulting from reaction of the cyclopentyl radical[4] had been observed, it would have been unlikely that they formed by fragmentation to the 4-penten-1-yl radical followed by cyclization to the cyclopentyl radical[5,6] since reaction of CH_2=$CH(CH_2)_3I$ with benzoyl or di-*t*-butyl peroxide in benzene does not yield any detectable cyclopentane, cyclopentene, cyclopentyl benzoate, or cyclopentylbenzene, all of which are formed to a significant extent when cyclopentyl iodide is allowed to react under the same conditions.[4]

Reaction of cyclobutylcarbinyl iodide (I) at room temperature and cyclobutylcarbinyl chloride (II)[7] at 148° with triphenyltin hydride in benzene resulted in formation of methylcyclobutane (III) with no detectable cyclopentane.

Reaction of I, which is thermally stable at all temperatures used, with approximately equimolar amounts of benzoyl peroxide (114 and 76°) or di-*t*-butyl peroxide (167 and 133°) in benzene yielded complex mixtures of products which contained no detectable cyclopentane or cyclopentene. Use of only 5 mol % peroxide revealed the reason for the failure of our approach. With both peroxides, a 2:1 mixture of 5-iodo-1-pentene and I resulted. Thus, I apparently opened to 5-iodo-1-pentene in a radical-chain process by way of the cyclobutylcarbinyl and 4-penten-1-yl radicals. We estimate[8] the cyclobutylcarbinyl radical → 4-penten-1-yl radical fragmentation to be less favorable than rearrangement to cyclopentyl radical by about 19 kcal/mol in ΔH and about 15 kcal/mol in ΔF.

The complete trapping, before fragmentation, of the cyclobutylcarbinyl radical by Ph_3SnH is in accord with our earlier conclusion that Ph_3SnH is a very good radical-trapping agent.[9]

Experimental Section

Benzene, cyclopentane, cyclopentene, benzoyl peroxide, di-*t*-butyl peroxide, 5-chloro-1-pentene, cyclopentyl chloride, and cyclopentyl iodide were commercial materials.

Cyclobutylcarbinyl chloride,[10] triphenyltin hydride,[11] and 5-iodo-1-pentene[12] were prepared by use of literature procedures.

Cyclobutylcarbinyl iodide was prepared by use of a procedure reported for cyclopropylcarbinyl iodide.[13] Cyclobutylcarbinyl chloride (1.06 g, 0.010 mol) and 1.5 g (0.010 mol) of sodium iodide were refluxed in 7.5 ml of acetone for 17 hr. The resulting mixture was filtered and the solvent removed from the filtrate. Ether was added to the heterogeneous residue and then removed from the resulting liquid phase. Cyclobutylcarbinyl iodide was obtained from the liquid residue by separation from unreacted chloride by use of preparative gas chromatography. It, as did the cyclobutylcarbinyl chloride prepared as indicated above, contained no detectable amount of the cyclopentyl isomer. Its nmr spectrum (CCl_4) consisted of a multiplet at τ 6.8 (2 H) and complex absorption between τ 7.0 and 8.6 (7 H).

Anal. Calcd for C_5H_9I: C, 30.64; H, 4.63; I, 64.73. Found: C, 30.72; H, 4.56; I, 64.89.

(1) For reviews, see C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 407, and R. Kh. Freidlina in "Advances in Free-Radical Chemistry," Vol. I, G. H. Williams, Ed., Academic Press Inc., New York, N. Y., 1965, p 211.

(2) Calculated assuming that D(cyclobutylcarbinyl–H) = D(CH_3-CH_2CH_2–H) and using known[3] values of the heat of formation of cyclobutane, cyclopentane, H·, and the cyclopentyl and *n*-propyl radicals.

(3) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).

(4) L. Kaplan, *J. Org. Chem.*, **32**, 4059 (1967).

(5) In the course of a study of ring-size effects in the neophyl rearrangement, Wilt observed the formation of some phenylcyclopentane and 1-phenylcyclopentene in the decarbonylation of (1-phenylcyclobutyl)acetaldehyde and presented arguments which he felt supported an elimination–addition mechanism.[6]

(6) J. W. Wilt, L. L. Maravetz, and J. F. Zawadzki, *J. Org. Chem.*, **31**, 3018 (1966).

(7) Reaction of II with Ph_3SnH at 148° resulted in the gradual accumulation of III over a period of about 28 hr. At this point the remaining II was very rapidly converted into cyclopentene. When the reaction was run for 20 min at 205°, the essentially exclusive product was cyclopentene. 5-Chloro-1-pentene did not give cyclopentene under these conditions. At both temperatures, the final reaction mixture was heterogeneous. The precipitated gray solid was found to convert II into a mixture of cyclopentene and cyclopentyl chloride under the reaction conditions.

(8) Calculated assuming that D(CH_2=$CHCH_2CH_2CH_2$–H) = D(CH_3-CH_2CH_2–H) and using known[3] values of the thermodynamic parameters of cyclopentane, 1-pentene, H·, and the cyclopentyl and *n*-propyl radicals.

(9) L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 4531 (1966).

(10) H. G. Richey, Jr., and E. A. Hill, *J. Org. Chem.*, **29**, 421 (1964).

(11) H. G. Kuivila and O. F. Beumel, Jr., *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

(12) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).

(13) P. T. Lansbury, V. A. Pattison, W. A. Clement, and J. D. Sidler, *J. Amer. Chem. Soc.*, **86**, 2247 (1964).

Registry No.—Cyclobutylcarbinyl radical, 16447-31-7; cyclobutylcarbinyl iodide, 16408-62-1.

Acknowledgment.—We are grateful to Professor W. D. Walters for a sample of methylcyclobutane.

The Reaction of Triethyl *trans*-1,2,3-Tricyanocyclopropane-1,2,3-tricarboxylate with Base. Formation of a Substituted Cyclopropane Anion Radical

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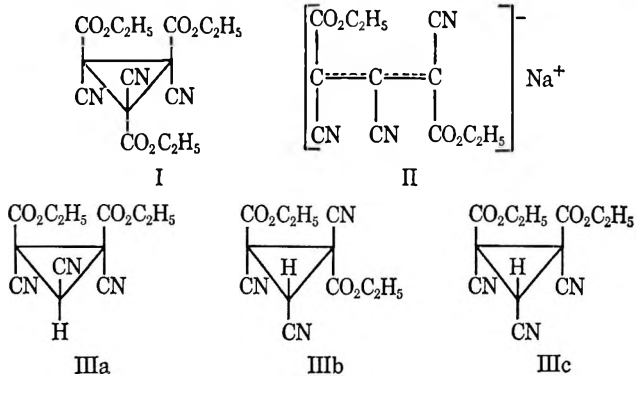
Received December 20, 1967

In the synthesis of triethyl *trans*-1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate (I) by reaction of ethyl sodiocyanoacetate and ethyl bromocyanoacetate according to the general procedure of Felton,[1b] we obtained, in addition to I, two other compounds, sodium 1,2,3-tricyano-1,3-dicarbethoxypropenide (II) and diethyl 1,2,3-tricyanocyclopropane-1,2-dicarboxylate (IIIa–c) (21 and 6% yield, respectively) (Chart I).

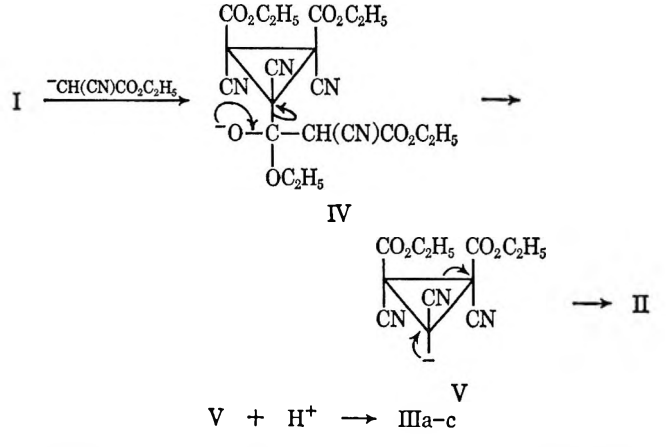
CHART I



Compounds II and IIIa–c were characterized and identified as follows. The yellow salt II gave the correct elemental analysis and was soluble in water and insoluble in nonpolar solvents. The infrared spectrum showed the presence of conjugated nitrile,[2] exhibiting a strong, sharp absorption peak at 4.51 μ and a less intense peak at 4.47 μ. The absorption bands at 5.88 and 6.78 μ are assigned to C=O and C=C stretching vibrations, respectively. The ultraviolet spectrum of II showed $\lambda_{max}^{C_2H_5OH}$ 425 mμ (ϵ 22,203) and 218 (13,192). These ultraviolet absorption features are similar to those reported for pentacyanopropenides.[3]

Assignment of structures IIIa–c is based primarily on analysis of spectral data. The proton nmr spectrum exhibited signals centered at δ 4.55 (two protons, quartet), 4.54 (two protons, quartet), 3.58 (one proton), and 1.45 ppm (six protons, triplet). The two low-field signals are attributed to the ester methylene protons, the 3.58-ppm signal to the cyclopropyl proton,[4] and the 1.45-ppm triplet to the ester methyl protons. Absorption bands in the infrared spectrum at 3.29 (cyclopropyl C—H),[5] 5.73 (C=O), and 4.44 μ (C≡N) and elemental analysis also indicate structures IIIa–c. The spectra are compatible with the structures IIIa–c for the cyclopropane derivative.

Regan[6] has observed propenide formation in the reaction of diethyl 2,2,3,3-tetracyanocyclopropane-1,1-dicarboxylate with ammonia. It would appear that formation of compound II results from base-catalyzed ring opening of I and that this type of ring opening could be general for highly negatively substituted cyclopropane derivatives with at least one carbalkoxy group. These results are consistent with the initial involvement of a Haller-Bauer[7] type of cleavage reaction. The transformations involved in the derivation of II and IIIa–c might be rationalized by initial formation of pentasubstituted cyclopropyl carbanion (V), which is formed by the elimination of diethyl cyanomalonate from intermediate IV, which, in turn, results from the nucleophilic addition of ethyl cyanoacetate anion to an electron-deficient ester carbonyl of I. Rearrangement of V would lead to the propenide (II) while proton capture would give IIIa–c. This rationalization is supported by the fact that compound II and its potassium salt were formed upon treatment of I with ethyl sodiocyanoacetate and potassium acetate in anhydrous 1,2-dimethoxyethane in 78 and 51% yield, respectively. Moreover, reaction of I with ethyl sodiocyanoacetate gave IIIa–c in 4–8% yield. On the other hand, the strongly basic sodium hydride gave an 11% yield of II and no cyclopropane product could be detected after 1 week at room temperature. These products are identical with those isolated in the original reaction as evidenced by comparison of infrared and ultraviolet absorption spectra and mixture melting point determinations.



That the cyclopropane derivative (IIIa–c) did not arise from a mechanism involving protonation of II was demonstrated by treating II with *p*-toluenesulfonic acid in ethanol. Only 1,2,3-tricyano-1,3-dicarbethoxy-

(1) (a) Address correspondence to the author at the Union Carbide Corp., Research and Development Department, South Charleston, W. Va. (b) D. G. I. Felton, *J. Chem. Soc.*, 515 (1955).

(2) C. E. Looney and J. R. Downing, *J. Amer. Chem. Soc.*, **80**, 2840 (1958).

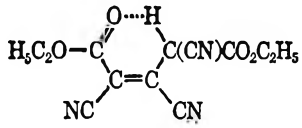
(3) W. J. Middleton, E. L. Little, D. D. Coffman, and V. A. Engelhardt, *ibid.*, **80**, 2795 (1958).

(4) H. Hart and F. Freeman, *J. Org. Chem.*, **28**, 1220 (1963).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 18.

(6) T. H. Regan, *J. Org. Chem.*, **27**, 2236 (1962).

(7) F. J. Impastato and H. M. Walborsky, *J. Amer. Chem., Soc.*, **84**, 4838 (1962).



VI

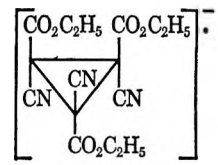
propene (VI) was obtained. The structure of the acid (VI) was confirmed by carbon and hydrogen analysis, molecular weight, and infrared and nmr spectral data. The nmr spectrum supports a *cis* configuration for VI which showed an extremely low-field absorption for the acidic proton at δ 14.65 ppm, characteristic for a hydrogen-bonded proton. Also, Dreiding models indicated a steric preference for this *cis* configuration and a normal hydrogen-bond distance of 2.6 Å for the C–H–O bond in VI.[8]

The stability of IIIa–c under the alkaline conditions of the reaction is interesting and deserves comment. The yields of cyclic product from treatment of I with various bases indicate the formation of V and proton abstraction by V to be a function of the nucleophilicity and structure of the attacking reagent. A rationale for ring-strain relief and product resonance stabilization is provided by propenide formation. Probably the latter accounts for the irreversibility of the cyclopropane forming reaction. Dreiding stereo models suggest no driving force for the rearrangement of V owing to steric interaction of the carbethoxy groups. In contrast to the reported[6] steric interference existing in ammonium 1,1,3,3-tetracyano-2-carbethoxypropenide no steric effects were observed in models of II. In view of the known double-bond character of cyclopropanes[9] the stability of V must be attributed to its similarity to a carbanion formed at a trigonal carbon atom through delocalization of its charge by interaction with the α-cyano group.[10]

On mechanistic grounds it appears reasonable that the cyclopropane product be assigned the configuration as shown by IIIa. This would be expected from attack by base on the least hindered carbethoxy group of I followed by proton capture. On the other hand, isomerization of the intermediate carbanion V would be expected to lead to the thermodynamically stable isomer, IIIb. Indeed, Walborsky[10] has shown that the energy barrier for the inversion of a α-cyano cyclopropane carbanion in aprotic solvents is lower than expected and that racemization occurs readily.

The nmr spectrum agrees with the proposed structure IIIb. In addition to the cyclopropyl proton, the nmr spectrum showed two equivalent carbethoxy methyl groups and a quartet due to the methylenic protons of the ester which under resolution were discernible as two quadruplets. On the other hand, the nonequivalency of the ester groups of starting *trans* I is clearly shown by its nmr spectrum which exhibited two overlapping quadruplets centered at δ 4.47 and 4.54 ppm and two overlapping triplets centered at δ 1.40 and 1.45 ppm, each in a 2:1 proton ratio, respectively. The assignment of configuration to IIIa–c with certainty must await the synthesis of all three isomers.

In the course of investigating the reactions of I, formation of the stable anion radical VII was observed. Treat-



VII

ment of I with potassium iodide in acetone solution under an inert atmosphere proceeded with the liberation of iodine and gave an orange solution. Likewise, colored solutions were obtained when potassium cyanide and triethylamine were used in the reaction. Anion radical formation in these reactions was substantiated by examination of an esr spectrum of the electrolytic reduction product of I with n-$Bu_4N^+ClO_4^-$ as the electrolyte in acetonitrile. A spectrum consistent with the cyclopropane structure VII was obtained with $a_N = 0.70$, $a_H = 1.48$ Oe, and $g = 2.0033$. In contrast to I, *cis*- and *trans*-1,2,3-tricyanocyclopropanes failed to oxidize potassium iodide, cyanide ion, and triethylamine and to undergo electrolytic reduction under the conditions described for I.

The observed influence of substituents on anion radical formation of cyclopropane derivatives is of significance in view of the current confusion that exists in the literature concerning anion radical existence of the parent cyclopropane.[11]

Experimental Section[12]

Reaction of Ethyl Sodiocyanoacetate and Ethyl Bromocyanoacetate.—The reaction was carried out by a modification of the procedure of Fenton.[1b] To a suspension of 2.0 mol of ethyl sodiocyanoacetate [prepared by adding 226 g (2.0 mol) of ethyl cyanoacetate in 500 ml of anhydrous 1,2-dimethoxyethane (glyme) to a suspension of 90 g (2.0 mol) of 50% sodium hydride dispersion in mineral oil in 1 l. of anhydrous glyme at 5°] was added 160 g (1.0 mol) of liquid bromine at −60 to −70° during 1.5 hr. When the addition was complete, the reaction mixture was held at room temperature overnight. The reaction mixture was filtered to remove sodium bromide, and the filtrate was concentrated under reduced pressure to a yellow oil. The oil was washed with two 50-ml portions of petroleum ether (bp 35–60°) and the solvent discarded. The semisolid was filtered to give 57.0 g (51%) of crude colorless **triethyl *trans*-1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate** (I). Recrystallization from ethanol afforded 45.7 g (41%) of pure product, mp 119–120° (lit.[1b] mp 122–123°). A mixture melting point with an authentic sample of I prepared by the reaction of ethyl bromocyanoacetate and potassium acetate in anhydrous glyme[13,14] showed no depression, 119–120°.

Anal. Calcd for $C_{15}H_{15}N_3O_6$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.19; H, 4.64; N, 12.72.

The infrared absorption spectrum was consistent with that reported for I.[15] There is a very weak absorption at 4.43 attributable to nitrile and at 5.68 μ for carbonyl.

The filtrate, a yellow oil, was extracted with two 50-ml portions of water. The combined water layers were evaporated to dryness to give 20 g (21%) of crude yellow product. Recrystal-

(8) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 283.

(9) M. Yu. Lukina, *Russ. Chem. Rev.*, **31**, 419 (1962).

(10) H. M. Walborsky and F. M. Hornyak, *J. Amer. Chem. Soc.*, **78**, 872 (1956), and references therein.

(11) (a) F. Gerson, E. Heilbronners, and J. Heinzer, *Tetrahedron Lett.*, 2095 (1966); (b) K. W. Bowers, G. J. Nolfi, Jr., T. H. Lowry, and F. D. Greene, *ibid.*, 4063 (1966).

(12) Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 21, ultraviolet on a Cary Model 14, and nmr spectra on a Varian Associates 60-Mc high-resolution spectrometer. Nmr spectra were obtained in deuteriochloroform using tetramethylsilane as internal standard.

(13) G. W. Griffin and L. I. Peterson, *J. Org. Chem.*, **28**, 3219 (1963).

(14) T. Sadeh and A. Berger, *Bull. Res. Council Israel*, **7A**, 98 (1958).

(15) D. G. I. Felton and S. F. D. Orr, *J. Chem. Soc.*, 2170 (1955).

lization from ethanol–ether gave 8.0 g (9%) of bright yellow salt, **sodium 1,2,3-tricyano-1,3-dicarbethoxypropenide (II)**, mp 241–246° dec. An analytic sample was prepared by recrystallization from ethanol, mp 299–300° dec.

Anal. Calcd for $C_{12}H_{10}NaN_3O_4$: C, 50.89; H, 3.56; N, 14.84. Found: C, 50.71; H, 3.80; N, 14.51.

The water-insoluble oil crystallized on standing 1 week. The solid was washed with ether and dried: yield 5.0 g (6%) of crude, colorless **diethyl 1,2,3-tricyanocyclopropane-1,2-dicarboxylate (IIIa–c)**, mp 109–111°. Recrystallization from ethanol gave 4.1 g (5%) of pure IIIa–c, mp 118–119°. A mixture melting point with I was depressed, 100–104°.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.15; H, 4.48; N, 15.78.

Reaction of Triethyl *trans*-1,2,3-Tricyanocyclopropane-1,2,3-tricarboxylate (I) with Potassium Acetate.—Powdered anhydrous potassium acetate (3.0 g, 0.03 mol) was added to a solution of triethyl *trans*-1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate in 300 ml of anhydrous glyme at 23°. The mixture was stirred for 2 days at room temperature and then evaporated to dryness under reduced pressure. The residue was recrystallized from 95% ethanol to give 4.6 g (51%) of yellow potassium 1,2,3-tricyano-1,3-dicarbethoxypropenide, mp 244–246° dec.

Anal. Calcd for $C_{12}H_{10}KN_3O_4$: C, 48.15; H, 3.37; K, 13.06; N, 14.04. Found: C, 47.96; H, 3.65; K, 13.30; N, 13.90.

The infrared absorption spectrum revealed bands at 4.54 (s) and 4.49 (w) attributable to conjugated nitrile, 5.87 (C=O), and 6.78 μ (C=C). The ultraviolet spectrum showed absorption at $\lambda_{max}^{C_2H_5OH}$ 425 mμ (ϵ 22,806) and 218 (13,678).

Reaction of Triethyl *trans*-1,2,3-Tricyanocyclopropane-1,2,3-tricarboxylate (I) with Ethyl Sodiocyanoacetate.—A suspension of ethyl sodiocyanoacetate (0.03 mol) in anhydrous glyme was prepared by adding 3.4 g (0.03 mol) of ethyl cyanoacetate to a mixture of 1.4 g (0.03 mol) of sodium hydride (as a 50% dispersion in mineral oil) in 200 ml of anhydrous glyme at 10°. The mixture was stirred and warmed at 30° until the theoretical amount of hydrogen gas had evolved. Triethyl *trans*-1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate (I, 10.0 g, 0.03 mol) in 150 ml of anhydrous glyme was added at 5–10° during 40 min. After stirring overnight at room temperature, the solvent was evaporated under reduced pressure, and the red oil (approximately 30 ml) was shaken with three 100-ml portions of ether and the combined ether washings were saved. The precipitated solid, from treatment with ether, was dissolved in warm water and filtered (in several experiments some unreacted I was recovered at this point) and the filtrate evaporated to dryness. Recrystallization of the residue from ethanol gave sodium 1,2,3-tricyano-1,3-dicarbethoxypropenide (II): yield 6.6 g (78%), mp 295° dec. A mixture melting point and comparison of infrared spectra with authentic II showed them to be identical.

The ether washings were evaporated to give a mixture of orange oil and solid. The solid was collected by filtration, washed with cold ethanol and ether, and dried: yield 1.1-g (11%) recovery of starting cyclopropane I, mp 120–122°; mixture melting point with authentic I, 120.5–122°. (I was recovered in yields up to 14% in one experiment.)

The red oily filtrate was washed with water and then allowed to stand at room temperature for 1 week. During this time a white solid crystallized. The product solid was separated from the mineral oil by filtration, washed with cold ethanol and ether, and dried: yield 0.6 g (8%) of **diethyl 1,2,3-tricyanocyclopropane-1,2-dicarboxylate (IIIa–c)**, mp 114–116°. Recrystallization from ethanol raised the melting point to 117–119°. Mixture melting point with starting cyclopropane I was depressed, 99.5–104°. Mixture melting point with authentic IIIa–c was not depressed, 118–119°. An infrared spectrum was identical with that of authentic IIIa–c. In three experiments yields of IIIa–c ranged from 4 to 8%.

Reaction of Sodium 1,2,3-Tricyano-1,3-dicarbethoxypropenide (II) with *p*-Toluenesulfonic Acid.—A solution of 2.68 g (0.014 mol) of *p*-toluenesulfonic acid in 150 ml of absolute ethanol was added to 4.0 g (0.014 mol) of sodium 1,2,3-tricyano-1,3-dicarbethoxypropenide (II) in 100 ml of absolute ethanol all at one time, with swirling, and the mixture was allowed to stand for 2 days. The red mixture was concentrated to a total volume of about 15 ml and filtered. The white solid which had been collected by filtration was washed with a small portion of cold ethanol and dried, yield 2.4 g. The solid product was then washed thoroughly with water to remove sodium *p*-toluenesulfonate and dried: yield 0.40 g (11%) of *cis*-1,2,3-tricyano-1,3-dicarbethoxypropene (VI). Recrystallization from ethanol gave 0.30 g (8.2%) of white product, mp 149.5–151°.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09; mol wt, 261. Found: C, 55.05; H, 4.24; N, 15.98; mol wt (cryoscopic method in DMSO), 245.

An infrared spectrum had absorption bands at 3.20 (C–H), 4.48 (CN), 5.95 (C=O), and 6.05 μ (C=C). The nmr spectrum showed two overlapping quadruplets (δ 4.63 and 4.60 ppm, four protons) and two overlapping triplets (δ 1.53 and 1.49 ppm, six protons), in addition to acidic proton (δ 14.65 ppm).

The filtrate from the original reaction mixture was evaporated to dryness to give an orange tacky residue. Various attempts at isolating other reaction products were unsuccessful.

Registry No.—I, 16408-63-2; II, 12259-90-4; IIIa, 16408-64-3; IIIb, 16408-65-4; IIIc, 16408-66-5; VI, 16408-67-6; potassium 1,2,3-tricyano-1,3-dicarbethoxypropenide, 12259-91-5.

Acknowledgment.—The author is deeply indebted to Dr. M. T. Jones of the Central Research Department for obtaining and interpreting the esr spectra.

Kinetics of Neutral and Alkaline Hydrolyses of Trimethylsulfonium and Benzylmethylphenylsulfonium Salts[1,2]

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Neutral Hydrolyses.—The decomposition of neutral trimethylsulfonium halides in aqueous acetone[3] or absolute ethanol[4] is a second-order process involving nucleophilic displacement of dimethyl sulfide by the anion. In contrast, trimethylsulfonium salts incorporating such relatively inert anions as perchlorate, picrate, and arenesulfonate have now been found to decompose in water solution by a first-order process. Seven different salts liberate acid at the same rate at 158°, with no important change in rate accompanying a tenfold increase in anion concentration (Table I).

TABLE I

HYDROLYSIS OF $(CH_3)_3SX$

X	Concn, *M* at 25°	Addend	Concn, *M* at 25°	Temp, °C	$10^5 k_w$, sec^{-1}
ClO_4	0.0100	None		157.8	0.37
ClO_4	0.0100	$NaClO_4$	0.100	157.8	0.37
ClO_4	0.0100	$HClO_4$	0.0100	157.8	0.39
$O_3SC_6H_5$	0.0100	None		157.8	0.41
$O_3SC_6H_4$-*p*-CH_3	0.0100	None		157.8	0.38
$O_3SC_6H_4$-*p*-Br	0.0100	None		157.8	0.36
$O_3SC_6H_4$-*p*-NO_2	0.0100	None		157.8	0.37
O_3S-β-$C_{10}H_9$	0.0100	None		157.8	0.37
OC_6H_2-2,4,6-$(NO_2)_3$	0.0100	None		157.8	0.37
ClO_4	0.0100	None		138.0	0.055

(1) Supported in part by the National Science Foundation and by the National Institutes of Health.

(2) For further details on benzylmethylphenylsulfonium salts, see the Ph.D. Thesis of B. J. Schowen, Massachusetts Institute of Technology, Cambridge, Mass., 1964.

(3) C. G. Swain and L. E. Kaiser, *J. Amer. Chem. Soc.*, **80**, 4089 (1958).

(4) E. D. Hughes, C. K. Ingold, and Y. Pocker, *Chem. Ind.* (London), 1282 (1959).

The decomposition of trimethylsulfonium perchlorate or fluoroborate in 100% ethanol at 100° is likewise independent of anion concentration.[4] The simplest mechanism consistent with these results involves a nucleophilic attack on carbon by a solvent molecule, displacing dimethyl sulfide.

Ethanolysis is more rapid than hydrolysis. The rate constant for solvolysis of trimethylsulfonium perchlorate in absolute ethanol solution at 100° is 17.8×10^{-8} sec^{-1},[3] compared to a hydrolysis constant k_w of 0.81×10^{-8} sec^{-1} extrapolated to 100° by the Arrhenius equation. This 20-fold increase in rate of solvolysis contrasts with the 20,000-fold increase in rate of decomposition of trimethylsulfonium hydroxide on changing from water to ethanol.[5]

Hydrolytic rate constants for three benzylmethylphenylsulfonium tosylates are included in Table II.

TABLE II

NEUTRAL AND ALKALINE HYDROLYSES OF BENZYLMETHYLPHENYLSULFONIUM TOSYLATES AT 60°

Benzylic substituent	$10^4 k_{H_2O}$, sec^{-1}	$10^4 k_{OH}$, M^{-1} sec^{-1}	$r^{\pm}$, Å
p-CH_3	2.00 ± 0.02	38.8 ± 3.0	1.1
H	0.2169 ± 0.0002	21.9 ± 0.2	0.9
m-Cl	0.140 ± 0.001	176 ± 3	0.7

Alkaline Hydrolyses.—The decomposition of trimethylsulfonium hydroxide, also studied at 158°, exhibits second-order kinetics and the strong negative salt effect typical of a reaction proceeding with charge destruction (Table III). An approximate value for

TABLE III

DECOMPOSITION OF $(CH_3)_3SOH$

$(CH_3)_3SOH$ concn, M at 25°	Addend	Concn, M at 25°	Temp, °C	k_2, M^{-1} sec^{-1} [a]
0.0104	None		158.0	0.0117
0.00858	$NaClO_4$	0.100	158.0	0.0077
0.00846	$NaClO_4$	0.082	158.0	0.0078
	NaOH	0.0175		
0.00840	$NaClO_4$	0.082	158.0	0.0070
	$(CH_3)_3SClO_4$	0.0174		
0.00957	None		138.0	0.0014

[a] Second-order rate constants are corrected by 9 and 7% for the thermal expansion of water at 158 and 138°, respectively.

k_2^0, the second-order rate constant at zero ionic strength, may be calculated by means of the limiting Brønsted–Debye equation

$$\log k_2 = \log k_2^0 - 2A\sqrt{\mu}$$

by substituting for k_2 the value for the run without added inert salt and for μ the average ionic strength, 0.0060, throughout the measured course of the reaction.[6] The derived k_2^0 of 0.015 M^{-1} sec^{-1} may be compared with the second-order hydrolysis constant ($k_{w2} = k_w/50.5$) of 0.73×10^{-7} M^{-1} sec^{-1} at 158°. The drastic, but still useful, assumption that hydroxide ion and water differ in nucleophilicity only because the ion is charged[7] leads to the relation

$$\Delta F^{\pm}_{el} = \Delta\Delta F^{\pm} = -RT \ln \frac{k_2^0}{k_{w2}} = -10.5 \text{ kcal}$$

where $\Delta F^{\pm}_{el}$ is the electronic free energy of activation for the hydroxide reaction. From the coulomb law expression[8]

$$\Delta F^{\pm}_{el} = -\frac{e^2}{Dr^{\pm}}$$

the value of 0.7 Å is derived for $r^{\pm}$, the transition-state charge separation,[9] if the dielectric constant of the bulk solvent at the reaction temperature is used.

Effect of Substituents on Transition-State Charge Separation.—The neutral and alkaline hydrolyses of benzyl-, *p*-methylbenzyl-, and *m*-chlorobenzylmethylphenylsulfonium tosylates at 60° proceed with nearly exclusive cleavage of the benzyl–sulfur bond. The transition-state charge separation, $r^{\pm}$, calculated the same way as above (except with $[H_2O] = 54.6$ M and $D = 63$ for 60°) and tabulated in Table II, decreases when electron-withdrawing substituents are present in the benzyl portion that is undergoing displacement. This is in qualitative accord with both the reacting bond rule[10] and the more generally applicable perturbation method of Thornton,[11] which predict that, in the transition states for these reactions, electron withdrawal at the benzyl group should result in contraction of the reacting O–C and C–S bonds, and thereby reduce the charge separation.

Experimental Section

Trimethylsulfonium Salts (Table IV).—Trimethylsulfonium perchlorate, *p*-bromobenzenesulfonate, and *p*-nitrobenzenesulfonate were prepared from trimethylsulfonium iodide and the silver salt of the appropriate acid. The benzenesulfonate, *p*-toluenesulfonate, β-naphthalenesulfonate, and picrate were prepared by adding a stoichiometric volume of the acid to an aqueous solution of trimethylsulfonium hydroxide prepared from trimethylsulfonium iodide and silver oxide. In each case the water solution of the sulfonium salt was filtered and lyophilized. The dried salt was recrystallized using methanol for the perchlorate, ethanol for the picrate, and isopropyl alcohol for arenesulfonates.

Benzylmethylphenylsulfonium Tosylates (Table IV).—Substituted benzyl tosylates were prepared from the alcohol and *p*-toluenesulfonyl chloride by the general procedure of Gilman and Beaber.[2,12] Freshly prepared benzyl tosylate was dissolved in a twofold excess of thioanisole and allowed to stand for 18 hr at room temperature. The crystalline material was removed by filtration and washed with ether. *m*-Chlorobenzyl tosylate was treated for 3 weeks with thioanisole and enough acetone to effect solution, and the product was washed with acetone and ether. Yields were 75–85%.

(5) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1955).

(6) $A = 0.67$ at 158° and 0.63 at 138°. The dielectric constant of water, interpolated from the data of G. C. Akerlof and H. I. Oshry [*J. Amer. Chem. Soc.*, **72**, 2844 (1950)] is 42.3 at 158° and 46.4 at 138°. For discussion of the limiting Brønsted–Debye equation, *cf.* S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp 427–430.

(7) It is also assumed that the gross mechanistic features are the same for both reactions, and that the decomposition of trimethylsulfonium hydroxide does not proceed *via* the ylide intermediate.

(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p 144.

(9) The electronic entropy of activation may be calculated from the relation

$$\Delta S^{\pm}_{el} = -(\partial \Delta F^{\pm}_{el}/\partial T)_p = \Delta F^{\pm}_{el} (\partial \ln D/\partial T)_p = 49 \text{ eu}$$

Cf. L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp 80–87. Activation parameters were not obtained with accuracy sufficient to provide a test of these equations, but the measured value of $\Delta\Delta S^{\pm}$, 35 ± 10 eu, indicates that the major difference in the rates of the two reactions is indeed an entropy effect.

(10) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **84**, 817 (1962).

(11) E. R. Thornton, *ibid.*, **89**, 2915 (1967).

(12) H. Gilman and N. J. Beaber, *ibid.*, **47**, 518 (1925).

TABLE IV

PROPERTIES OF TRIMETHYLSULFONIUM SALTS AND BENZYLMETHYLPHENYLSULFONIUM TOSYLATES

Formula	Registry no.	Mp, °C (cor)	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
$(CH_3)_3SClO_4$		295 dec[a]						
$(CH_3)_3SC_6H_5SO_3$		166.5–168.5[b]						
$(CH_3)_3S$-*p*-$CH_3C_6H_4SO_3$	3084-73-9	173.5–175	48.55	6.49		48.53	6.37	
$(CH_3)_3S$-*p*-$BrC_6H_4SO_3$	16317-16-1	170–172	34.51	4.18		34.62	3.94	
$(CH_3)_3S$-*p*-$NO_2C_6H_4SO_3$	16317-12-7	195–196.5	38.70	4.69		38.33	4.55	
$(CH_3)_3SC_{10}H_7SO_3$	14343-63-6	187–188.5	54.90	5.67		55.22	5.81	
$(CH_3)_3SC_6H_2N_3O_7$		198–199[c]						
$C_6H_5CH_2$ \ CH_3—$SC_7H_7SO_3$ / C_6H_5	16317-13-8	104.5–105.5	65.25	5.74	16.59	65.43	5.87	16.56
p-$CH_3C_6H_4CH_2$ \ CH_3—$SC_7H_7SO_3$ / C_6H_5	16317-14-9	107–108	65.97	6.04	16.01	65.43	5.95	15.72
m-$ClC_6H_4CH_2$ \ CH_3—$SC_7H_7SO_3$ / C_6K_5	16317-15-0	129–131	59.92	5.03	15.23	60.56	5.48	14.92

[a] K. Lohmann (Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., Jan 1959, p 67) reports mp 292°. [b] D. Vorlander [*Ber.*, 64B, 1736 (1931)] reports mp 164–166°. [c] T. R. Lewis and S. Archer [*J. Amer. Chem. Soc.*, 73, 2109 (1951)] report mp 164–166°.

Kinetics of Hydrolysis of Trimethylsulfonium Salts.—Solutions were prepared quantitatively under nitrogen atmosphere using carbonate-free water, and 7-ml samples were sealed in Pyrex ampoules. Measurements were begun after the ampoules had been in the constant temperature bath for about 30 min, and reactions were followed through two half-lives. Accurate 5-ml aliquots were titrated with 0.01 *M* sodium hydroxide to the bromthymol blue end point. Because the acid generated in the reaction was consumed by the Pyrex ampoules over long periods (up to 5% consumed after 8 days at 158°), "infinite time" points were calculated, not measured. Rate constants were evaluated by conventional first-order plots.

Kinetics of Trimethylsulfonium Hydroxide Decomposition.—Solutions containing added sodium perchlorate were prepared quantitatively under nitrogen from trimethylsulfonium perchlorate, sodium perchlorate, 0.1 *M* sodium hydroxide, and carbonate-free water. Solutions containing only sulfonium hydroxide were prepared by agitating a solution of trimethylsulfonium iodide and fresh silver oxide, filtered under nitrogen pressure, and diluted to volume. Measurements were begun after the ampoules had been in the bath for about 10 min, and the reactions were followed to 80% completion. Accurate 5-ml aliquots were treated with barium chloride and titrated with 0.01 *M* hydrochloric acid to the bromthymol blue end point. Rate constants were evaluated by conventional second-order plots.

Kinetics of Hydrolysis of Benzylmethylphenylsulfonium Tosylates.—Sufficient salt to prepare a 0.1 *M* solution (0.07 *M* in the case of the *m*-chloro derivative) was dissolved in carbonate-free water, and samples were sealed in Pyrex ampoules. Because of the limited solubility of the *p*-methyl and *m*-chloro derivatives it was necessary to maintain the solution at 60° while preparing samples. Ampoules were withdrawn periodically from the constant temperature bath, and accurate 3- or 4-ml aliquots were titrated with standard 0.1 *M* sodium hydroxide to the phenolphthalein or bromocresol green–methyl red end point. Reactions were followed through at least two half-lives. The first-order rate constants for these hydrolyses were evaluated by a computer program.[13]

Kinetics of Benzylmethylphenylsulfonium Hydroxide Decomposition.—Solutions 0.1 *M* in sulfonium salt and 0.2 *M* in sodium hydroxide in carbonate-free water were prepared under nitrogen, and samples were sealed in Pyrex ampoules. At intervals the tubes were removed from the constant temperature bath, and 3-ml aliquots were added to excess standard 0.1 *M* hydrochloric acid and back titrated with standard 0.1 *M* sodium hydroxide to the phenolphthalein end point. With the *p*-methyl and *m*-chloro derivatives the reaction was rapid enough that sealed ampoules were not used. Sufficient salt to prepare 50 ml of a solution 0.1 *M* in the methyl derivative or 0.07 *M* in the chloro derivative was dissolved in carbonate-free water at 60°. Enough aqueous sodium hydroxide to make the final solution 0.2 *M* in base was quickly added, and the entire flask was immersed in the constant temperature bath. At intervals 3-ml aliquots were withdrawn and treated as above.

All reactions were followed to at least 70% completion, and "infinite time" points were measured after at least ten half-lives. Rate constants were evaluated by means of a conventional second-order plot. Because hydrolysis of the *p*-methyl compound was a significant side reaction, a special graphic method was devised to calculate the second-order rate constant for that reaction.[2]

Products of Benzylmethylphenylsulfonium Hydroxide Decomposition.—Solutions prepared as above for the kinetic runs and allowed to stand ten half-lives at 60° were neutralized with hydrochloric acid and treated with a molarity of anisole equal to the calculated benzyl alcohol or thioanisole present. A solution for comparison, prepared by combining in aqueous sodium hydroxide the precise quantities of benzyl alcohol or *m*-chlorobenzyl alcohol and thioanisole predicted to be present in the reaction mixture, was treated in the same manner with hydrochloric acid and anisole. The dried, concentrated ether extracts of the mixtures were analyzed by glpc, using 12-ft columns of Carbowax on Chromosorb P for benzyl alcohol and silicone rubber on Chromosorb P for *m*-chlorobenzyl alcohol. The ratios of peak areas were identical with ±3% for both extracts and, after correction for relative peak sensitivity, the molar ratio of anisole/thioanisole/benzyl alcohol or *m*-chlorobenzyl alcohol was 1.0:1.0:1.0. No additional products were detected.

(13) The program used was developed by K. G. Harbison from a general onlinear least squares curve fitting Fortran subroutine, ID code OR-NLLS, by Dr. P. D. Wood, Oak Ridge National Laboratory, Tenn. All computations were performed on an IBM 7090 electronic digital computer at the MIT Computation Center.

Reaction of Carbenes with Hexafluorobenzene

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The addition of carbenes to aromatics has been well documented.[1] However, it has been suggested that

(1) See, *e.g.*, J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964.

hexafluorobenzene may serve as an inert solvent for the singlet–triplet interconversion of fluorenylidene.[2] We wish to report that certain carbenes generated from diazo compounds react with hexafluorobenzene; therefore, the latter should not generally be used as an inert solvent for carbene reactions.

Thermolysis of bis(trifluoromethyl) diazomethane[3] in excess hexafluorobenzene gave perfluoro-7,7 dimethyl-1,3,5-cycloheptatriene (Ia) in 20% yield. The tropylidene[4] constitution of the product was suggested by spectral data. The ultraviolet spectrum of Ia [$\lambda_{max}^{ethanol}$ 262 mμ (ε 6000) and 222 mμ (ε 7700)] excludes perfluoro-7,7-dimethylbicyclo[2.2.1]hepta-2,5-diene as a possible alternate structure, and is consistent with a cycloheptatriene chromophore. Another alternate structure, perfluoro-7,7-dimethylnorcaradiene (Ib), is more difficult to exclude. The tropylidene formulation is preferred, however, for the following reasons. (1) The trifluoromethyl groups are equivalent in the F^{19} nmr spectrum (triplet at +65.4 ppm from internal $FCCl_3$, J = 17 Hz; each line split further into triplets, $J \cong 1.5$ Hz; coupling constants assigned to CF_3–$F_{yy'}$ and CF_3–$F_{xx'}$, respectively) at room temperature to −99°.[5] (2) By analogy with 7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene for which the geminal trifluoromethyl groups show no tendency to force the ring into a norcaradiene form and, in fact, are believed to cause the triene ring to be more planar than usual.[3a] (3) Photoisomerization of Ia to bicyclic diene II in high yield parallels the behavior of 7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene[3a] and not that of 7,7-dicyanonorcaradiene.[6] (4) Fluorine atoms y and y′ do not appear at high enough field to be on a cyclopropane ring.[7]

Cycloheptatriene III was prepared in fair yield by the photolytic decomposition of ethyl diazoacetate in excess hexafluorobenzene. The tropylidene formulation is preferred over that of the isomeric norcaradiene because (1) a close correlation of vinylfluorine chemical shifts (see Experimental Section) with those of Ia was observed, (2) only one isomer was found (there are two norcaradienes), (3) neither the 7-carbethoxy group[8] nor ring fluorine atoms (see above) are known to cause the norcaradiene form to be stabilized, and (4) the methyne proton (τ 5.7) seems at too low a field to be on a cyclopropane ring.[9]

(2) M. Jones, Jr., and K. R. Rettig, *J. Amer. Chem. Soc.*, **87**, 4013, 4015 (1965).

(3) (a) D. M. Gale, W. J. Middleton, and C. G. Krespan, *ibid.*, **88**, 3617 (1966). (b) We are indebted to Dr. M. L. Ernsberger for suggesting this investigation.

(4) For a review of the norcaradiene–tropylidene problem, see G. Maier, *Angew. Chem. Intern. Ed. Engl.*, **6**, 402 (1967).

(5) If the norcaradiene formulation (Ib) were correct, the CF_3 groups would be expected to have different chemical shifts because of their markedly different environments, and thereby lead to a more complicated spectrum. The possibility of a rapid equilibrium between Ia and Ib, causing the CF_3 groups to become equivalent to the nmr time scale, is not excluded. Attempts to "freeze out" Ib at low temperatures were unsuccessful.

(6) E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1458 (1967). A problem with this argument is that the multiplicity of the excited state for each reaction may not be the same.

(7) P. B. Sargent, to be submitted. This argument is weakened by a lack of closely analogous model compounds.

Experimental Section

Perfluoro-7,7-dimethyl-1,3,5-cycloheptatriene (I).—A 7-g sample of bis(trifluoromethyl)diazomethane and 18 g of hexafluorobenzene (excess) were heated at 150° for 8 hr in an autoclave. Distillation (spinning band) afforded 3.9 g of product, bp 98–100° (not refluxing). Gas chromatographic analysis at 75° on a diglyceride column revealed at least 36 compounds in this fraction; a major product (68.8% of the area, 20% yield), however, was clearly present. The major "peak" was collected and shown to be perfluoro-7,7-dimethyl-1,3,5-cycloheptatriene on the basis of spectral data. Repetition of the experiment on a larger scale showed the product to have bp ~125°.

The F^{19} nmr spectrum (in CCl_4 with internal $CFCl_3$) showed a triplet (area 6) at +65.4 ppm (J = 17 Hz; split further into triplets of $J \cong 1.5$ Hz) assigned to the equivalent trifluoromethyl groups and a symmetrical "septet" (area 2) at +126 ppm (J = 17 Hz; split further) assigned to the yy′ fluorine atoms. The remaining absorption (area 4) was a "weak–strong–strong–weak" pattern (with the weak and strong lines nearly equal in intensity, however) with "weak–strong" and "strong–weak" halves (considerable further splitting) centered at +143.5 and +149.5 ppm, assigned to the aa′ and xx′ fluorines, respectively, on the basis of complexity of the splitting and their chemical shift. The spectrum was essentially unchanged at −99° (in $CFCl_3$ solvent). The infrared spectrum showed >C=C< bands at 1700 and 1650 cm^{-1}. The mass spectrum[10] showed a parent ion at m/e 336, a base peak at m/e 267 (P − CF_3), and a large fragment at m/e 217 ($C_7F_7^+$).

Anal. Calcd for C_9F_{12}: C, 32.16; F, 67.84. Found: C, 32.50; F, 68.51.

Perfluoro-2,2-dimethylbicyclo[3.2.0]hepta-3,6-diene (II).—A 1.5-g sample of the perfluorocycloheptatriene Ia was sealed in a Pyrex tube and irradiated for 2 weeks with a G. E. H85A3 lamp. The reaction was followed by nmr and uv analysis; the conversion was about 99%. The nmr spectrum (neat) clearly showed the product to be diene II ($n^{25}D$ 1.3332): $C(CF_3)_2$ as an A_3B_3 pattern split further, centered at +68.5; >CF− at +178 and +180; vinyl-F at +120 (a quartet, J = 10 Hz; split further), +126, +143, and +148 (chemical shifts given in parts per million from external $FCCl_3$). The ultraviolet spectrum showed end absorption. The infrared spectrum showed double bonds at 1776 and 1745 cm^{-1}. The mass spectrum[10] showed a parent ion at m/e 336, a base peak at m/e 267 (P − CF_3), and a large fragment at m/e 217 ($C_7F_7^+$).

Anal. Calcd for C_9F_{12}: C, 32.16; F, 67.84. Found: C, 32.48; F, 67.70.

Ethyl 2,3,4,5,6,7-Hexafluoro-2,4,6-cycloheptatrienecarboxylate (III).—A 2-g sample of ethyl diazoacetate (Aldrich Chem. Co.) dissolved in 200 g of hexafluorobenzene was irradiated for 96 hr with a sun lamp through Pyrex. Copper powder (0.5 g) was added and the suspension was stirred and refluxed for 6 hr. (In another experiment, the copper powder and refluxing were omitted and a comparable result was obtained.) The copper powder was filtered off, most of the hexafluorobenzene was removed at 40° (100 mm), and the remaining material was distilled through a spinning-band column. The product, bp 55° (2.5 mm), 0.5 g (16%), was shown to be fluorinated cycloheptatriene III. The mass spectrum showed the parent ion at m/e 272, peaks at m/e 244 (P − ethylene) and m/e 227 (P − OCH_2CH_3), and a

(8) E. Ciganek, *J. Amer. Chem. Soc.*, **87**, 1149 (1965).

(9) The reaction of a carbene with hexafluorobenzene was discovered independently by Professor M. Jones, Jr. We are indebted to Professor Jones for informing us of this work prior to publication.

(10) Partly fluorinated analogs show a similar cracking pattern: D. M. Gale, *Tetrahedron*, **24**, 1811 (1968).

base peak at m/e 199 ($C_7F_6H^+$). The H^1 nmr spectrum (CCl_4) showed a triplet (J = 7½ Hz) at τ 8.70 ($-CH_3$) and a quartet at 5.71 (CO_2CH_2-) superimposed on a multiplet for the methyne proton. The F^{19} nmr spectrum showed three multiplets of equal area (in CCl_4 from external fluorotrichloromethane). The following assignments were made using F–F and F–H spin–spin decoupling: $J_{HFAA'}$ = 22.5 Hz; δ_A 110 ppm, δ_B 149 ppm, and δ_C 155 ppm. When the BB'CC' portion of the spectrum (A decoupled) was assigned $J_{BB'}$ = 19, J_{BC} = $J_{B'C'}$ = 3.5, $J_{B'C'}$ = $J_{BC'}$ = 26.5, and $J_{CC'}$ = 1 or 2 Hz, reasonable (but not exact) fits were obtained when observed, and computer-calculated spectra were compared. The spectrum remained essentially unchanged to −99° (in $CFCl_3$ solvent).

Anal. Calcd for $C_{10}H_6F_6O_2$: C, 44.13; H, 2.22. Found: C, 44.17; H, 2.77.

Registry No.—Ia, 16021-14-0; II, 16021-15-1; III, 16021-16-2; hexafluorobenzene, 392-56-3.

The Addition of Cyclopentadienylidene to Hexafluorobenzene[1]

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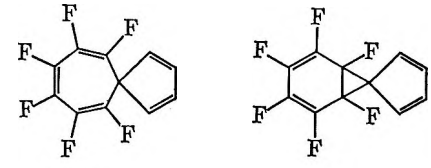
In the course of our investigations of reactions of carbenes in hexafluorobenzene we chanced to observe that, whereas fluorenylidene[3] does not react with hexafluorobenzene, the more reactive cyclopentadienylidene[4] does. The caveat of Gale[5] should therefore certainly be heeded: hexafluorobenzene is by no means always inert toward divalent carbon.

Irradiation of a solution of diazocyclopentadiene in hexafluorobenzene with a medium-pressure Hanovia mercury arc gave, after removal of the hexafluorobenzene and bulb-to-bulb distillation, a yellow oil in *ca.* 30% yield. The high resolution mass spectrum establishes the composition as $C_{11}F_6H_4$. The infrared spectrum shows evidence of carbon–fluorine bonds by several strong bands in the 1000–1400-cm^{-1} region and of fluorinated double bonds by a strong band at 1682 cm^{-1}.[6] The pmr spectrum shows a single symmetrical signal centered at τ 3.59; the ^{19}F nmr[7] spectrum shows three multiplets of equal intensity centered at 110, 145, and 151 ppm upfield from internal fluorotrichloromethane. The ultraviolet spectrum exhibits maxima at 221 and 266 mμ (ϵ 7300 and 3600).

In considering the structure of the adduct, attention is inevitably focused on I and II. While the products of additions of carbenes to benzenes are usually (but not always[8]) tropilidenes, it might be expected that the notorious[9,10] preference of fluorine for saturated over unsaturated carbon would lead to the norcaradiene being favored. Two facts argue strongly against structure II. First, one would not expect a symmetrical pmr pattern



I II

for II, and, second, there appears to be no signal in the ^{19}F nmr spectrum at high enough field to be reconcilable with a tertiary cyclopropyl fluorine.[11–13a] Accordingly we prefer structure I. The question arises as to why the tropilidene is favored over the norcaradiene which has two fewer fluorines on double bonds. Conceivably the aversion of fluorine for double bonds is an effect of hybridization[14] and fluorine feels little difference between a carbon–carbon double bond and a cyclopropane ring. This would also explain why the fluorine in fluorobullvalene prefers the triallylic rather than cyclopropyl position.[10] Other structures which fit the nmr data and which contain exocyclic double bonds can be constructed, but these suffer a variety of deficiencies including the lack of an appropriate infrared stretching frequency and extreme mechanistic improbability.

On heating, either in a flow system or on incautious gas chromatography, I rearranges cleanly to III. The infrared spectrum is qualitatively similar to that of I, but the ultraviolet spectrum shows a maximum at 250 mμ (ϵ 6 040) and a shoulder at 290 mμ (ϵ 2200) and the pmr spectrum has undergone a striking change. There are now two signals of equal area at τ 3.25 (symmetrical multiplet) and 6.54 (multiplet). These are thought to correspond to two vinyl protons and to two protons adjacent to an extensively conjugated system. Indene is a good model and shows, in addition to peaks for aromatic protons, a symmetrical multiplet at τ 3.35 and

(1) We thank the National Science Foundation for support of this work in the form of GP-5257. Grants GP-6803 and GP-5200 to Princeton University for the purchase of high resolution mass and nuclear magnetic resonance spectrometers are also gratefully acknowledged. We further thank the Lilly Research Laboratories for a generous unrestricted grant.

(2) Alfred P. Sloan Research Fellow, 1967–1968.

(3) M. Jones, Jr., and K. R. Rettig, *J. Amer. Chem. Soc.*, **87**, 4013, 4015 (1965).

(4) R. A. Moss, *J. Org. Chem.*, **31**, 3296 (1966).

(5) D. M. Gale, *ibid.*, **33**, 2536 (1968). We thank Dr. Gale for advising us of his work and for graciously suggesting simultaneous publication.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, pp 42 and 329.

(7) We are most grateful to Drs. B. Stewart of the Allied Chemical Co., Morristown, N. J., and L. A. Wilson of Varian Associates, Linden, N. J. for measuring the fluorine nmr spectra.

(8) E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1454 (1967).

(9) E. W. Schlag and W. B. Peatman, *ibid.*, **86**, 1676 (1964).

(10) G. Schröder and J. F. M. Oth, *Angew. Chem. Intern. Ed. Engl.*, **6**, 414 (1967).

(11) This is not an easy assignment to make. If one takes 142 ppm as the shift of geminate cyclopropyl fluorines,[12] then the usual shift to higher field of *ca.* 50–60 ppm in going to the tertiary system leads to an estimate of 190–200 ppm. Addition of a double bond, thus making the fluorine allylic, should lead to a downfield shift of 7–15 ppm.[12,13] The final estimate of 180–190 ppm for structure II seems significantly higher than any signal in the spectrum. A similar treatment for cyclobutenyl fluorine leads to a prediction of 175 ppm in good agreement with the shifts of 178 and 180 ppm observed by Gale.[5]

(12) R. A. Mitsch, *J. Amer. Chem. Soc.*, **87**, 758 (1965).

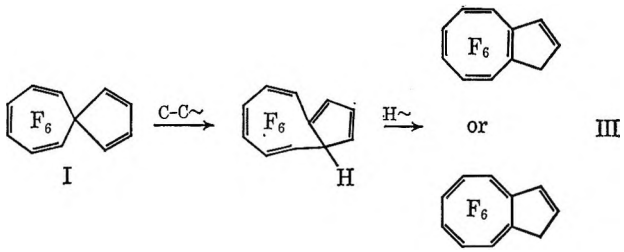
(13) J. W. Emsley, J. Feeney, and L. M. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Ltd., London, 1966, Chapter 11.

(13a) NOTE ADDED IN PROOF.—1,2,3,4,5,6-Hexafluorotropilidene has recently been synthesized. Here the distinction between tropilidene and norcaradiene is easy. The ^{19}F nmr of this compound (signals at 113, 146, and 156 ppm upfield of fluorotrichloromethane) is very similar to that of I. Accordingly the assignment of structure I seems secure: L. S. Kobrina, G. G. Yakobson, and N. N. Vorozhtsov, *Zh. Vses. Khim. Obshchest.*, **12**, 597 (1967).

(14) D. Peters, *J. Chem. Phys.*, **38**, 561 (1963).

a triplet at τ 6.67.[15] The fluorine nmr spectrum of III shows peaks for six different fluorines grouped roughly in pairs at 107, 113, 120, 122, 131, and 133 ppm upfield from internal fluorotrichloromethane.

These chemical shifts seem inconsistent with any structure containing the valence–tautomeric bicyclo[4.2.0] system[11] and III is preferred, although the structure cannot be regarded as unequivocably proved.



A mechanism for the conversion of I into III can be constructed and involves a carbon–carbon bond shift (possibly in the norcaradiene form II) followed by a hydrogen shift. These steps have rather good analogy, albeit in much more simple systems.[16–18]

Experimental Section

Spiro[4.6]-6,7,8,9,10,11-hexafluoroundeca-1,3,6,8,10-pentaene (I).—A solution of 1 ml of diazocyclopentadiene[19,20] in 122 g of hexafluorobenzene was irradiated through a Pyrex filter with a 450-W Hanovia medium-pressure mercury arc for 14 hr. The hexafluorobenzene was removed by distillation at 0.1 mm leaving a dark brown, thick oil. This was distilled in a bulb-to-bulb apparatus at room temperature and 0.025 mm to yield 500 mg of a yellow oil. Spectral analysis revealed this to be I contaminated with traces of dicyclopentadiene.

Anal.[21] Calcd for $C_{11}H_4F_6$: C, 52.82; H, 1.61. Found: C, 53.01; H, 1.72.

Pyrolysis of I. A. Flow System.—A solution of 10 mg of I in 0.5 ml of cyclohexane was dropped slowly into a 12-in. Pyrex tube packed with glass helices under nitrogen at 220°. Residence time was *ca.* 1 sec. Under these conditions I is converted into a mixture of 40% I and 60% III with *ca.* 90% recovery. Increasing the temperature to 255° resulted in 90–95% conversion into III with somewhat reduced recovery.

B. Gas Chromatography.—Compound I is easily converted into III in the injector or detector–collector of a gas chromatograph. The peak corresponding to I is simply collected and reinjected. Injection on a 5-ft SE 30 silicone oil column operated at 95° (injector, 130°, and detector, 210°) with a flow rate of 100 cc of helium/min results, as revealed by reinjection, in *ca.* 25% I (retention time 22 min) and 75% III (retention time 42 min, mp 50–52°).

Anal. Found: C, 52.71; H, 1.66.

Registry No.—I, 16033-88-8; III, 16021-17-3; diazocyclopentadiene, 1192-27-4; hexafluorobenzene, 392-56-3.

(15) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 227.

(16) J. W. De Haan and H. Kloosterziel, *Rec. Trav. Chim. Pays-Bas*, **84**, 1594 (1965), and references therein.

(17) W. R. Roth, *Tetrahedron Lett.*, 1009 (1964).

(18) S. McLean and R. Haynes, *ibid.*, 2385 (1964).

(19) W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, **75**, 5955 (1953).

(20) T. Weil, *J. Org. Chem.*, **28**, 2472 (1963).

(21) Although acceptable carbon and hydrogen analyses could be obtained on I, fluorine analysis was poor. We do not know the precise cause of this but can point out that I is most unstable. Exposure to air results in rapid darkening and eventual deposition of a brown-black solid.

Electron-Transfer Polymers. XXXIII. Compounds Related to Tocopherol

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Redox polymers[1a] have been prepared by polycondensation of 2,5-disubstituted benzoquinones.[1b] In the resulting linear polymers the redox group is part of the chain. In this paper we report the preparation of redox monomer from a quinonyl glycol. In this polymer the redox groups are pendant from the chain.[2] In the course of preparing this monomer several interesting new compounds, analogs of tocopherol derivatives, were prepared, and new behaviors were observed.

Trimethylhydroquinone (1,3,4-trimethyl-2,5-dihydroxybenzene) was converted into 3-hydroxy-6-methoxy-2,4,5-trimethylbenzyl chloride (I).[3] Treatment with sodioethyl malonate produced ethyl(3-hydroxy-6-methoxy-2,4,5-trimethylbenzyl)malonate (II). Reduction of II with lithium aluminum hydride yielded 2-(3′-hydroxy-6′-methoxy-2′,4′-5′-trimethylbenzyl)propane-1,3-diol (III). (See Chart I.) Oxidative cleavage of the methoxy group in III with lead tetraacetate suspended in 50% aqueous tetrahydrofuran (THF) produces the desired monomer, 2-(duroquinonyl)propane-1,3-diol (V), as yellow crystalline material. If, however, III is oxidized with lead tetraacetate suspended in dry THF there is produced a white, crystalline material with a carbonyl band at 1683 cm^{-1}, and no hydroxyl band in the ir spectrum and λ_{max} at 244 mμ (ϵ 1.09 × 10^4) in the uv spectrum. The uv spectrum closely resembles that of 9-substituted α-tocopherol.[4] This new substance appeared to be 8a,3-epoxymethano-5,7,8-trimethyl-6H,8aH-dihydrochroman-6-one (IV). Then IV, shaken with cation exchange resin in the acid form in 50% aqueous THF, gives V in good yield. Reduction of IV in the presence of palladium charcoal yields 3-hydroxymethyl-5,7,8-trimethylchroman-6-ol (VII) quantitatively. Reoxidation of VII produces IV by using ceric ammonium nitrate or silver oxide in dry THF quantitatively. When yellow V is reduced in an attempt to obtain 2-(durohydroquinyl)propane-1,3-diol (VI), a white crystalline material could be isolated but in air it quickly oxidizes to red (quinhydrone!) then yellow quinone V. If the reduction is carried out in acid, there is obtained stable VII, presumably *via* VI. When the methoxy group of III is cleaved with HCl, there is formed VII, presumably *via* the VI pathway (Chart I). These behaviors bear strong analogy to those of the tocopherols. Structure VII differs from α-tocopherol only in the substituents on the oxygen ring. When the corresponding ring is opened there is

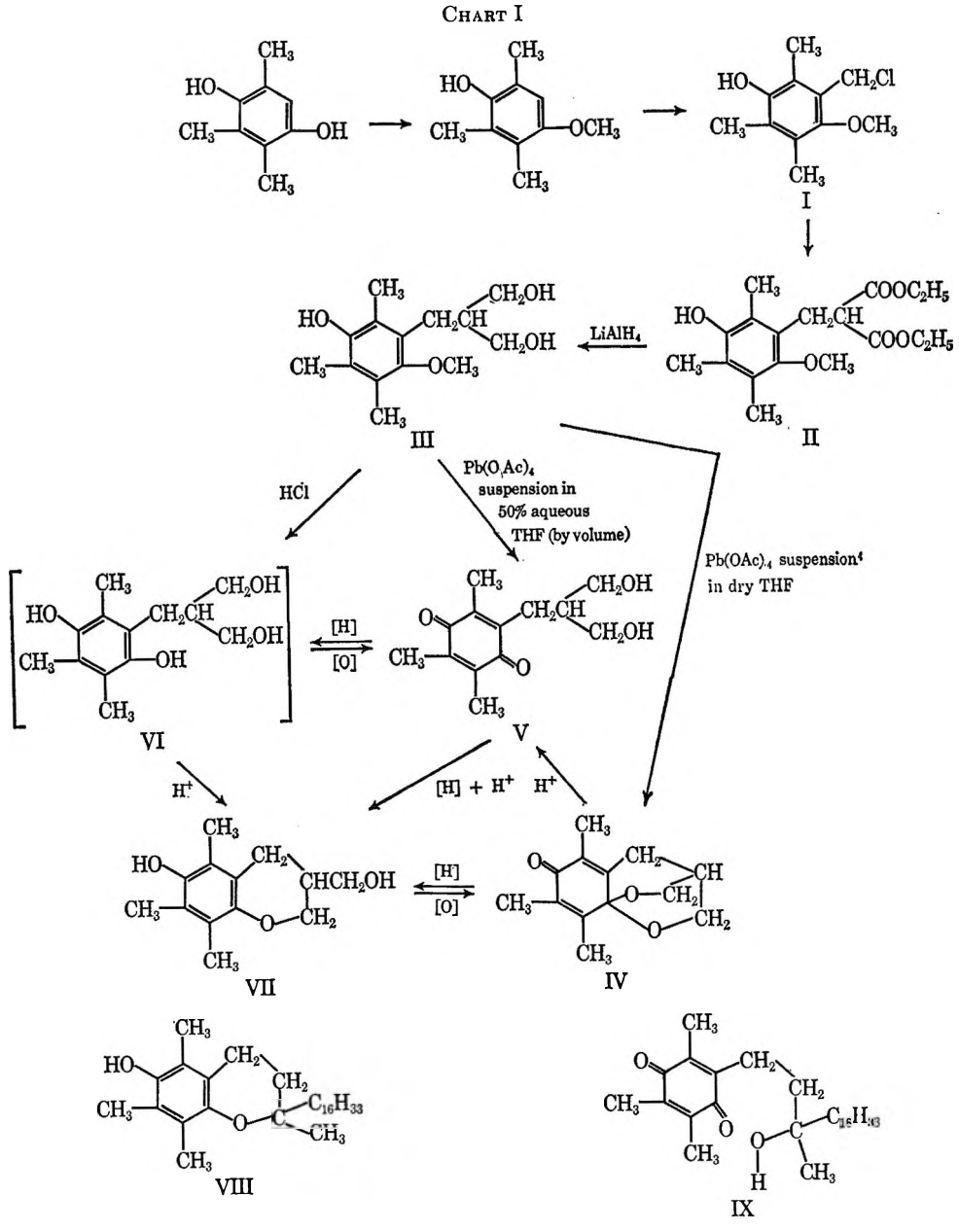
(1) (a) H. G. Cassidy and K. A. Kun, "Oxidation–Reduction Polymers," Interscience Publishers, Inc., New York, N. Y., 1965; (b) G. Wegner, N. Nakabayashi, and H. G. Cassidy, *J. Org. Chem.*, **32**, 3155 (1967).

(2) Syntheses and properties of the polymers will be published elsewhere.

(3) W. John and F. H. Rathmann, *Ber.*, **74**, 890 (1941).

(4) W. H. Harrison, J. E. Gander, E. R. Blakley, and P. D. Boyer, *Biochim. Biophys. Acta*, **21**, 150 (1956).

CHART I



obtained the unstable hydroquinone which is readily oxidized to α-tocopherolquinone (IX).[5,6]

The intriguing correspondence of IV, V, VI, and VII to 9-substituted-α-tocopherone, α-tocopherolquinone (IX), α-tocopherolhydroquinone, and α-tocopherol (VIII)[4,6] leads us to point out the important role of the γ-hydroxyl. The redox potential of durohydroquinone is low; the hydroquinone form is very easily oxidized. By building into the molecule a suitably placed hydroxyl we provide automatic stabilization of the reduced form (VII) through ring closure.

Experimental Section

Preparation of II.—To a sodium ethylate solution [6.10 g (0.265 g-atom) of sodium in 135 ml absolute ethanol] was added 23.2 g (0.145 mol) of ethyl malonate in 40 ml of absolute ethanol, dropwise with cooling. After 15 min, 28.2 g (0.131 mol) of I in 100 ml of dry THF was added slowly. The reaction mixture was refluxed 1.5 hr. Refluxing longer than 2 hr decreased the yield. After neutralization with acetic acid, the solvent was removed and the residue was suspended in water and extracted with ether. The ether solution was dried with magnesium sulfate, the solvent was removed, and the residue was crystallized from carbon tetrachloride (refrigerator) to yield 13.9 g (31.4%) of white crystals: mp 118–119°; ir spectrum, OH (3475), C=O (1750, 1725), -CO- (1250 cm^{-1}); nmr,[7] CH_3 (ring) and CH at τ 7.90 and 7.84 (10) and α-CH_2 at 6.80 (2), C_2H_5 (ester) at 8.81 (6) and 5.88 (4) CH_3-O- at 6.38 (3).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.75. Found: C, 63.90; H, 7.68.

When the synthesis was carried out with 1.20 g (0.052 g-atom) of sodium, 8.0 g (0.050 mol) of ethyl malonate, and 10.7 g (0.050 mol) of I, a yield of 5.3 g (31%) of II was obtained.

Preparation of III.—To a stirred suspension of 1.2 g of lithium aluminum hydride in 50 ml of dry THF, cooled in ice, was added dropwise 50 ml of THF containing 5.5 g (0.0162 mol) of II. After the vigorous reaction had subsided the mixture was refluxed for 2 hr. Excess hydride was removed by careful addition of water, and the mixture was neutralized with acetic acid. Saturated aqueous ammonium chloride solution was added, and the upper, organic layer was decanted. The water layer was washed with ether, and the washings and organic layer were combined and dried with magnesium sulfate. The solvent was removed by evaporation from the dried mixture, and the residue

(5) J. Bunyan, D. McHale, and J. Green, *Brit. J. Nutr.*, **17**, 391 (1963).
(6) J. Green and D. McHale in "Biochemistry of Quinones," R. A. Morton, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 8.
(7) Nmr data were obtained with a Varian Associates Model A-60 spectrometer. The chemical shifts are given in τ values; the numbers within parentheses indicate the number of protons.

was recrystallized from methanol to give 2.55 g (61.5%) of white crystals: mp 173–175°; ir, OH (3415, 3308), -C-O (1240, 1167, and 1036 cm^{-1}); nmr,[7] CH_3 (ring) and CH at τ 8.03, 7.88, 7.71 (total 10), α-CH_2 at 7.23 (2), CH_3O at 6.63 (3), $-CH_2O-$ at 6.17 (4).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.72; H, 8.57.

Preparation of IV and V. A.—To a stirred solution of 0.62 g (0.0024 mol) of III in 20 ml of dry THF was added 1.2 g (0.0027 mol) of lead tetraacetate. The suspension was refluxed 15 min. Aqueous sodium hydroxide was added and the mixture was extracted with ether. On evaporation of the solvent from the dried ether solution there was obtained a red-yellow oily residue. This was dissolved in a small amount of acetonitrile and refrigerated. White plates crystallized in a yield of 0.15 g (28%), mp 159–160°. From the mother liquor, by recrystallization from THF–*n*-heptane a further yield of 0.13 g (23%) of white crystals, mp 159–160°, was obtained, and 0.07 g (12%) of yellow crystals melting at 79–79.5° were also obtained. The white crystalline material is IV and the yellow is V.

Anal. Calcd for $C_{13}H_{16}O_3$ (IV): C, 70.89; H, 7.32. Found: C, 71.02; H, 7.28.

Calcd for $C_{13}H_{18}O_4$ (V): C, 65.53; H, 7.61. Found: C, 65.46; H, 7.58.

The ir spectrum of IV showed C=O at 1683, 1644, and 1633 (C=C) and -C-O- at 1260, 1197, 1099, and 1040. That for V showed -OH at 3285; C=O (quinone) at 1630; and -CO- at 1303, 1260, and 1070 cm^{-1}. The nmr spectra[7] of IV showed CH_3 (ring) and CH_2 at 8.00 (3), 8.14 (6), and 7.77 (1); α-CH_2 at 7.24 (2); $-CH_2-O$ at 6.06, 5.91, 5.72, and 5.58 (total 4).

B.—To 22.0 g (0.0866 mol) of III in 700 ml of THF was added 700 ml of water, then 44.0 g (0.995 mol) of lead tetraacetate. The suspension was stirred and refluxed for 30 min. After addition of sodium hydroxide, extraction with ether, and drying and evaporation of the ether, there was obtained a red-yellow residue. This was dissolved in a small amount of THF, and *n*-heptane was added. Compound V crystallized. The crude material was recrystallized from THF–*n*-heptane to yield 11.0 g (63.4%), mp 79.0–79.5°. From the mother liquor there was obtained 2.0 g (10.5%) of IV.

Preparation of VII. A.—A suspension of 1.0 g (0.0039 mol) of III in 30 ml of water and 30 ml of concentrated hydrochloric acid was refluxed, with stirring, for 9.5 hr. On cooling, the product crystallized. Recrystallization from acetonitrile gave 0.62 g (72%) of VII as white crystals: mp 171–172°; ir spectrum, OH [3300, 3150, (chromanol, 1610)] and -C-O- (1255, 1241, 1125 cm^{-1}); nmr,[7] CH_3 (ring) and CH at 8.29, 8.25, 8.17, (total 10), CH_2 at 7.92 (2), $-CH_2O-$ at 6.69 (2), and 6.43 (2).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.16. Found: C, 70.06; H, 8.09.

B.—A solution of 0.50 g (0.0023 mol) of IV in 20 ml of THF was shaken in an atmosphere of hydrogen with a catalytic amount of 10% palladium charcoal at room temperature. Within 10 min 60 cc of hydrogen was absorbed (theory, 51 cc; probably the excess went to the solvent.) From the filtered solution there was obtained a pale yellow powder which on recrystallization from acetonitrile, yielded 0.40 g (80%) of white crytals, mp 171–172°. No depression was observed in mixture melting point with VII.

C.—A solution of 0.5 g (0.0021 mol) of V in 5 ml of glacial acetic acid and 15 ml of water was refluxed with 0.5 g of zinc powder for 0.5 hr. The mixture was neutralized with sodium hydroxide, extracted with ether, and the extract was dried and evaporated. The reddish residue was recrystallized from acetonitrile to give 0.28 g (60%) of VII, mp 171–172°.

Oxidative titration of VII with ceric ammonium nitrate in 90% aqueous acetic acid at 25° gave an equivalent weight of 114.5 (calcd, 111). The midpoint potential was about 0.657 V.

Ultraviolet Spectra.—The solvent, λ_{max} in mμ, and the molar extinction coefficient are given in that order: IV (CH_2Cl_2, 244, 1.09×10^4); V (CH_2Cl_2, 272, 1.65×10^4; CH_3OH, 269, 1.99×10^4); VI (CH_3OH, 289, 3.9×10^3); VII (CH_2Cl_2, 296, 2.29×10^3).

Registry No.—II, 16526-47-9; III, 16526-48-0; IV, 16526-49-1; V, 16526-50-4; VII, 16526-51-5; VIII, 16526-52-6.

Acknowledgment.—We thank Mrs. Irmlind Stronkowski for technical assistance. The work was supported by Research Grant GM 10864 from the Research Grants Branch, National Institute of General Medical Sciences, U. S. Public Health Service, for which we express our thanks.

Reaction of Pseudoxazolones and Hydrazoic Acid

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The reaction of 4-arylidene-5-oxazolones with hydrazoic acid was reported by Awad, *et al.*[1,2] to produce tetrazolylacrylic acid derivatives in good yields. In examining the reactivity of 2-isopropylidene-4-methyl-3-oxazolin-5-one[3] (Ia, pseudooxazolone) with more than 2 mol of hydrazoic acid, we obtained white crystalline materials in 38% yield by their reaction condition as shown in Table I.

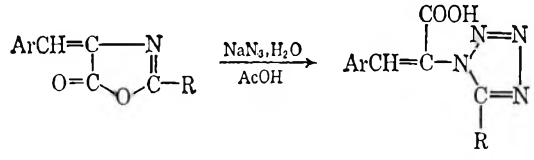


TABLE I

ELEMENTAL ANALYSES OF IV

R	Mp, °C	Crude yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Me	210[a]	38	42.40	6.56	38.10	42.77	6.61	37.81
i-Pr	216[a]	71	48.10	7.60	33.00	48.59	7.55	32.18
i-Bu	216[a]	96	50.50	8.01	30.90	50.71	7.94	30.95

[a] Melted with decomposition.

That this product was a urea derivative was established by several spectral methods. The infrared spectrum showed strong absorptions at 3310, 2140,[4] and 1660 cm^{-1} arising from amide and urea N–H stretching, azide asymmetric stretching, and amide and urea carbonyl stretching vibrations, respectively. The nmr spectrum of the product displayed a 12-proton singlet at δ 1.44 due to four *gem*-methyl groups, a 6-proton doublet centered at 1.47; a 2-proton quartet centered at 5.65 (J = 6 cps); and a broad NH proton singlet at 3.66 in pyridine.

Mass spectra of IV offered a good indication of the presence of azide linkages and of the structure of IV. Each peak corresponded well to fragments formed from the molecular ion peak by cleavage at positions as shown in Chart I. In addition, elimination of methyl and isobutyl radicals gave rise to m/e 353 and 395 in IVa and IVc, respectively.

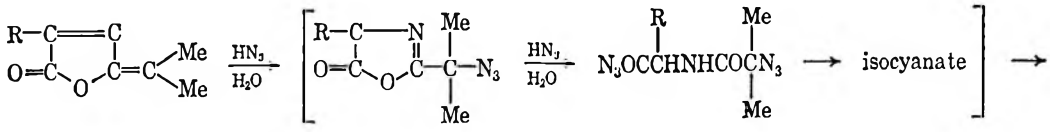
The first step in this transformation is postulated to be 1,4 addition of hydrazoic acid to I forming a satu-

(1) W. I. Awad, A. F. M. Fahmy, and A. M. A. Sammour, *J. Org. Chem.*, **30**, 2222 (1965).

(2) H. Behringer and W. Grimme, *Chem. Ber.*, **92**, 2967 (1959).

(3) Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron*, **22**, 3363 (1967).

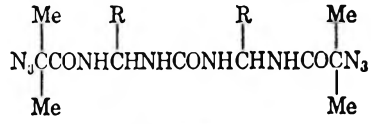
(4) C. N. R. Rao, T. S. Chao, and C. W. W. Hoffman, *Anal. Chem.*, **29**, 916 (1957).



Ia, R = Me
b, R = *i*-Pr
c, R = *i*-Bu

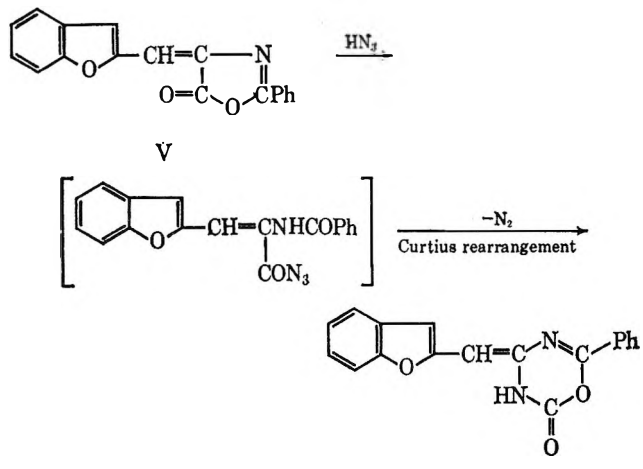
IIa, R = Me
b, R = *i*-Pr
c, R = *i*-Bu

IIIa, R = Me
b, R = *i*-Pr
c, R = *i*-Bu



IVa, R = Me
b, R = *i*-Pr
c, R = *i*-Bu

rated 5-oxazolone (II) containing an alkyl azide group.[5,6] The acyclic intermediate (III) can then undergo Curtius rearrangement to the azido isocyanate which would immediately produce a symmetrical urea (IV) in the presence of water. For an example of the similar type of reaction, an oxadiazinone compound (VI) is prepared from hydrazoic acid and the 5-oxazolone (V) of 2-formylbenzofuran derivative *via* an isocyanate intermediate.[7]



V

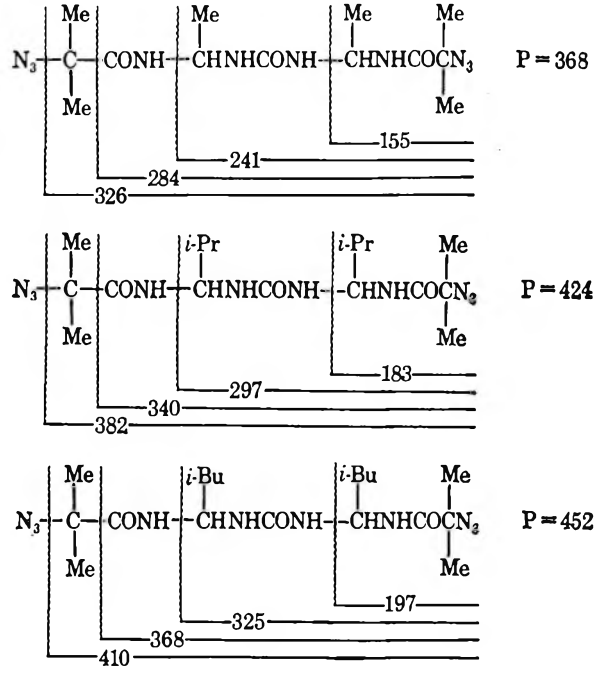
VI

Although we tried to make IVb react with two dipolarophiles, N-phenylmaleimide and N-morpholino-1-cyclohexene, to see whether triazoline derivatives could be obtained, IVb was recovered unchanged by the procedure reported in the literature[8,9] presumably owing to its steric hindrance. In fact, *t*-butyl azide does not satisfactorily form such derivatives as mentioned above.[10]

Experimental Section

A solution of sodium azide (10 g in 20 ml of water) was added to a solution of Ib (10 g in 20 ml of acetic acid) and the mixture was heated on a water bath for 1 hr. (In the case of Ia, a violent exothermic reaction occurred suddenly on heating). The resulting reaction slurry was then poured on crushed ice and the precipitate was collected, washed with water, and dried. The yield of the crude crystals of IVb was 71%. The crystals were recrystallized from a large amount of ethanol.

CHART I
FRAGMENT ION PEAKS OF IV



Major peaks in mass spectra were as follows: IVa, *m/e* 368, 353, 326, 284, 241, 225, 155, 113, 70, 56, 44, 42; IVb, 382, 340, 297, 253, 183, 169, 156, 125, 98, 72, 56, 43, 42; IVc, 410, 395, 368, 325, 267, 197, 86, 70, 69, 56, 44, 43, 42.

Nmr measurements. Nmr spectra were recorded on a Japan Electron Optics Lab. Co., Ltd. Model 4H-100, as an *ca.* 10% solution in CCl_4 with tetramethylsilane as an internal standard at 90°.

Registry No.—IVa, 16012-04-7; IVb, 16012-05-8; IVc, 16012-06-9; hydrazoic acid, 7782-79-8.

Acknowledgment.—We wish to thank Dr. J. Okamoto, of Hitachi, Ltd., for kindly obtaining the mass spectra and Dr. Kenzo Fujii, of Toyo Koatsu Ind., Inc., for kindly determining the elemental analyses.

(5) Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron Lett.*, 5461 (1966).
(6) W. Steglich, H. Tanner, and R. Hurnaus, *Chem. Ber.*, **100**, 1824 (1967).
(7) D. S. Deorha and P. Gupta, *J. Indian Chem. Soc.*, **42**, 199 (1965).
(8) R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkene," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 739.
(9) R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849 (1961); *Chem. Abstr.*, **56**, 14019*f* (1962).
(10) P. A. S. Smith, J. M. Clegg, and J. Lakritz, *J. Org. Chem.*, **23**, 1595 (1958).

The Synthesis of Fused Azolones from *ortho*-Substituted Arenecarbohydroxamic Acids

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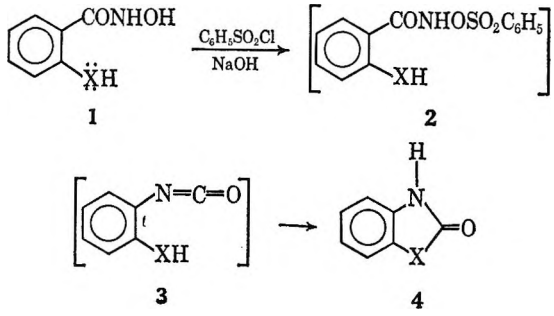
It has been observed that sulfonyl halides convert benzohydroxamic acid into O-phenylcarbamoyl benzohydroxamate,[2] the product of O-acylation of the hydroxamic acid by the expected degradation product, *viz.*, phenyl isocyanate. A cognate reaction on phthalohydroxamic acid (**1**, XH = CONHOH) proved to be somewhat different: one of the hydroxamic acid groups was degraded to an isocyanate, which then N-acylated the neighboring hydroxamic acid to form 3-hydroxy-2, 4-quinazolinedione [**4**, X = CON(OH)].[3]

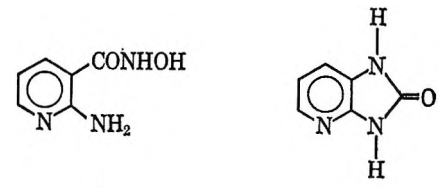


1 **2** **3** **4**

In the present study, anthranilo- and salicohydroxamic acids were subjected to benzenesulfonyl chloride in dilute aqueous sodium hydroxide solution at 25°. In these systems (**1**, XH = NH_2 or OH), it is predictable that the excellent nucleophilicity of the hydroxamate ion[4] would dictate preferential reaction with the acid halide to form an O-sulfonyl hydroxamate (**2**) faster than the sulfonamide or aryl sulfonate. On such a premise and the known rapid degradation[2,5] of **2** to **3**, the reaction sequence took place as anticipated, the final step being the cyclization of **3** to **4**. It was found that benzenesulfonyl chloride converted anthranilohydroxamic acid into 2-benzimidazolone (**4**, X = NH) quantitatively. This synthesis represents a considerable improvement over the Lossen rearrangement of O-benzoyl anthranilohydroxamate previously reported (in unspecified yield).[6] 2-Benzimidazolone was also produced in apparently negligible yield from two less conventional Lossen degradations, from the pyrolyses of either anthranilohydroxamic acid at 150–170° for 7 min[7] or sodium anthranilohydroxamate "until evidence of sublimation was noted."[6] It should be noted that the 2-benzimidazolone was the product of the related Hofmann rearrangements of anthranilamide (34%)[8] and the Curtius rearrangement of anthraniloyl azide (45%).[7]

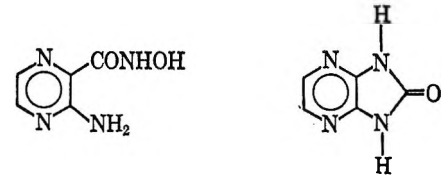
Salicylohydroxamic acid (**1**, X = OH) reacted quickly with benzenesulfonyl chloride to furnish 2-benzoxazolone (**4**, X = O), in excellent yield. This preparation of 2-benzoxazolone represents an improvement over the one utilizing the "standard" Lossen rearrangement, *via* O-benzoyl salicylohydroxamate,[9] or by the more unusual reaction of salicylohydroxamic acid with thionyl chloride.[10]

In view of the successful application of this modified Lossen rearrangement using sulfonyl halides, the behavior of two heteroaromatic amino hydroxamic acids was examined. The only Lossen type of reaction hitherto reported for 2-aminonicotinohydroxamic acid (**5**) was its pyrolysis at 210–220° for 5 min to give, among other products, a minute quantity of the fused imidazolone, **6**.[7] However, benzenesulfonyl chloride



5 **6**

transformed **5** into **6** in excellent yield. It is of interest to note that the related Hofmann rearrangement on 2-aminonicotinamide[8,11] and the Curtius rearrangement on 2-aminonicotinoyl azide[7,11] afforded **6** in 34%[8] and 96%[7] yield, respectively.



7 **8**

The other example described in this work involved 2-aminopyrazinecarbohydroxamic acid, **7**.[12] Rearrangement of **7** with benzenesulfonyl chloride readily made **8** available in 60–70% yield. Although **8** can be obtained in good yield from the fusion of 2,3-diaminopyrazine with urea at 160° for 2 hr,[13] the synthesis of the diamine is quite tedious whereas the starting material for the present synthesis, 2-amino-3-pyrazinecarboxylic acid is commercially available.[14]

(1) National Science Foundation Trainee.

(2) D. Samuel and B. L. Silver, *J. Amer. Chem. Soc.*, **85**, 1197 (1963), and references quoted therein.

(3) For a review of these reactions, see L. Bauer and C. S. Mahajanshetti, *J. Heterocycl. Chem.*, **4**, 325 (1967).

(4) The "α effect" would make the $-CONHO^-$ group a most effective nucleophile: J. D. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

(5) It is not surprising that the rearrangement of O-benzenesulfonyl benzohydroxamates occur almost spontaneously since it had been demonstrated by R. D. Bright and C. R. Hauser [*ibid.*, **61**, 618 (1939)] that the rate of the Lossen reaction increases with the pK_a of the acid corresponding to the departing anion.

(6) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

(7) D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 3157 (1959).

(8) A. Dornow and O. Hahmann, *Arch. Pharm.* (Weinheim), **290**, 20 (1957).

(9) A. W. Scott and J. H. Mote, *J. Amer. Chem. Soc.*, **49**, 2545 (1927).

(10) R. Marquis, *Compt. Rend.*, **143**, 1164 (1906).

(11) A. Dornow, German Patent 1,024,974 (1958); *Chem. Abstr.*, **54**, 7748 (1960).

(12) W. B. Wright and J. M. Smith, *J. Amer. Chem. Soc.*, **77**, 3927 (1955).

(13) F. L. Muehlmann and A. R. Day, *ibid.*, **78**, 242 (1956).

(14) Aldrich Chemical Co., Milwaukee, Wis.

Experimental Section[15]

Anthranilohydroxamic Acid.—This procedure consistently gave good results in the synthesis of the hydroxamic acid from ethyl anthranilate. When the published conversion of methyl anthranilate into anthranilohydroxamic acid[16] was applied to ethyl anthranilate in hot ethanol, little hydroxamic acid was isolated.

Sodium ethoxide, prepared from 4.6 g (0.2 g-atom) of sodium in 50 ml of ethanol, was added to a stirred solution of dried hydroxylamine hydrochloride (14.0 g, 0.2 mol) in ethanol (130 ml). After 1 hr the solution was filtered and to the filtrate was added ethyl anthranilate (16.5 g, 0.1 mol) followed by sodium ethoxide, prepared from 2.3 g (0.1 g-atom) of sodium in 50 ml of ethanol. The reaction mixture was stirred at 25° for 2 days. The solid was collected, washed with petroleum ether (bp 30–60°), dissolved in the minimum amount of water, filtered, and acidified with acetic acid. Recrystallization from water yielded the hydroxamic acid in 60% yield, mp 144–145° (lit. mp 142–143°,[14] 149°[6]).

2-Benzimidazolone.—Benzenesulfonyl chloride (14.13 g, 0.08 mol) was added dropwise to a stirred solution of anthranilohydroxamic acid (6.1 g, 0.04 mol) in freshly prepared 5% NaOH solution (64 ml). The reaction mixture was stirred at 25°, maintaining the pH at 8 or above by the addition of 10% NaOH as required. After 2 hr, the presence of the hydroxamic acid group could not be detected by means of the ferric chloride test. The solution was cooled in an ice–water bath and acidified with dilute HCl (1:1) to pH 4. The crystalline product was collected, washed with petroleum ether (bp 30–60°), dried *in vacuo*, and recrystallized from 95% ethanol to give the product (5.09 g, 95%), mp 309–310°, (lit. mp 300°,[6,17,18] 307–308°,[19] 310°,[20,21] 313–316°[7]). Its ir spectrum, melting point, and mixture melting point were identical with that of an authentic sample:[14] ir, 3120 (NH) and 1725 cm^{-1} (C=O); nmr (DMSO), δ 7.0 (s, C_6H_4).

2-Benzoxazolone.—Salicylohydroxamic acid (6.1 g, 0.04 mol) was treated with benzenesulfonyl chloride (7.07 g, 0.04 mol) as described above. After 0.75 hr, at which time the reaction mixture did not give a purple color with ferric chloride, it was treated with 20% NaOH solution (20 ml) and filtered, and the filtrate was acidified with dilute HCl (1:1). The product (4.65 g, 86%, mp 122–125°) was recrystallized from water: mp 131–133° (lit.[9] mp 139°); ir, 3215 (NH) and 1750 cm^{-1} (C=O); nmr (DMSO), δ 7.15 (s, C_6H_4); mass spectrum (70 eV), *m/e* (relative intensity) 136 (9.6), 135 (100), 91 (24), 79 (53), 78 (7.7), 67.5 (5.8), 64 (17.4), 63 (12.5), 53 (6.7), 52 (45), 51 (21), 50 (11.5), 39.5 (7.7), 39 (8.6), 38.5 (4.8), 38 (9.6), 32 (7.7), 28 (26).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyridine.—Benzenesulfonyl chloride (1.06 g, 0.006 mol) was added dropwise to a stirred solution of 2-aminonicotinohydroxamic acid (0.9 g, 0.006 mol) in 10% NaOH (10 ml). After 10 min the reaction mixture was filtered and the filtrate was acidified to pH 6 with dilute HCl (1:2). The solid (0.85 g, mp 259–262°). was recrystallized from 95% ethanol to furnish the pure product (0.58 g, 71%): mp 269–272° (lit. mp 238–239°,[22] 265–266°,[8,11] 270–272°,[7] 274°[23]); ir, 3100 (NH) and 1700 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (d of d, H_6 $J_{4,6}$ = 1.6 Hz), 7.00 (d of d, H_5, $J_{4,5}$ = 7.6 Hz), 7.34 (d of d, H_4, $J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV), *m/e* (relative intensity) 136 (8.34), 135 (100), 108 (4.2), 107 (23), 92 (6.2), 80 (20.8), 79 (5.2), 64 (12.5), 63 (6.2), 55 (5.2), 53 (19.8), 52 (13.5), 39 (7.3), 38 (10.4), 32 (7.3), 28 (26.1).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyrazine.—Benzenesulfonyl chloride (15.90 g, 0.09 mol) was added dropwise to a stirred solution of 2-amino-3-pyrazinecarbohydroxamic acid (14.05 g, 0.09 mol) in 4% NaOH solution (200 ml). The reaction mixture was stirred at 25° for 1 hr, then acidified at 0° to pH 4 with dilute HCl (1:3). The red-brown product (7.95 g, 65%) was recrystallized from water: mp 334–336° (lit.[13] mp 336°); ir, 3480, 3330 (NH) and 1720 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (s); mass spectrum (70 eV), *m/e* (relative intensity) 137 (5.1), 136 (66.8), 109 (7.9), 108 (6.5), 94 (13.5), 81 (9.8), 71 (6.1), 69 (6.5), 66 (10.7), 57 (13.5), 56 (5.6), 55 (10.28), 54 (13.08), 53 (10.7), 44 (7.0), 43 (12.1), 41 (11.7), 40 (5.6), 39 (8.4), 32 (42.5), 28 (100), 27 (7.5).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.03; H, 3.10; N, 41.18.

Registry No.—**4** (X = NH) 615-16-7; **4** (X = O) 59-49-4; **6**, 16328-62-4; **8**, 16328-63-5.

(15) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls (NaCl plates) with a Perkin-Elmer spectrophotometer, Model 337. Nmr spectra were determined with a Varian A-60 spectrometer, calibrated with tetramethylsilane (TMS) (0) and $CHCl_3$ (7.28); chemical shifts are reported in parts per million (δ) downfield from internal TMS. Mass spectra were obtained from a Hitachi Perkin-Elmer model RMU-6D spectrometer. The analysis (C, H) was performed by Dr. Kurt Eder, Geneva, Switzerland and that for N by Leo Horner using a Coleman Nitrogen Analyzer.

(16) M. A. Stolberg, W. A. Mosher, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **79**, 2615 (1957).

(17) L. C. Raiford, E. Conrad, and W. H. Coppock, *J. Org. Chem.*, **7**, 346 (1942).

(18) F. Montanari and A. Risaliti, *Gazz. Chim. Ital.*, **83**, 278 (1953).

(19) A. Hartman, *Ber.*, **23**, 1046 (1890).

(20) S. von Niementowski, *Ber.*, **43**, 3012 (1910).

(21) D. G. Crosby and C. Niemann, *J. Amer. Chem. Soc.*, **76**, 4458 (1954).

(22) J. R. Vaughan, Jr., J. Krapcho, and J. P. English, **71**, 1885 (1949).

(23) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

Nitration of 2-Methylthiazole

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Although it is known that 4-methyl- and 5-methylthiazoles undergo nitration[1] with relative ease, 2-methylthiazole has been nitrated only in very low yield (3–4%) through the use of fuming sulfuric acid and potassium nitrate at 330°.[2] The product, mp 131–133°, was reported to be 2-methyl-5-nitrothiazole, but no proof of structure was given. Under milder conditions, Ganapathi and Kulkarni[3] obtained similar yields of what was presumably the same compound. Since we intended to utilize 2-methyl-5-nitrothiazole as an intermediate, the nitration of 2-methylthiazole was investigated using nitronium tetrafluoroborate[4] and the nitrogen tetroxide–boron trifluoride complex.[5,6] These reagents, however, were unstable in the presence of 2 methylthiazole. Nitrogen dioxide was evolved and only low yields[7] (8–19%) of a 2-methyl nitrothiazole, mp 70.5–72.5°, were obtained.[8] This material was homogeneous by glpc and did not appear to be the same compound as that which had been alleged to be 2-methyl-5-nitrothiazole by Babo and Prijs. It was suspected that decomposition of the reagent could be cir-

(1) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 634.

(2) H. v. Babo and B. Prijs, *Helv. Chim. Acta*, **33**, 306 (1950).

(3) K. Ganapathi and K. D. Kulkarni, *Curr. Sci.*, **21**, 314 (1952); *Proc. Indian Acad. Sci., Sect. A*, **37**, 758 (1953).

(4) G. A. Olah, S. Kuhn, and A. Mlinko, *J. Chem. Soc.*, 4257 (1956).

(5) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Amer. Chem. Soc.*, **77**, 6188 (1955).

(6) The stoichiometry involved in the formation of the complex is believed to be

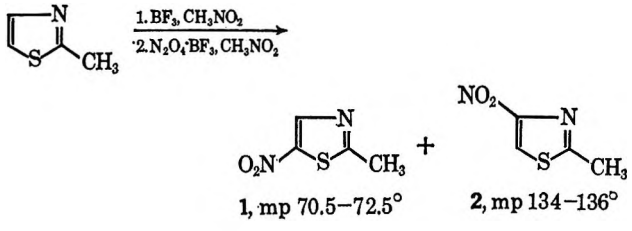
$$3N_2O_4 + 8BF_3 \longrightarrow 3NOBF_4 + 3NO_2BF_4 + B_2O_3$$

Cf. G. A. Olah and M. W. Meyer in "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1963, pp 124, 125, and 684.

(7) The higher yield was obtained by using the method of R. A. Parent [*J. Org. Chem.*, **27**, 2282 (1962)].

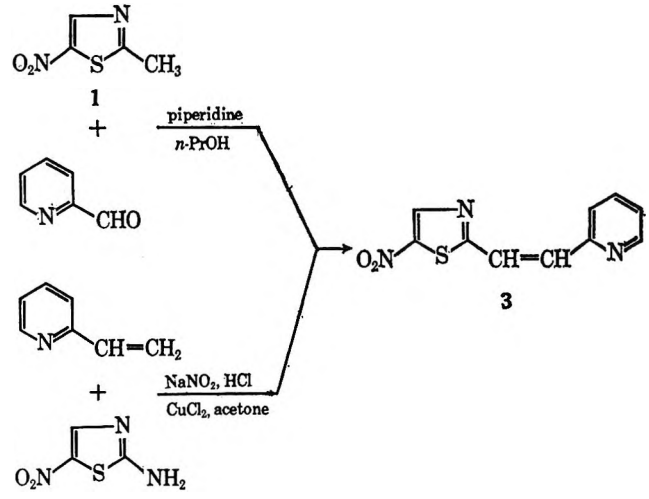
(8) For nucleophilic attack by pyridine on nitronium tetrafluoroborate, *cf.* G. A. Olah, J. A. Olah, and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965); J. Jones and J. Jones, *Tetrahedron Lett.*, 2117 (1964).

cumvented by prior complexing of 2-methylthiazole with boron trifluoride. Indeed, when boron trifluoride-complexed 2-methylthiazole was treated with excess nitrogen tetroxide–boron trifluoride complex in nitromethane at room temperature, a crude yield of *ca.* 86% of a mixture which contained predominantly mononitro products **1** and **2**, in a ratio of *ca.* 3.6:1, was isolated after 19.5 hr. Purification subsequently led to combined yields of 50–60% of **1** and **2**. The reaction proceeded equally well with nitronium tetrafluoroborate as the nitrating agent. Because it is well documented[9] that electrophilic substitution



occurs preferentially at the 5 position when an *ortho,-para* directing group is in the 2 position, it appeared on the basis of the isomer ratio that **1** was the 5-nitro isomer and **2** was the 4-nitro isomer. To support the contention the nmr spectra of **1** and **2** were compared with those of thiazole, 2-methylthiazole, and 2-bromo-5-nitrothiazole. The spectrum of thiazole in cyclohexane (TMS as the internal reference) is reported[10] to contain bands at τ 2.17 (H_4) and 2.91 (H_5) and of 2-methylthiazole[11] as a pure liquid (water as the external reference) at τ 2.8 (H_4) and 3.25 (H_5). In this work[12] 2-methylthiazole showed two doublets (J = 3.8 Hz) at τ 2.37 (H_4) and 2.87 (H_5), whereas 2-bromo-5-nitrothiazole exhibited a singlet at 1.67 (H_4). The spectrum of **1** revealed a singlet at τ 1.53 whereas that of **2** showed a singlet at 1.80. Thus it is clear that **1** is the 5-nitro isomer and **2** is the 4-nitro isomer and this is in accord with theory since the H_4 proton is deshielded more than the H_5 proton owing to the proximity of both the electronegative ring nitrogen[10,11] and the C_5-nitro group.

On the basis of this assignment, it is reasonable to predict that **1** should contain a more acidic methyl group than **2** because the methyl anion of **1** will be stabilized by conjugation with the nitro group. In good agreement with this prediction, **1** condensed readily with aromatic aldehydes,[13] whereas **2** did not; *e.g.*, **1** condensed with 2-picolinaldehyde to give the olefin **3** in 65% yield, whereas no reaction occurred with **2** under the same conditions. The structure **3** was confirmed by an alternate synthesis *via* the Meerwein arylation[14] of the diazonium chloride derived from 2-amino-5-nitrothiazole[15] with 2-vinylpyridine.



For comparative purposes, 2-methylthiazole was also nitrated with a mixture of nitric and fuming sulfuric acids at 180–197°, and the course of the reaction was followed by glpc. The analyses revealed the isomer ratio of 5-nitro/4-nitro changed from 5:4 in 0.5 hr to 1:2 in 1 hr. After 18 hr there was no 5-nitro isomer remaining, clearly showing that it was unstable under the reaction conditions. Thus there is undoubtedly a preference for electrophilic substitution at the 5 position even under these conditions at the outset of the reaction.

Since the nitration with the 2-methylthiazole–boron trifluoride complex was facile as compared with the mixed acid nitration, it was thought that this reaction might be another example of the "swamping catalyst effect" which has been studied by Pearson.[16] Under the same conditions, however, 2-methylthiazole hydrochloride was also readily nitrated to give a 54% yield of isomers, which indicated that ease of nitration is not dependent upon the presence of a Lewis acid and absence of a proton acid.

The scope of the prior-complexing nitration technique appears to be limited; BF_3-complexed pyridine and 2-picoline gave only traces (1–2%) of nitrated products with N_2O_4–BF_3.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Glpc analyses were performed on an F & M Model 720 dual column unit. Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Nitration of 2-Methylthiazole. A. N_2O_4–BF_3.—To 150 ml of nitromethane at 10°, 45 ml (*ca.* 0.705 mol) of nitrogen tetroxide was added and boron trifluoride was bubbled into this solution while the temperature was maintained below 10°. After excess boron trifluoride was observed at the top of the condenser, the flow was terminated. In a separate flask, 30 g (0.30 mol) of 2-methylthiazole in 50 ml of nitromethane at −20 to −10° was also saturated with boron trifluoride, and this solution was added over a 0.5-hr period to the slurry of nitrogen tetroxide–boron trifluoride complex at 5–25°. The heterogeneous mixture was stirred at ambient temperature for 19.5 hr and then heated[17] to 65–70° for 2 hr. The mixture was cooled, poured on ice, made alkaline with 10% sodium hydroxide, extracted with six 100-ml

(9) See ref 1, pp 495 and 552.

(10) B. Bak, J. T. Nielsen, J. Rastrup-Anderson, and M. Schottländer, *Spectrochim. Acta*, **18**, 741 (1962).

(11) A. Taurins and W. Schneider, *Can. J. Chem.*, **33**, 1237 (1960).

(12) Nmr spectra were taken in deuterated chloroform on a Varian A-60 instrument with tetramethylsilane (TMS) as the reference.

(13) Biological test results on these and related compounds will be published elsewhere.

(14) C. S. Rondestvedt, Jr., *Org. Reactions*, **11**, 189 (1960).

(15) Although the nitration of 2-aminothiazole has long been assumed to give 2-amino-5-nitrothiazole (ref 1, p 609), its structure has been confirmed only recently by Parent' by reductive acetylation to give 2,5-diacetamidothiazole, which differed from 2,4-diacetamidothiazole which had been synthesized unequivocally.

(16) D. E. Pearson, W. W. Hargrove, J. K. Chow, and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

(17) Heating was found to be unnecessary in subsequent runs.

volumes of methylene chloride, dried, and evaporated to dryness *in vacuo* to afford 37.55 g (86%) of a red-brown semisolid. Analysis by glpc on a 2% SE 30, 6-ft column starting at 100° and temperature programmed at 30°/min, showed that only *ca.* 2.6% of the starting material was present after stirring overnight at room temperature and that the ratio of 5-nitro(1)/4-nitro(2) was approximately 3.6:1. Only *ca.* 5% of volatile side products were detectable. The crude mixture was triturated with 150 ml of carbon tetrachloride and then filtered to leave, predominantly, 5.89 g of **2**, mp 80–125°. Recrystallization from methanol gave two fractions, 3.71 g (mp 133–136°) and 1.35 g (mp 125–132°).

Anal.[18] Calcd for $C_4H_4N_2O_2S$ (**2**): C, 33.32; H, 2.80; N, 19.43; S, 22.24. Found: C, 33.24; H, 2.97; N, 19.30; S, 22.10.

The carbon tetrachloride filtrate was evaporated to dryness *in vacuo*, the residue was redissolved in methylene chloride, the solution was decolorized with activated carbon and evaporated to dryness, and the solid was recrystallized from methanol to give 9 g of **1**, mp 70–72°. Subsequently, 11.98 g of lower melting fractions (mp 58–71°) were obtained by work-up of mother liquors. The combined isolated yield was 59.5%.

Anal.[18] Found for **1**: C, 33.37; H, 2.98; N, 19.54; S, 22.11.

Similarly, 2-methylthiazole hydrochloride afforded a 54% yield of mixed product but the **1**:**2** ratio was 2.8:1.

B. Mixed Acids.—To 7 ml of 20% fuming sulfuric acid at 20°, 1.7 g (93% pure by glpc, 1.6 mmol) of 2-methylthiazole was added and the mixture was heated to 100° before 2 g of potassium nitrate was gradually added. At the end of the addition the temperature was 170°, and, at this point, 1 ml of fuming nitric acid was added. The temperature was then kept at 180–197° for 18 hr. Glpc analysis (on a 6-ft, 10% SF 96 column[19]) of a 1-hr sample which had been basified, extracted, and dried over magnesium sulfate indicated a 1:2 ratio of 1:2; after 18 hr. Compound **2** was detected but **1** was no longer detectable. In a similar run using concentrated nitric acid instead of fuming nitric acid a 0.5-hr sample showed a 1:2 ratio of 5:4.

2-[2-(5-Nitro-2-thiazolyl)vinyl]pyridine (3). A. Condensation Method.—In 15 ml of 1-propanol containing 0.5 ml of piperidine, 2 g (14 mmol) of 2-methyl-5-nitrothiazole was refluxed with 3 g (28 mmol) of 2-pyridinecarboxaldehyde for 1 hr. The mixture was cooled and the solid was collected and washed with cold methanol to give 2.12 g (65%) of product, mp 179–181°. Recrystallization from methanol afforded yellow crystals: mp 181.5–183°; ir spectrum (Nujol), 3050, 1500, 1350, and 980 (*trans* H?) cm^{-1}. The AB quartet for the olefinic protons could not be resolved in deuterated chloroform on the Varian Model A-60 nmr instrument.

Anal. Calcd for $C_{10}H_7N_3SO_2$: C, 51.49; H, 3.03; N, 18.02; S, 13.75. Found: C, 51.22; H, 3.16; N, 17.97; S, 13.59.

B. Meerwein Reaction.—To 450 ml of concentrated hydrochloric acid and 100 ml of water, 145 g (1 mol) of 2-amino-5-nitrothiazole was added and the slurry was cooled to about −70°. To this mixture, 69 g (1 mol) of sodium nitrite in 100 ml of water was introduced over a 0.5-hr period to give a pale green mixture. After an additional 10 min of stirring, 160 g (1.52 mol) of 2-vinylpyridine in 600 ml of acetone was added rapidly while the temperature was kept below −30°. Cupric chloride dihydrate (28 g) was then added and the mixture was stirred for 10 min before it was allowed to rise to room temperature. At −10° the green mixture became reddish and evolution of nitrogen was vigorous. After cessation of nitrogen evolution, the mixture was added to 500 ml of water. The mixture was neutralized with sodium bicarbonate, methylene chloride was added, the mixture was filtered, and the organic phase was separated. The aqueous layer was further extracted with methylene chloride, the combined organic phases were dried over magnesium sulfate and then evaporated to dryness *in vacuo* to give a viscous mixture. This was triturated with methanol and filtered to give 25.3 g of product, mp 179–182°. An additional 6 g of crude product was obtained from the methanol filtrate. Purification of products from chloroform and decolorization with activated carbon gave 25.43 g (10.5%) of yellow product, mp 180–183°, which was identical (infrared spectrum and melting point) with that obtained by the condensation reaction (*vide supra*).

(18) The analytical samples from earlier runs melted at 134–136° (hexane) for **2** and 70.5–72.5° (hexane) for **1**.

(19) The column temperature was set at 120° and then abruptly reset at 250° after 2-methylthiazole passed through the column in order to get well-defined, reproducible peaks.

Registry No.—2-Methylthiazole, 3581-87-1; **1**, 16243-71-3; **2**, 16243-72-4; **3**, 16243-73-5.

Acknowledgment.—The author is indebted to Dr. G. Berkelhammer for his continued interest and Dr. J. E. Lancaster and Mr. R. S. Wayne for the nmr data and interpretations.

The Revised Structure of the Condensation Product of N-(*p*-Methoxyphenyl)anthranilic Acid with Formamide

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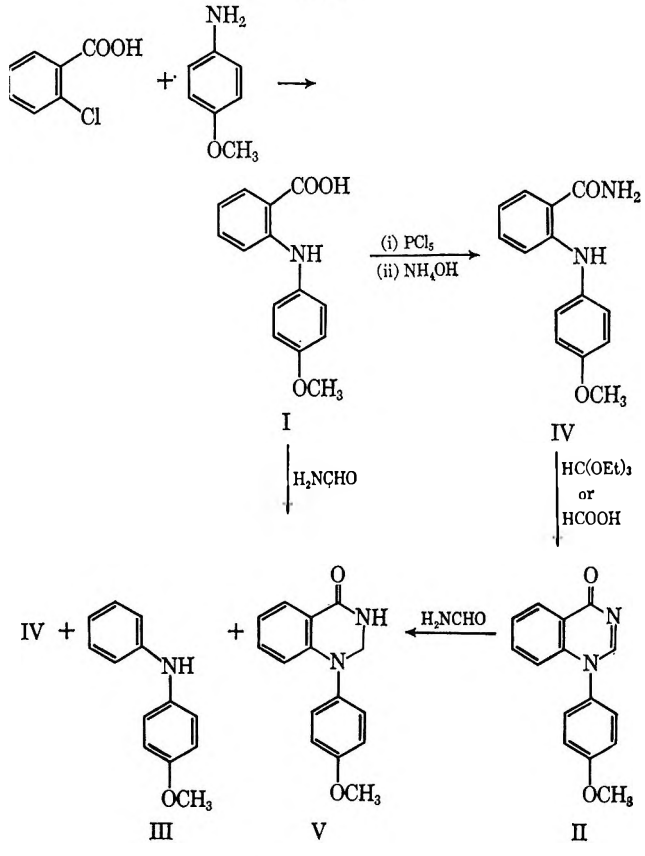
In an attempt to synthesize 1-aryl-1H-quinazolin-4-ones following the general route[1] to the synthesis of their 1-alkyl analogs, Mukherjee, *et al.*,[2] condensed N-(*p*-methoxyphenyl)anthranilic acid (I) with formamide and reported a product to which they assigned the structure II. The same experiment in our hands gave a mixture of three products (Chart I), *viz.*, 4-methoxydiphen-

CHART I



ylamine (III) and 2-(*p*-methoxyanilino)benzamide (IV) and a third one which was proven identical in all respects (melting point, mixture melting point, and uv, ir, and nmr spectra) with the compound believed to have

(1) N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, **13**, 903 (1948).

(2) S. Somasekhara, G. M. Shah, and S. L. Mukherjee, *Curr. Sci.*, **33**, 521 (1964).

the formulation II. But on the basis of the mass spectrometrically derived molecular weight (M^+ 254), elemental analysis, and nmr proton count (14 H), the molecular formula of the compound had to be revised as $C_{15}H_{14}N_2O_2$, instead of $C_{15}H_{12}N_2O_2$ suggested by the previous workers.[2]

The uv spectrum of the compound [λ_{max}^{EtOH} 280 (log ϵ 3.99) and 342 mμ (log ϵ 3.71)] resembled that of 2-(*p*-methoxyanilino)benzamide rather than that of 1-phenyl-1H-quinazolin-4-one[3] and the ir spectrum showed a strong NH band at 3226 cm^{-1}. These observations and the fact that the nmr spectrum lacked the C-2 proton signal[3,4] of quinazolin-4-ones and instead exhibited a two-proton signal at δ 5.25, led us to propose the tetrahydro structure V. The mass spectrum of the compound which showed characteristic peaks at M − 29 and at *m/e* 210 and 182 presumably due to the sequential expulsion of the groups CH_2–NH, $-CH_3$, and C=O also provides tenuous support for the formulation V. The formation of V, instead of II seems to involve the reduction of II as the obligatory intermediate by hydride transfer from formamide molecules,[5] a contention which received experimental verification by the formation of V as the sole product on heating II (formed by condensation of 2-(*p*-methoxyanilino)benzamide with ethyl orthoformate) with formamide at 170–180°.

Experimental Section

The melting points were determined on the Kofler block and were uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol (aldehyde free), the ir spectra were taken on a KBr disk unless otherwise stated. The analytical samples were dried at 80° over P_2O_5 for 24 hr *in vacuo*. Anhydrous sodium sulfate was used for drying organic solvents and for column chromatography; Brockmann alumina was used throughout.

N-(*p*-methoxyphenyl)anthranilic acid (I) was prepared by Ullmann condensation of *o*-chlorobenzoic acid with *p*-anisidine in presence of anhydrous potassium carbonate and activated copper powder. The product was crystallized from methanol as pale yellow needles: mp 182–183°, ν_{max} 3278, 2985, 2597, 1652, and 900 cm^{-1}; λ_{max}^{EtOH} 288 mμ (log ϵ 3.97) and 333 mμ (log ϵ 3.54); nmr ($CDCl_3$), δ 3.68 (s, 3 H), 6.02–7.28 (m, 8 H), 7.66 (d, 1 H, J = 6 cps) and 8.60 (NH, W_H = 12 cps).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.35; N, 5.76; O, 19.75. Found: C, 69.20; H, 5.27; N, 5.80; O, 19.89.

2-(*p*-Methoxyanilino)benzamide (IV) was synthesized according to the method of Blatter, *et al.*,[3] starting from I. The crude solid was crystallized from methanol as light yellow needles: mp 128–130°; ν_{max} 3508, 3322, and 1669 cm^{-1}; λ_{max}^{EtOH} 284 (log ϵ 3.97) and 342 mμ (log ϵ 3.61); nmr ($CDCl_3$), δ 3.82 (s, 3 H), 6.42 (NH_2, W_H = 20 cps), 6.56–7.60 (m, 8 H) and 9.5 (NH, W_H = 15 cps).

Anal. Calcd for $C_{14}H_{14}O_2N_2$: C, 69.42; H, 5.78; N, 11.56; O, 13.22. Found: M^+ 242; C, 69.61; H, 5.97; N, 11.58; O, 13.54.

1-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydroquinazolin-4-one (V).—Compound I was heated with 3–4 equiv of formamide in a sealed tube at 150–160° for 4 hr following exactly the method reported by Mukherjee, *et al.*[2] The residue was chromatographed. 4-Methoxydiphenylamine (III), obtained from the earlier fractions of the petroleum ether (60–80°) eluate, crystallized from petroleum ether as white needles (32% yield), mp 104–105° (lit.[6] mp 105°). Later fractions of the petroleum ether eluate furnished pale yellow needles (22% yield), mp 130° from benzene, and it was found to be identical in all respects (melting point, mixture melting point, and uv, ir, and nmr spectra) with IV. The major product (V), obtained from the chloroform eluate, crystallized from methanol as white rods (30% yield): mp 186°; ν_{max} 3226, 1681, and 1628 cm^{-1}; nmr ($CDCl_3$), δ 4.11 (s, 3 H), 5.25 (d, 2 H, J = 3 cps), 6.88–7.78 (7 H), 8.00 (NH, W_H = 15 cps) and 8.33 (d, 1 H, J_1 = 8 cps, J_2 = 2 cps).

Anal. Calcd for $C_{15}H_{14}O_2N_2$: C, 70.86; H, 5.51; N, 11.02; O, 12.59. Found: M^+ 254; C, 70.27; H, 5.73; N, 10.91; O, 12.82.

1-(*p*-Methoxyphenyl)-1H-quinazolin-4-one (II). A.—A mixture of 2-(*p*-methoxyanilino)benzamide (0.5 g) and ethyl orthoformate (5 ml) in diethylene glycol (5 ml) was heated at 120° for 15 hr. Excess of ethyl orthoformate was removed under reduced pressure and the residue was taken in chloroform and extracted with 5 *N* HCl. Acid extract was basified with ammonia and extracted with ether. Ether extract was washed, dried, and distilled. The residue was crystallized from acetone as white granules (0.3 g): mp 186–188°; ν_{max} 1642 and 1589 cm^{-1}; λ_{max}^{EtOH} 235 mμ (log ϵ 4.47), 280 (3.88), 304 (4.08) and 314 (4.0); nmr ($CDCl_3$), δ 3.96 (s, 3 H), 7.20 (d, 2 H, J = 9 cps), 7.36 (m, 3 H), 7.49 (d, 2 H, J = 9.0 cps), 8.33 (s, 1 H), and 8.38 (doublet of doublets, J_1 = 8.5 cps, J_2 = 2 cps).

Anal. Calcd for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.76; N, 11.11; O, 12.69. Found: M^+ 252; C, 71.29; H, 4.88; N, 11.34; O, 12.99.

B.—A solution of IV (0.5 g) in formic acid (10 ml) was heated in a sealed tube at 110–120° for 24 hr. Excess formic acid was removed under reduced pressure and worked up as before. The crude product was chromatographed. The solid, obtained from the benzene–chloroform (1:1) eluate, crystallized from acetone as white granules (0.07 g), mp 186–188°. It was found to be identical in all respects (melting point, mixture melting point, tlc, and uv, ir, and nmr spectra) with II.

Conversion of II into V.—Compound II was heated with 6–8 equiv of formamide at 170–180° for 5 hr. Excess formamide was removed under reduced pressure and the residue was crystallized from methanol into white rods (92% yield), mp 186°. It was found to be identical with V in all respects (melting point, mixture melting point, tlc, and uv, ir, and nmr spectra).

Registry No.—I, 13501-67-2; II, 16328-59-9; IV, 16328-60-2; V, 16328-61-3.

Acknowledgment.—The authors wish to express their sincere thanks to Dr. B. C. Das, Institut de Chimie des Substances Naturelles, C. N. R. S., France, for mass spectral data and to Dr. S. K. Kundu, University of Pittsburgh, Pittsburgh, Pa., for nmr spectra. R. R. is grateful to the C. S. I. R. (India) for financial assistance.

(3) H. M. Blatter, H. Lukaszewski, and G. deStevens, *J. Org. Chem.*, **30**, 1020 (1965).

(4) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

(5) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, **86**, 4721 (1964).

(6) R. Willstätter and H. Kubli, *Ber.*, **42**, 4135 (1909).

Benzyne Formation by Desulfamylation

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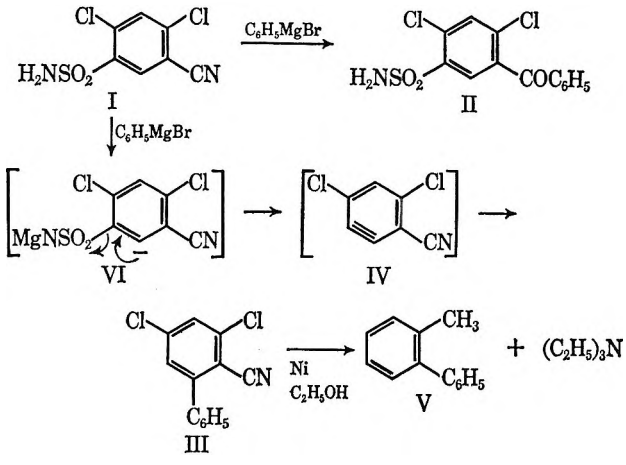
In a study of the chemistry of 2,4-dichloro-5-sulfamylbenzonitrile (I)[1] the reaction with an excess of phenylmagnesium bromide was carried out in anticipation that the product would be 2,4-dichloro-5-sulfamylbenzophenone. This product was formed in low yield, but the major product ($C_{13}H_7Cl_2N$) was shown to be 3,5-dichloro-2-biphenylcarbonitrile (III) by conversion into 2-methylbiphenyl (V) with Raney nickel. We were led to try this reaction because we had previously observed dehalogenation accompanying Raney

(1) W. Siedel, K. Sturm, and W. Scheurich, *Ber.*, **99**, 345 (1966).

nickel desulfurizations of chlorosulfamylanthranilic acids.[2]

The loss of nitrogen could be rationalized by reduction of the nitrile to the primary amine followed by alkylation by ethanol and debenzylation all catalyzed by the Raney nickel.[3] This explanation is supported by isolation of triethylamine hydrochloride from this reaction.

The *cine* substitution found in the replacement reaction implicates the benzyne IV as an intermediate. The hydrogen on the phenyl flanked by the sulfamyl and cyano groups should be quite acidic, so the formation of the anion VI seems plausible. This could be converted into IV by loss of $MgNSO_2^-$. The addition of the phenyl *ortho* to the cyano seems contrary to the generalization that the reaction proceeds to place the negative charge adjacent to the most strongly electron-withdrawing group.[4] It is possible that phenylmagnesium bromide is complexed to the cyano group, and this directs phenylation to the adjacent carbon.



Experimental Section[5]

Reaction of Phenylmagnesium Bromide and 2,4-Dichloro-5-sulfamylbenzonitrile.—Phenylmagnesium bromide was prepared by the reaction of 12.16 g (0.5 g-atom) of magnesium and 78.5 g (0.5 mol) of bromobenzene in 225 ml of tetrahydrofuran. After addition of 25 g (0.1 mol) of 2,4-dichloro-5-sulfamylbenzonitrile dissolved in 100 ml of tetrahydrofuran the reaction mixture was stirred at 25° for 30 min and refluxed for 90 min. After chilling, ice–water (350 ml) and 12 *N* sulfuric acid (200 ml) were added and the resulting solution was extracted with ether. The ether was extracted with 10% sodium hydroxide and the organic phase was concentrated to give 15 g (60%) of **3,5-dichloro-2-biphenylcarbonitrile** (III). Recrystallization from an ethanol–water mixture gave white crystals, mp 149–150°.

Anal. Calcd for $C_{13}H_7Cl_2N$: C, 62.92; H, 2.84; N, 5.64. Found: C, 63.01; H, 3.04; N, 5.33.

Acidification of the basic ether extract with hydrochloric acid gave 4.0 g (12%) of **2,4-dichloro-5-sulfamylbenzophenone** (II). This was dissolved in dilute sodium hydroxide, treated with charcoal, and reprecipitated by addition of acid. Recrystallization from an ethyl acetate–hexane mixture gave white crystals, mp 200–201°.

Anal. Calcd for $C_{13}H_9Cl_2NO_3S$: C, 47.29; H, 2.75; N, 4.24. Found: C, 47.56; H, 2.73; N, 4.28.

Dehalogenation of 3,5-Dichloro-2-biphenylcarbonitrile.—A mixture of 500 mg of 3,5-dichloro-2-biphenylcarbonitrile and a teaspoon of activated Raney nickel in 60 ml of ethanol was refluxed for 2.5 hr. The nickel was then removed by filtration and the volatile solvents were evaporated under vacuum. Addition of ether to the oily residue caused the separation of a white solid which was collected by filtration and identified by its nmr and infrared spectra as triethylamine hydrochloride. Evaporation of the ether gave an oil which on thin-layer chromatography (silica gel G, $CHCl_3$ development) showed a major spot (at highest R_f) and three traces. Chromatography on silica gel developing with chloroform gave four drops of the major product free of contamination. This was distilled in a small alembic (pot temperature 110°, 15 mm) to give a few drops of a colorless oil. The infrared and nmr spectra were identical with those of authentic 2-methylbiphenyl and very different than that of 3-methylbiphenyl.

Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.20. Found: C, 92.93, 92.69; H, 7.27, 7.18.

Registry No.—Benzyne, 462-80-6; II, 16355-12-7; III, 16355-13-8; V, 643-58-3.

(2) J. Weinstock and N. C. F. Yim, unpublished results.

(3) For precedents for the last two steps, see G. R. Pettit and E. E. van Tamelin, *Org. Reactions*, **12**, 356 (1961).

(4) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961).

(5) We wish to thank Miss M. Carroll and her staff for microanalytical data and Mr. R. J. Warren for nmr spectral data. Infrared spectra were determined on a Perkin-Elmer Infracord spectrometer and nmr spectra were obtained on a Varian A-60 spectrometer.

The Chemistry of 3-Oxo-2-phenylindolenine[1]

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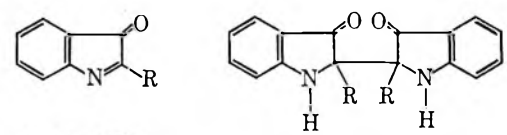
Received November 21, 1967

Recently Hassner and Haddadin[2] have shown that 17-keto steroids react with *o*-nitrobenzaldehyde to produce an exocyclic unsaturated indoxyl, which was postulated to have arisen from a 3-oxoindolenine of type **1a**, by a tautomeric shift. Little is known about endocyclic unsaturated indoxyls **1**. Although several workers have claimed to have isolated 3-oxoindolenines, these structures have either been shown to be erroneous, *e.g.*, the compounds are dimers of type **2**, or are subject to debate in the literature.[3-7]



1a, R = C_6H_5
b, Ia·HCl

2a, R = CH_3
b, R = C_6H_5

We decided to investigate the chemistry of 3-oxoindolenines and chose the 2-phenyl derivative because it could not undergo isomerization to an exocyclic unsaturated isomer. 3-Oxo-2-phenylindolenine (**1a**) was first described by Baeyer as an unstable red solid melting at 102°.[8] This compound was reported to readily react with base or acid and to dimerize on heating in benzene. That such endocyclic unsaturated indoxyls might be unstable and isomerize to an exocyclic unsaturated indoxyl or dimerize is not surprising; they contain a

(1) Stereochemistry. XXXIV. Nitro Compounds. VII. For paper XXXIII, see F. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **80**, 2875 (1968).

(2) A. Hassner, M. J. Haddadin, and P. Catsoulacos, *J. Org. Chem.*, **31**, 1363 (1966).

(3) O. Neunhoeffer and G. Lehman, *Chem. Ber.*, **94**, 2960 (1961).

(4) A. Hassner and M. Haddadin, *J. Org. Chem.*, **28**, 224 (1963).

(5) D. A. Jones, Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., 1961 discussed several reactions in which 3-oxoindolenines have been postulated as intermediates but in no case have they been isolated.

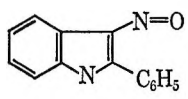
(6) R. K. Callow and E. Hope, *J. Chem. Soc.*, 1191 (1929).

(7) R. Pummerer, *Chem. Ber.*, **44**, 338, 810 (1911).

(8) A. Baeyer, *ibid.*, **45**, 2157 (1912); L. Kalb and J. Bayer, *ibid.*, **45**, 2150 (1912).

strained five-membered ring and resemble the heretofore unknown cyclopentadienone.

The method employed by Baeyer[8] in the synthesis of **1** involved the reaction of 2-phenylindole with sodium nitrite in acetic acid. The identity of the product has aroused considerable controversy.[9-11] Two structures were put forth, a nitroso compound **3** and an isonitroso compound **4a**. We feel that on the basis of spectral evidence neither of these structures are acceptable.



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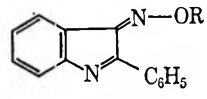
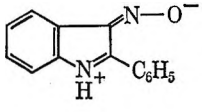


4a, R = H
b, R = Ac

Our product prepared by Baeyer's method, *i.e.*, sodium nitrite in acetic acid, corresponds in every way to that reported by other workers.[8,10,11] However, its infrared spectrum indicated the presence of a salt at 2300–2700 cm^{-1}, and, unlike a true oxime, there was no OH or C=N absorption and no N=O absorption. The compound yields an acetylated product **4b** which is identical with that reported by Campbell and Cooper.[11] The fact that the same product was obtained regardless of whether the synthesis was carried out under acidic or basic conditions and that salt formation occurred even on treatment of a 2-phenylindole with amyl nitrite in ether in the absence of catalyst leads us to the conclusion that the compound is a zwitterion **5**. This salt is unaltered by acid or base. A molecular weight determination indicates a monomer.

Attempts to continue with Baeyer's procedure, that is, to reduce the oxime **5** to an amine with zinc in acetic acid led to intractable tars even when the reaction was run under a nitrogen blanket. We finally obtained the desired 3-amino-2-phenylindole by carrying out the reduction with sodium dithionite ($Na_2S_4O_4$) in alcohol. The amine was highly unstable, turning from tan to green a few minutes after isolation, and was immediately oxidized with lead tetraacetate to the imine **6**. The latter was hydrolyzed to **1b**, the hydrochloride of oxoindolenine **1a**.



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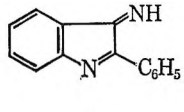

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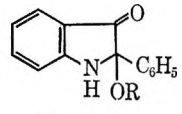


7a, R = H
b, R = CH_3

Neutralization and work-up of **1b** yielded two indoxyls, the 3-oxo-2-phenylindolenine (**1a**) in 25% overall yield and 2-hydroxy-2-phenylindoxyl (**7a**) in 10% yield. That the final product is indeed **1a** and not a dimer was established by the melting point correspondence to that found by Baeyer, who obtained a correct elemental analysis of **1a** the molecular weight determination in carbon tetrachloride [210 (calcd 207)] and the uv spectrum—250, 265, and 433 mμ (ε 37,200, 42,700, and 4680)—which fits the spectrum expected for such a system, by comparison with spectra of indoxyl derivatives. The long wave length maximum at 433 mμ is nearly the same for the isatogen **8** (438 mμ, ε 1120) as for **1a** in keeping with similar trends in pyridine and pyridine N-oxide. On the other hand, the bathochromic shift in the lower wavelength maximum from 265 to 290 mμ going from **1a** to its N-oxide **8** is probably attributable to the N→O auxochrome in the latter. Conjugated indoxyls absorb at a higher wavelength (455 mμ)[2] whereas simple indoxyls, *i.e.*, **2** and **7** absorb at 400 mμ.

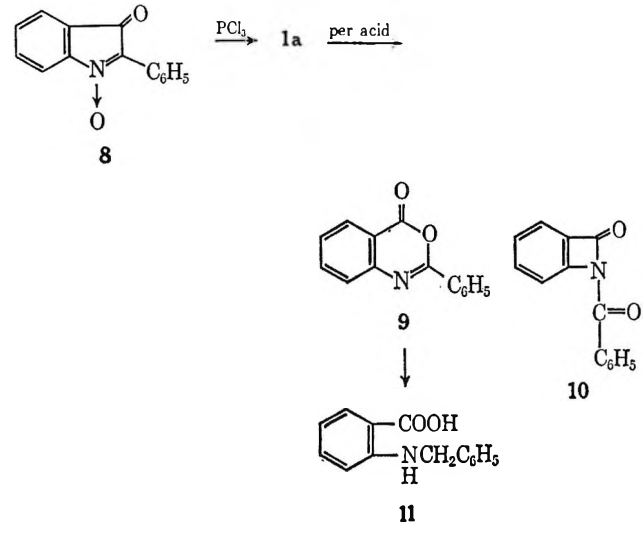
The second product obtained from the neutralization of **1b** is presumed to be 2-hydroxy-2-phenylindoxyl (**7a**). This conclusion is based upon the following data: the infrared spectrum of **7a** indicates OH and NH absorption and its ultraviolet spectrum shows typical indoxyl absorption at 400 mμ. Alcohol **7a** also results on addition of water to **1a**. It is possible to acetylate **7a** as inferred by the disappearance of the OH and appearance of acetoxy C=O absorption in the infrared. Since neither product could be purified, further analysis did not seem feasible.

3-Oxo-2-phenylindolenine (**1a**) was stable to air oxidation and did not appear to undergo dimerization to **2b** in benzene as previously reported.[8] On treatment with base it formed intractable tars, with water it gave **7a**, and with alcohol it formed a heat-sensitive 2-methoxy derivative **7b** that was converted reversibly into **1a**.

The similarity in structure between 2-phenylisatogen (**8**) and 3-oxo-2-phenylindolenine **1a** suggested the possibility of interconversion of these two compounds. Several deoxygenating agents were tried in an attempt to convert the isatogen into the corresponding oxoindolenine. Finally phosphorous trichloride was found successful but the yield of **1a** was poor.

We then attempted the conversion of the oxoindolenine **1a** into isatogen **8** (see Scheme I). It was expected that, like pyridine, the indolenine when treated with per acid would yield the N-oxide. This was not the case. With *m*-chloroperbenzoic acid, an isomer of **8** was obtained which corresponded in every way to that obtained by Jones from 3-acetoxy-2-phenylindole with per acid.[5] Jones assigned structure **9** to the product, based upon the work of Zentmyer and Wagner.[12] The latter authors dismissed structure **10** on the basis of

SCHEME I



(9) E. Fischer, *Chem. Ber.*, **21**, 1073 (1888).
(10) A. Angeli and F. Angelico, *Gazz. Chim. Ital.*, **30**, 268 (1900).
(11) N. Campbell and R. Cooper, *J. Chem. Soc.*, 1208 (1935).
(12) D. Zentmyer and E. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

strain in the four-membered ring.[13] We were able to unequivocally confirm[14] the assigned benzoxazine structure **9** by sodium borohydride reduction to N-benzylanthranilic acid (**11**). It is not possible to tell yet if per acids undergo reaction with **1a** on the carbonyl to yield **9** by a Baeyer–Villiger rearrangement, or by attack on the C=N either through an oxaziridine or *via* a peroxy compound.

Experimental Section[15]

3-Oximino-2-phenylindole(5). A. Using Sodium Nitrite in Acetic Acid.—A solution of 4.036 g of 2-phenylindole[16] in 90 ml glacial acetic acid was heated on a steam bath in order to obtain complete solution. Excess sodium nitrite (1.5 g) was slowly added to the dark green solution. A yellow-green precipitate quickly formed. The mixture was allowed to stand for 1 hr and then was diluted with water (200 ml), and the solid was filtered and dried. The product was redissolved in hot concentrated sodium hydroxide, and any residue was filtered off. The purified yellow-orange compound was precipitated by the addition of glacial acetic acid. The yield of dried oxime was 3.824 g (82%): mp 272–274° dec (lit.[10] mp 272–273° dec); ir, 2750–2300 (multiplet), 1838, 1517, 757, 746, 714, and 667 cm^{-1}; uv, λ_{max} (95% C_2H_5OH), 386 mμ (ε 3160), 330 (3800), 264 (35,500), 230 (12,000); molecular weight in pyridine, 236 (calcd 222).

B. Using Sodium Ethoxide and Amyl Nitrite.—Product **5** was obtained in 81% yield from a reaction of 2-phenylindole with isoamyl nitrite and sodium ethoxide in ethanol at 0°, following work-up with boric acid.

C. Using Amyl Nitrite in Ether Without a Catalyst.—The reaction was carried out with 3.96 g of 2-phenylindole in 60 ml of anhydrous ether, and 2.4 ml of isoamyl nitrite. After 2 hr at 25° a small amount of precipitate began to form from the yellowish solutions. After 26 hr, the product was filtered off and dried. The yield of **5** was 2.84 g, mp 276–277° dec, no purification was necessary. The product was identical in every way with **5** as prepared above.

Acetylation of Oxime 5.—Oxime **5** (753 mg) was acetylated by refluxing overnight in 15 ml of acetic anhydride and 9 ml of pyridine. The product was dissolved in acetone, and the resulting solution was filtered and then evaporated to dryness. The resulting red gum was crystallized from ethanol. The yield was 600 mg: mp 116° (lit.[11] mp 117°); ir, 1785 (C=O), triplet at 1178, 1165, and 1153 (oxime acetate), 1000, 918 cm^{-1}.

3-Imino-2-phenylindolenine (6).—To a solution of 86.9 g of **5** in 300 ml of ethanol and 500 ml of 2 *N* sodium hydroxide was added slowly an excess (16.7 g) of sodium dithionite ($Na_2S_2O_4$). The mixture was heated on the steam bath until the solution turned a light yellow color. The resulting product was filtered off, washed with 150 ml of water and 5 ml of ethanol, and then dried for 10 min under vacuum. The yield of 3-amino-2-phenylindole was 82%, mp 174–176° (lit.[10] mp 180°). The amine (20.4 g) in 100 ml of anhydrous benzene was oxidized with 150 g of activated lead dioxide by heating for 15 min and the imine **6** was obtained from benzene in 81% yield: mp 112–115° (lit.[8] mp 114°); ir, 1639, 1605, 1600, 1520, 766, 748, 685 cm^{-1}.

3-Oxo-2-phenylindolenine (1a).—A slurry, prepared from 6.90 g of imine **6** in concentrated hydrochloric acid was filtered under suction and the product 3-oxo-2-phenylindolenine hydrochloride (1b) was dried under vacuum over sodium carbonate; the ir spectrum showed absorptions at 2650–2550 (multiplet), 1730 (C=O), 1625, 1575, 768, 720, and 674 cm^{-1}.

The compound was placed in benzene, and the mixture was concentrated to drive off any excess hydrochloric acid. Excess calcium carbonate was added, and the mixture was heated briefly on the steam bath and then filtered. The residue was washed with hot benzene and the filtrates were combined and then evaporated down to a small volume, whereupon petroleum ether (20–40°) was added. Immediately upon addition of petroleum ether an unstable yellow product (**7a**) precipitated and was filtered off; uv maxima in carbon tetrachloride were at 407 mμ (ε 2630), 265 (46,800), and 250 (ε 24,600).

The filtrate from **7a** was concentrated until red crystals began to form. The solution was cooled and allowed to stand overnight. The red crystalline material was collected and dried and then recrystallized from ether to give 4.62 g of **1a**: mp 102° (lit.[8] mp 102°); mol wt 209.3 (calcd 207); uv, λ_{max} (CCl_4), 433 mμ (ε 4680), 270 (40,070) sh, 265 (42,700), 250 (37,200); ir, 1739 (C=O) and 1608 cm^{-1}.

2-Methoxy-2-phenylindoxyl (7b).—A solution of 445 mg of 3-oxo-2-phenylindolenine (**1a**) in 100 ml of absolute methanol was refluxed 2 hr and then evaporated to dryness under vacuum at room temperature. Recrystallization of the product from ether–petroleum ether afforded a mixture of indolenine **1a** and the methoxy compound **7b**, mp 104–107°. This product could not be further purified.

The above procedure was repeated with 422 mg of material. This time the product was recrystallized from methanol by first concentrating the solution, then by keeping the solution at −10°, and constantly scratching the flask with a glass rod until brilliant yellow crystals began to form. After crystallization began, the flask was allowed to sit for 2 hr at −10°, then the yellow crystals of **7b** were filtered off. The yield was 400 mg: mp 87°; mol wt 226 (calcd 239); uv, λ_{max} (CCl_4), 405 mμ (ε 4790), 265 (50,100), 250 (37,200); ir, 3436, 1703, 1626, 762, 753, 717, 701 (sh), 664 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}O_2N$: C, 75.34; H, 5.47. Found: C, 75.18; H, 5.42.

If the methoxy compound **7b** was heated in methanol and the solution was concentrated, the product obtained was a mixture of indolenine **1a** (predominantly) and indoxyl **7b**.

2-Phenylisatogen (8).—A modification of the procedure by Krohnke and Meyer-Delius[17] was employed. A solution of 4 g of *o*-nitrostilbene–pyridinium bromide (mp 253–255°)[17] in 200 ml of 50% aqueous acetic acid, was placed in white porcelain dishes and kept in the sunlight. The solution slowly turned orange and finally red-orange crystals were deposited. The product was recrystallized from methanol: 2.13 g; mp 188–189° (lit.[5] mp 189–190°); uv, λ_{max} (CCl_4), 438 mμ (ε 1120), 290 (35,500), 285 (34,700); ir, 1720 (C=O), 1709, 1385 cm^{-1} (ArN—O).

Deoxygenation of 2-Phenylisatogen (8) to 1a.—To a solution of 2 g of 2-phenylisatogen in 20 ml of chloroform was added 1.7 g of phosphorous trichloride (excess) at 0° for 1 hr. The solution was allowed to remain at room temperature for 30 hr and was then evaporated to dryness under vacuum. To the residue (a greenish-yellow oil) was added 2.5 ml of concentrated hydrochloric acid. The resulting slurry was filtered and the solid was dried. The solid mass was placed in benzene and then concentrated from 150 to 35 ml. To this solution excess calcium carbonate was added, and then the mixture was boiled for 15 min. The suspension was filtered, and the residue was washed with hot benzene. The filtrates were combined and concentrated. Petroleum ether was then added and the resulting yellow green tar was filtered off. The solution was further concentrated until red amorphous material began to precipitate. Three recrystallizations from ether yielded 65 mg of a product melting at 101–102°. The infrared and ultraviolet spectra were identical with those of 3-oxo-2-phenylindolenine (**1a**). A mixture melting point experiment with authentic **1a** showed no depression.

Attempts to deoxygenate **8** with triethyl phosphite in benzene at 0° led to tarry material. Refluxing of **8** with triphenylphosphine in benzene or methylene chloride led to recovery of starting material.

Oxidation of 3-Oxo-2-phenylindolenine (1a) to 9.—To a solution of 433 mg of **1a** in 25 ml of chloroform was added 685 mg of *m*-chloroperbenzoic acid (85% pure). The red solution which turned pale yellow after 15 min was kept at room tempera-

(13) There are several recent reports of the possible intermediacy of benzazetidones in reactions: G. Ege, *Angew. Chem. Intern. Ed. Engl.*, **4**, 699 (1965); E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966); R. K. Smalley, H. Suschitzky, and E. M. Tarner, *ibid.*, 3465 (1966).

(14) J. L. Pinkus recently found confirmatory evidence for structure **9** from mass spectra data. He also isolated **9** from peracid oxidation of **1a**. We are grateful to Professor Pinkus, University of Pittsburgh, Pittsburgh, Pa., for communicating these results to us prior to publication.

(15) All melting points were taken on a Fisher–Johns melting point apparatus, and are uncorrected. Infrared spectra were determined in the solid phase (KBr) using a Perkin-Elmer Infrared 21 spectrophotometer. Ultraviolet spectra were measured on a Cary Model XIV instrument. Molecular weights were determined in carbon tetrachloride, unless otherwise noted, using a Mechrolab Vapor osmometer, Model 301A.

(16) V. Sadovskaya, N. Grineva, and V. Ufimstov, *J. Gen. Chem. USSR*, **33**, 545 (1963).

(17) F. Krohnke and M. Meyer-Delius, *Chem. Ber.*, **84**, 932 (1951).

ture overnight. The solution was poured through a column of neutral alumina and then evaporated on the rotovac. The resulting material was crystallized from methanol affording yellowish needles of **9**: 316 mg (70.6%); mp 122.5° (lit.[5] mp 124°). The infrared spectrum indicated the presence of a carbonyl at 1764 cm^{-1}.

Anal. Calcd for $C_{14}H_9O_2N$: C, 75.34; H, 4.08. Found: C, 74.55; H, 4.04.

Hydrolysis of 120 mg of **9** in 15 ml of boiling 5% sodium hydroxide gave 105 mg of N-benzoylanthranilic acid, mp 181–181.5° (lit.[12] mp 182°).

Sodium Borohydride Reduction of 9 to 11.—To a solution of 300 mg of **9** in absolute ethanol was added 210 mg of sodium borohydride (excess), and the reaction mixture was allowed to sit 4 hr. The solution was evaporated to dryness in a vacuum, and the residue was extracted with hot chloroform. The chloroform solution was concentrated and cooled to yield brownish white crystals. After two recrystallizations from chloroform, 275 mg (90%) of **11**, mp 175°, was obtained (ir, 1661 (C=O), 1245, and 1235 cm^{-1}) identical in every respect with authentic N-benzylanthranilic acid.[18]

Registry No.—**1a**, 2989-63-1; **7b**, 16355-10-5; **9** 1022-46-4.

Acknowledgment.—This investigation was supported by Public Health Service Grant CA-04474 from the National Cancer Institute.

(18) G. Lockemann and H. Rein, *Chem. Ber.*, **80**, 485 (1947).

Dichloro(O,O′-1,4-dioxane)zinc(II)

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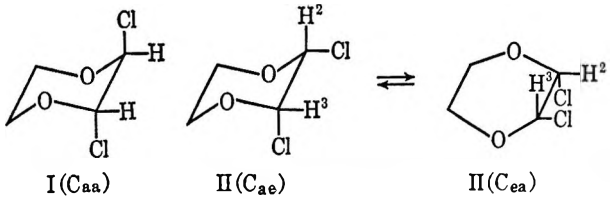
Received December 26, 1967

The reaction between 1,4-dioxane and chlorine produces a mixture of isomers of 2,3-dichloro-1,4-dioxane,[2] mp 30° (*trans*) and 51° (*cis*).[3,4] The *trans* isomer exists in a diaxial chair conformation [I (C_{aa})] while the *cis* isomer exists in an axial–equatorial chair conformation which is continuously inverting [II (C_{ae}), II (C_{ea})].[5–7]



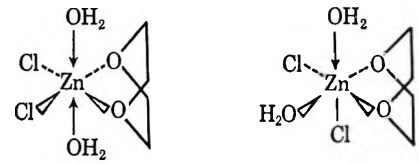
I(C_{aa}) II(C_{ae}) II(C_{ea})

Because *cis*- and *trans*-2,3-dichloro-1,4-dioxane constitute a valuable heterocyclic system with which to study axial/equatorial stereospecificity thresholds with respect to alkoxy substituents, it was desirable to develop a specific method for the synthesis of each isomer.

Preparation of pure I poses no problem since it is lower boiling and more thermodynamically stable than II. Preparation and isolation of pure II is more difficult owing to its ease of interconversion to I. The only method of preparing pure II reported in the literature[5] is low temperature (below 90°) chlorination of dioxane with subsequent vapor–liquid chromatographic separation of the two isomers.

The only catalyst reported used in the chlorination of 1,4-dioxane is $SnCl_2$.[8] The presence of $SnCl_2$ increased the 2,3-dichloro product yield by 28%; no product isomer distribution was reported. It was decided to try other metal chlorides (Lewis acids) but with electron configurations about the metal ion different from the $3d^{10}4s^2$ structure of Sn^{+2}, preferably those with vacant 4s orbitals. An added restriction was the solubility of the metal chlorides in dioxane. The metal chlorides most readily available and which meet these requirements are $ZnCl_2$, $CuCl_2$, $FeCl_3$, and $AlCl_3$. Zinc chloride, the first catalyst to be tried, selectively catalyzed the formation of II without detectable amounts of I. An investigation was then made of the structure of the zinc chloride–dioxane complex initially formed which apparently is the stereospecific catalyst for the formation of *cis*-2,3-dichloro-1,4-dioxane.

A white zinc chloride–dioxane complex has been reported as being polymeric units of $(ZnCl_2$–dioxane$)_n$ formed at ambient temperature with the dioxane ring in the chair conformation.[9,10] The infrared spectrum of the yellow zinc chloride–dioxane complex obtained in the present study shows an increased number of absorption frequencies in the regions 2950–2870, 1960–1480, 1440–1375, and 1325–1280 $cm.^{-1}$ as compared with the dioxane chair absorption frequencies. This suggests that the complexed dioxane ring exists in a boat conformation.[9] An absorption at 620 cm^{-1}, indicative of oxygen–zinc bonds, also supports the dioxane boat structure with zinc chelation as the stabilizing force for the less stable boat conformation.[11] The very pronounced hygroscopic property of the complex is considered as d-orbital participation which expands the coordination number of zinc from four to six, using the $4d_{z^2}$ and $4d_{x^2-y^2}$ orbitals.



IIIa IIIb

Although the nmr spectrum resolution of the complex in aqueous solution was insufficient to discern structure IIIa from IIIb, the respective absorption peak area ratios are sufficiently accurate to exclude the possibility of a second dioxane ring participation.

It is concluded that the structure of the zinc chloride–dioxane complex which catalyzes the stereospecific

(1) School of Science, The University of Texas at El Paso, El Paso, Tex.

(2) J. Boseken, F. Tellegen, and P. C. Henriquez, *J. Amer. Chem. Soc.*, **55**, 1284 (1933).

(3) W. Baker and A. Shannon, *J. Chem. Soc.*, 1598 (1933).

(4) R. K. Summerbell and H. E. Lunk, *J. Amer. Chem. Soc.*, **79**, 4802 (1957).

(5) C. Altona, "Molecular Structures and Conformation of some Halogeno-1,4-dioxanes," Druco Drukkerjbedrijven, Leiden, 1964.

(6) C. Altona and C. Romers, *Acta Crystallogr.*, **16**, 1225 (1963).

(7) R. R. Fraser and C. Reyes-Zamora, *Can. J. Chem.*, **43**, 3445 (1965).

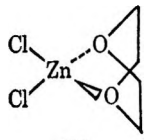
(8) J. J. Kucera and D. C. Carpenter, *J. Amer. Chem. Soc.*, **57**, 2346 (1935).

(9) P. J. Hendra and D. B. Powell, *J. Chem. Soc.*, 5105 (1960).

(10) R. Juhasz and L. F. Yntema, *J. Amer. Chem. Soc.*, **62**, 3522 (1940).

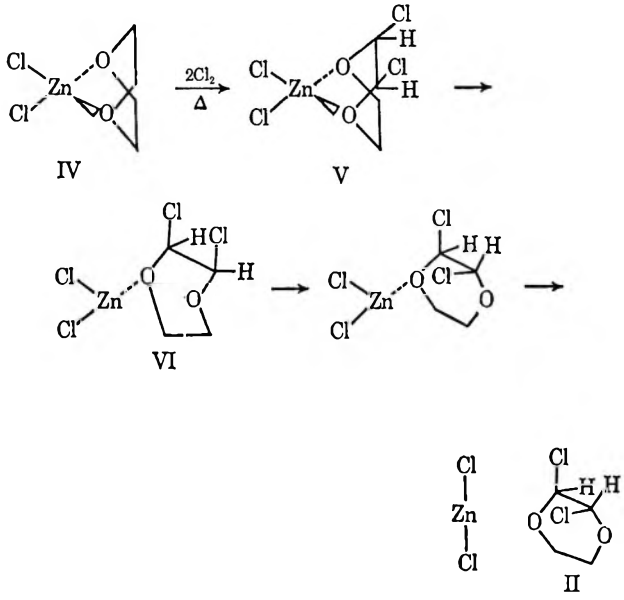
(11) K. Nakamoto, "Infrared Spectra of Inorganic and Coordination Compounds," John Wiley & Sons, Inc., New York, N. Y., pp 106 and 211.

dichloro substitution of 1,4-dioxane is dichloro(0,0′-1,4-dioxane)zinc(II).



IV

With the dioxane ring rigidly held in the boat conformation, chlorination of that ring yields the less sterically hindered *cis*-2,3-diequatorial product. The breaking of one of the chelate bonds produces the free dioxane conformer (VI). This boat to chair interconversion redefined the isomer as *cis*-2,3-axial, equatorial. Upon breaking of the second chelate bond the products are zinc chloride and *cis*-2,3-dichloro-1,4-dioxane.



IV V VI II

Experimental Section

cis-2,3-Dichloro-1,4-dioxane.—Dioxane (800 ml, 9.40 mol) was heated to reflux under nitrogen and 64 g of anhydrous zinc chloride was quickly added. After the zinc chloride dissolved, chlorine gas was added for a 5-hr period during each of 5 days. Vapor–liquid chromatographic analysis indicated a continuous increase in production of *cis*-2,3-dichloro-1,4-dioxane with time and there was no indication of *trans* isomer formation. Distillation of the reaction mixture at 3.0 mm gave a 30% yield of the *cis* isomer, bp 55.0 ± 0.05°. The nmr spectrum of this material was essentially identical with the spectrum reported in the literature.[6]

Dichloro(0,0′-1,4-dioxane)zinc(II).—Anhydrous zinc chioride (3.44 g) was added to 120 ml of dioxane distilled over lithium aluminum hydride. The mixture was heated for 48 hr at 90°. When the yellow reaction mixture was cooled to ambient temperature, yellow crystals formed. Additional crystals were obtained by the addition of cyclohexane. The total yield was 6.08 g. The dry, very hygroscopic, crystals decomposed at 160°.

Anal. Calcd for $C_4H_8O_2Cl_2Zn$: C, 21.43; H, 3.60; Cl, 31.6. Found:[12] C, 21.11; H, 3.86; Cl, 30.8.

Gravimetric chloride ion determination indicated 1.96 ± 0.01 mol of Cl^-/mol of complex.

The infrared spectrum was obtained in potassium bromide pellets (30% concentration). The nmr spectrum was made on a 50% solution in water. This solution had the same color as the complex. There was a broad absorption band at τ 1.07 downfield from the water proton absorption with respective integration ratios of 12 and 2.

(12) Analysis by Clark Microanalytical Laboratory which reported "....frankly, this is the most hygroscopic material which we have ever seen."

Registry No.—IV, 16457-66-2.

Acknowledgment.—This research was supported by a grant from the Robert A. Welch Foundation.

Synthesis of 4-Oxoglutaraldehydic Acid Derivatives from Nitrofurans and Aminofurans

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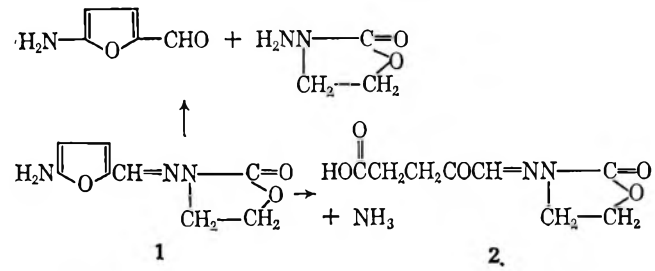
Received January 29, 1968

Certain nitrofurans are reduced both chemically[1] and biologically[2] to the corresponding aminofurans. Biologically, ^{14}C is found in metabolites, including glutamic acid, when ^{14}C-labeled nitrofurans are fed to chickens. Alkaline hydrolysis of ethyl 5-amino-2-furoate has also been reported; α-ketoglutaric acid was identified.[3] These observations suggested conversion of the five-carbon furaldehyde moiety into glutamic acid *via* α-ketoglutaric acid[4] and led to this study of the hydrolytic ring opening of nitrofurans and aminofurans.

In this note we reported the isolation of 4-oxoglutaraldehydic acid as a 3-amino-2-oxazolidinone derivative from the acid hydrolysis of 3-(5-aminofurfurylideneamino)-2-oxazolidinone and as a bissemicarbazone from the reaction of 5-nitro-2-furaldehyde dimethyl acetal with sodium methoxide. For comparison, 4-oxoglutaraldehydic acid was synthesized from 3,5-dibromolevulinic acid as described by Wolff[5] and the same derivatives were isolated. In addition, 5-methoxy-2-furaldehyde, found here to be an intermediate in the reaction of 5-nitro-2-furaldehyde with sodium methoxide, has been isolated as the oxime. The acid-labile methoxy intermediate readily hydrolyzes to 4-oxoglutaraldehydic acid.

The acid-catalyzed hydrolysis of 3-(5-aminofurfurylideneamino)-2-oxazolidinone (1) may occur in the azomethine linkage as well as in opening the furan ring. To suppress the former reaction, excess 3-amino-2-oxazolidinone was added to the solution of reactants. The isolated product, 5-(2 oxo-3-oxazolidylimino)-levulinic acid (2), was identical with the authentic compound.



1 2

(1) F. F. Ebetino, J. J. Carroll, and G. Gever, *J. Med. Pharm. Chem.*, **5**, 513 (1962).

(2) J. Olivard, S. Valenti, and J. A. Buzard, *ibid.*, **5**, 524 (1962).

(3) G. M. Klein, J. P. Heotis, and J. A. Buzard, *J. Biol. Chem.*, **238**, 1625 (1963).

(4) R. J. Herrett, C. W. Williams, J. P. Heotis, and J. A. Buzard, *J. Agr. Food Chem.*, **15**, 433 (1967).

(5) L. Wolff, *Ann.*, **260**, 79 (1890).

Under the same conditions, the hydrolytic reaction was followed spectrally. An isosbestic point at 290 mμ indicated negligible side reactions. At 70° in 2 *M* HCl with this method, the aminofuran was converted into the acid in 93% yield (spectrally) with a half-life ($t_{1/2}$) of about 5.5 min (Table I).

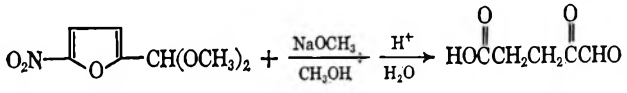
TABLE I
RATE OF CONVERSION OF 1 INTO 2 IN AQUEOUS ACID

Time, min	Absorbance 1[a]	Absorbance 2[b]
1	0.698	0.076
4	0.444	0.205
8	0.250	0.320
15	0.112	0.396
30	0.061	0.433

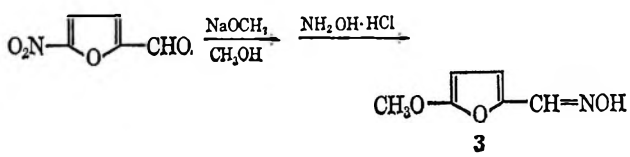
[a] uv max, 338 mμ (ε 22,300). [b] uv max, 266 mμ (ε 16,600).

To determine whether the aminofuran is hydrolyzed directly to the free acid or through an intermediate nitrile, 5-(2-oxo-3-oxazolidylimino)levulinonitrile prepared from 3,5-dibromolevulinonitrile was subjected to the exact conditions of the aminofuran hydrolysis. The nitrile group was not hydrolyzed. The infrared spectrum of the product exhibited nitrile absorption and no carbonyl group other than that of the amino-oxazolidinone ring. In the extraction of the nitrile, the partition coefficient (ethyl acetate:water) was 0.8. The partition coefficient for the corresponding acid is less than 0.2. If the nitrile had been present in the aminofuran hydrolysis mixture, it should have been recovered with (or in preference to) the acid.

With aqueous sodium hydroxide and several conditions of concentration of reactants, temperature and time of reaction, synthesis of 4-oxoglutaraldehydic acid derivatives from nitrofurans was unsuccessful. Only dark brown reaction mixtures and tars were obtained. However, when 5-nitro-2-furaldehyde dimethyl acetal at molarity less than 0.15 was treated with sodium methoxide in methanol solution, the reaction went to completion with only slight browning. 4-Oxoglutaraldehydic acid was isolated from the reaction mixture as the bissemicarbazone following acid hydrolysis of the acetal group.



When 5-nitro-2-furaldehyde was substituted for the acetal, some browning was observed. Addition of solid hydroxylamine hydrochloride to the methanolic solution yielded the oxime derivative of the acid-labile intermediate in the reaction, 5-methoxy-2-furaldehyde oxime (**3**).



3

Measurement of the rate of reaction of nitrofurans (0.0355 *M*) with sodium methoxide (0.25 *M*) utilized acid-stable absorbance near 310 mμ. Total absorbance represents both nitrofuran reactant and 5-methoxyfuran product. Acid stable absorbance represents nitrofuran only since the 5-methoxyfurans are hydrolyzed in acid solution to 4-oxoglutaraldehydic acid which exhibits only low end absorption in the ultraviolet spectrum. The rate of decrease in acid stable absorbance, *i.e.*, rate of decrease in nitrofuran concentration, is the rate of the reaction which yields 5-methoxyfurans provided there are no side reactions. The stability of total absorbance in methanol at 310 mμ indicated no side reactions with 5-nitro-2-furaldehyde and 5-nitro-2-furaldehyde dimethyl acetal. From the acid-stable absorption spectrum of the reaction of 5-nitro-2-furaldehyde with sodium methoxide at 38°, $t_{1/2}$ = 6.6 min was calculated. Doubling the sodium methoxide concentration decreased the half-life to 4.5 min, indicating the participation of the methoxide anion in a bimolecular rate-limiting step.

The rate of reaction of 5-nitro-2-furaldehyde dimethyl acetal with sodium methoxide in methanol solution was only slightly slower than that of the aldehyde; the half-life at 38° was 10.0 min. The approximate rate of acid hydrolysis of 5-methoxy-2-furaldehyde to 4-oxoglutaraldehydic acid also was measured spectrally. The calculated half-life in 0.25 *M* HCl at 67° was 2.7 min.

Experimental Section

Acid Hydrolysis of 3-(5-Aminofurfurylideneamino)-2-oxazolidinone (1).—Compound 1[1] (0.5 g) and 3-amino-2-oxazolidinone (1.0 g) were dissolved in 150 ml of water and heated to 70° in a water bath. The solution was combined with 150 ml of 4 *M* HCl at the same temperature. After 15 min the solution was cooled, partially neutralized with 100 ml of 4 *M* NaOH and extracted four times with equal volumes of ethyl acetate. The ethyl acetate extracts were concentrated *in vacuo* to yield a brownish crystalline product in 18% yield. Recrystallization from 95% ethanol (with charcoal treatment) yielded a white crystalline acidic product, 5-(2-oxo-3-oxazolidylimino)levulinic acid (**2**): mp 190°; uv max (water), 266 mμ (ε 16,600); and ir (mull) C=O at 1776 and 1672 cm^{-1}. All were identical with that of the authentic compound prepared from 4-oxoglutaraldehydic acid synthesized from 3,5-dibromolevulinic acid by the method of Wolff.[5]

Anal. Calcd for $C_8H_{10}N_2O_5$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.82; H, 4.69; N, 13.13.

The acid hydrolysis rate data for the conversion of the aminofuraldehyde **1** into the oxoglutaraldehydic acid derivative **2**, followed spectrally, is given in Table I.

5-(2-Oxo-3-oxazolidylimino)levulinonitrile was prepared from 3,5-dibromolevulinonitrile.[6]

4-Oxoglutaraldehydic Acid Bissemicarbazone.—In a typical experiment, 1 g of 5-nitro-2-furfuraldehyde dimethyl acetal was added to 40 ml of 0.5 *M* sodium methoxide in methanol at reflux and the heating was continued for 30 min. The solution was cooled, neutralized with carbon dioxide, and concentrated *in vacuo*, and the solids were removed by filtration. The filtrate was made acidic with 2 *M* HCl and nitrogen was bubbled through it to remove HNO_2 and CO_2. Semicarbazide hydrochloride (1.5 g) was added. After 12 hr in the refrigerator, off-white crystals were obtained; these were twice dissolved in 5% $NaHCO_3$ and reprecipitated with 2 *M* HCl added dropwise; the bissemicarbazone of 4-oxoglutaraldehydic acid was obtained in 15% yield: ir (mull) C=O at 1701 (sh), 1681 and 1575 cm^{-1}; uv max (water), 286 mμ (ε 29,700). All were identical with that of the authentic compound synthesized by an alternative route.[5]

Anal. Calcd for $C_7H_{12}N_6O_4$: C, 34.4; H, 4.95; N, 34.4. Found: C, 34.2; H, 4.81; N, 32.8.

5-Methoxy-2-furaldehyde Oxime (3).—5-Nitro-2-furaldehyde (1 g) was added to 100 ml of refluxing 0.25 *M* sodium methoxide in methanol and the reflux was continued for 10 min. Hydroxylamine hydrochloride (3.5 g) was added and the reflux was continued for 15 min. After cooling and concentration *in vacuo*, off-white crystals of 5-methoxy-2-furaldehyde oxime (**3**) precipi-

(6) F. L. Austin, *Chem. Ind.* (London), 523 (1957).

tated in 45% yield. The product, recrystallized from methanol–water with charcoal treatment, was white: mp 145–146°; uv (water), 287 mμ (ε 22,600), in dilute HCl a reversible shift in uv max to 337 mμ was found; ir (mull), 2740, 1629, 1575, 1615, 1299, 1220, 1050, and 1016 cm^{-1}; nmr (DMSO), δ 3.78 (s, 3, CH_3O), 5.43 (d, 1, J = 3 Hz, CH of C4), 7.12 (d, 1, J = 3 Hz, CH of C-3), 7.2 (s, 1, CH=N), and 11.5 (s, NOH).

Anal. Calcd for $C_8H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.96; H, 4.90; N, 9.78.

Kinetics of the Reaction of Nitrofurans with Sodium Methoxide.—For the determination of the rate of reaction the nitrofurans were mixed quickly with 0.25 *M* sodium methoxide in methanol already equilibrated at 38°. The final concentration of nitrofuran was 0.0355 *M*. At appropriate time intervals, two 0.5-ml aliquots were diluted (1) with methanol to determine total absorbance at 310 mμ and (2) with 4 *M* HCl to determine acid-stable absorbance at 310 mμ. The absorbance of the latter sample was measured after heating for 10 min in a 70° water bath. Spectra were recorded on the Beckman DB recording spectrophotometer.

Rate of Acid Hydrolysis of 5-Methoxy-2-furaldehyde.—5-Nitro-2-furaldehyde (3.55 mmol) was heated at reflux for 10 min in 100 ml of 0.25 *M* sodium methoxide in methanol. Without isolation of the 5-methoxy-2-furaldehyde the solution was diluted 1:10 with HCl to give a final acid concentration of 0.25 *M*. After appropriate intervals in a 67° water bath, aliquots were diluted with NaOH–phosphate buffer (final pH, 7.0) and the absorbance read at 310 mμ.

Registry No.—**2**, 16487-09-5; 4-oxoglutaraldehydic acid bissemicarbazone, 16487-29-9; **3**, 16487-30-2.

Acknowledgment.—Reference compounds were synthesized by Mr. Frank F. Ebetino of the Organic Chemistry Section, Eaton Laboratories. Dr. Julian Michels of the Analytical Chemistry Section, Eaton Laboratories, supplied the infrared spectra, and Dr. Jerrold Meinwald, Department of Chemistry, Cornell University, supplied the nmr spectra.

The Synthesis of Triarylalkyl Ammonium Salts[1]

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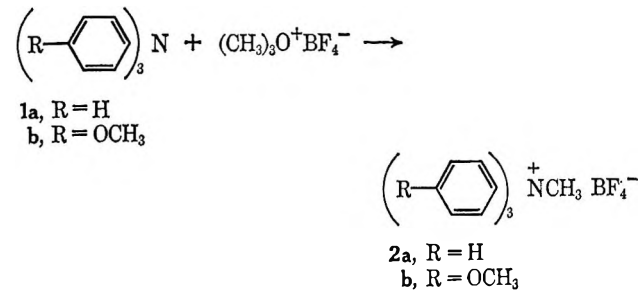
Received January 19, 1968

In contrast to the extensive studies of alkyl quaternary ammonium salts,[2] aryl quaternary ammonium salts have only been slightly investigated. In part, this is probably due to the marked decrease in the basic and nucleophilic properties of aryl amines making quaternization somewhat difficult. Diaryldialkylammonium salts are mentioned only rarely in the chemical literature,[3] and triarylalkylammonium salts have not yet been reported.[4] In the following, we report the synthesis of the hitherto unknown triarylalkylammonium salts.

The synthesis of triarylmethylammonium salts **2** was accomplished through alkylation of the required triarylamine with trimethyloxonium tetrafluoroborate[5] in methylene chloride at 75°. As expected, the nucleophilicity of the nitrogen atom is significantly increased by the substitution of a *para* methoxyl group **1b** and the rate of formation of **2b** is considerably greater than for **2a**.



Both of the triarylalkylammonium tetrafluoroborates **2** are quite stable solids. They do not appear to be appreciably hygroscopic and have shown no signs of decomposition on storage. Both salts can be held above their melting points and recovered essentially unchanged. (Some color does develop on heating, but the spectra of the recovered materials are superimposable on those of the original salts.)

In contrast to the thermal stability of these materials, they are quite labile to treatment with base. Thus, when **2a** is allowed to react with a series of basic reagents (*n*-butyl lithium–hexane or dichloromethane, *t*-butyl lithium–pentane or tetrahydrofuran, phenyl lithium–benzene–ether, potassium methoxide–methanol, potassium *t*-butoxide–dimethyl sulfoxide), demethylation occurs to yield the parent triarylamine. A similar result is observed with **2b** using *n*-butyl lithium–hexane, dichloromethane, or potassium methoxide–methanol.

Crude kinetics of demethylation by potassium methoxide in methanol-OD have been followed using nmr spectroscopy. The second order rate constants at 0° are approximately 3×10^{-5} l. mol^{-1} sec^{-1} and 7×10^{-6} l. mol^{-1} sec^{-1} for **2a** and **2b**, respectively. No hydrogen–deuterium exchange of the N-methyl hydrogen atoms was observed in these reactions.

Experimental Section

Analytical Data.—Nmr spectra were obtained using a Varian A-60 spectrometer and chemical shifts are reported as downfield from internal TMS. Infrared spectra were obtained on a Perkin-Elmer Infracord as solutions in carbon tetrachloride or chloroform. Ultraviolet spectra were obtained on a Cary spectrophotometer as a solution in absolute ethanol. Melting points were obtained on a Hoover apparatus and are corrected.

Triphenylmethylammonium Tetrafluoroborate (2a).—To 2.7 g of triphenylamine in 27 ml of dichloromethane was added 2.7 g of trimethyloxonium tetrafluoroborate.[5] The reaction vessel was degassed and sealed under vacuum. It was stirred at 75° for 22 days. The resulting blue solution was evaporated to dryness and the resulting solid successively washed with diethyl ether to yield an ether-insoluble material. Recrystallization from absolute ethanol gave 0.6 g of material with mp 182.0–183.5°. An analytical sample had mp 185.5–186.0°; nmr ($CDCl_3$), δ 4.67 (s, 3, $^+NCH_3$), 7.1–7.8 (m, 15, C_6H_5); ir ($CHCl_3$), 3.3 (m), 6.3 (s), 6.7 (s), 7.9 (s), 9.4 (v.s.), 11.0 μ (s); uv max (absolute

(1) We gratefully acknowledge the Los Angeles State College Foundation for partial support of this work.

(2) See, for example, (a) A. C. Cope and E. R. Trumbell, *Org. Reactions*, **11**, 317 (1960); (b) H. E. Zimmerman in "Molecular Rearrangements," P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 345.

(3) (a) D. A. Archer and H. Booth, *J. Chem. Soc.*, 322 (1963); (b) E. D. Hughes and D. J. Whittingham, *ibid.*, 806 (1960); (c) E. Muller, H. Huber-Emden, and W. Rundel, *Ann.*, **623**, 34 (1959).

(4) (a) P. A. S. Smith, "Chemistry of Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., N. Y., 1965, p 92; (b) I. T. Millar and H. D. Springall, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, London, 1966, p 162.

(5) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).

EtOH), 250 mμ (ε 0.9 × 10³), 257 (1 × 10³), 261 (1 × 10³), and 268 (0.9 × 10³).

Anal. Calcd for $C_{19}H_{18}NBF_4$: C, 65.73; H, 5.23; N, 4.03. Found: C, 65.71; H, 5.45; N, 3.68.

Tri-*p*-anisylmethylammonium Tetrafluoroborate (2b).—To 0.7 g of tri-*p*-anisylamine[6] in 7 ml of dichloromethane was added 0.7 g of trimethyloxonium tetrafluoroborate.[5] The reaction vessel was degassed and sealed under vacuum. It was stirred at 75° for 7 days. The resulting blue solution was evaporated to dryness and the recovered material was successively washed with diethyl ether to give an ether-insoluble solid. Recrystallization from absolute ethanol gave 0.5 g of solid with mp 173.0–175.0°. An analytical sample had mp 175.5–176.0°; nmr ($CDCl_3$), δ 3.85 (s, 9, OCH_3), 4.54 (s, 3, $^+NCH_3$), 6.8–7.4 (m, AA'BB', 12, C_6H_4); ir, 3.3 (m), 6.3 (s), 6.7 (s), 6.9 (s), 7.0 (s), 7.7 (s), 7.9 (s), 8.5 (s), 9.5 μ (vs); uv max (absolute EtOH), 234 mμ (ε 2.9 × 10⁴), 273 (5.1 × 10³), 281 (4.3 × 10³).

Anal. Calcd for $C_{22}H_{24}NO_3BF_4$: C, 60.43; H, 5.53; N, 3.20. Found: C, 60.47; H, 5.62; N, 3.28.

Base Reactions.—The lithium bases were obtained commercially (Foote or Alfa chemicals) as was the potassium *t*-butoxide (M. S. A. Research Corp., Callery, Pa.). The potassium methoxide was prepared by carefully adding potassium metal to ice-cold methanol. Solvents were dried and distilled.

A typical run is as follows. To the required amount of quaternary ammonium salt in a dry, nitrogen-purged vessel was placed the calculated amount of base and solvent was added. The materials were then allowed to react for the desired time. Water was added and the organic material was recovered by further extraction with ether or pentane.

The kinetic runs were carried out by adding the required amount of basic reagent to a solution of the salt in methanol-OD in an nmr tube at 0°. The tube was purged with nitrogen, then the progress of the reaction followed at 0° by observing the decrease in the aromatic resonance of the salt and the appearance of the aromatic resonance of the tertiary amine.

Registry No.—2a, 16457-64-0; 2b, 16457-65-1.

(6) H. Wieland and E. Wecker, *Chem. Ber.*, **43**, 699 (1910).

Benzene-Induced Nuclear Magnetic Resonance and Dipole Moment Shifts of Five-Membered Rings Containing Heteroatoms

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The five-membered ring heterocycles provide an interesting series of compounds to investigate the factors which affect the benzene solvent shift in the nmr spectra because their geometry is fixed, there are only two basic types of protons (if the plane of the ring is a symmetry plane), and the chemical shifts of the α and β protons are generally well separated. Benzene solvent shifts of the high resolution nuclear magnetic resonance (nmr) spectra have been reported[1-5] as useful in elucidating the proton geometry in carbonyl compounds. Protons behind the carbonyl carbon are shielded while those in front are deshielded with respect to the corresponding values in CCl_4. Shielding effects have also been observed for other functional groups.[6-14] Some generalizations have been made[11] concerning the mechanism of the shielding effects on the solute molecules in benzene. The solvent shifts are thought to result from the formation of a nonplanar association between the solute molecule and benzene at a local electron-deficient site in the solute. The orientation of the benzene is believed[11] to be such that the benzene ring avoids the negative end of the dipole in a nonplanar preferred configuration. A benzene molecule appears to be associated with each electron deficient site in the solute molecule. It is convenient to depict the nonplanar average association between benzene and the heteroatom-containing solute as a "complex;" however, the use of the term "complex" in this context only implies the effects resulting from a slight minimum in the potential energy surface of the benzene–solute molecular interactions.

The following expression, analogous to that of Bhacca and Williams,[15] was used to analyze the data

$$\Delta = \gamma_{CCl_4}{}^H - \gamma_{C_6D_6}{}^H \quad (1)$$

where $\gamma_{CCl_4}{}^H$ = the center of resonance for a particular kind of proton at infinite dilution in CCl_4 with respect to TMS in CCl_4 and $\gamma_{C_6D_6}{}^H$ = the corresponding center of resonance in C_6D_6. The γ values in eq 1 will approach the corresponding chemical shift values (δ) as the system approaches first-order behavior. When planar five-membered ring molecules exist with benzene in solution, there is a certain amount of ordering due to the average planarity of the rings. In order to study only the ordering due to the heteroatom, a Δ value is determined for cyclopentane. The Δ values for the five-membered rings containing heteroatoms are only significant if they exceed this Δ value of cyclopentane. If we assume that the average configuration of the five-membered ring is planar, we note that for all solutes the plane of the five-membered ring is a plane of symmentry of the molecule. These compounds, together with their Δ and γ values, are listed in Table I. Also given in this table are the available literature values for the dipole moments in benzene. It can be seen from the values given that, for most compounds listed, the γ values are indeed chemical shifts.

Figure 1 shows a plot of the solvent shift (Δ^β) of the protons β to the functional group *vs.* the dipole moment in benzene ($\mu_{C_6H_6}$) for the molecules. Except for the selenium compound, there seeems to be a linear relationship between $\mu_{C_6H_6}$ and Δ^β. A similar relationship between the solvent shift of the α protons (Δ^α) is not as apparent. A correlation of the Δ's with dipole moment is expected in the absence of steric effects.[6,9] In general, the larger the dipole moment, the greater the electron deficiency of certain sites in the molecule.

(1) J. D. Connally and R. McCrindle, *Chem. Ind.* (London), 379 (1965).
(2) N. S. Bhacca and D. H. Williams, *Tetrahedron*, **21**, 2021 (1965).
(3) C. J. Timmons, *Chem. Commun.*, 576 (1965).
(4) Y. Fujise and S. Itô, *Chem. Pharm. Bull.* (Tokyo), **14**, 797 (1966).
(5) D. W. Boykin, A. B. Turner, and R. E. Lutz, *Tetrahedron Lett.*, 817 (1967).
(6) T. L. Brown and K. Stark, *J. Phys. Chem.*, **69**, 2679 (1965). For a summary of earlier work, see the first eleven references therein.
(7) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1641 (1965).
(8) J. E. Anderson, *Tetrahedron Lett.*, 4713 (1965).
(9) J. H. Bowie, J. Ronayne, and D. H. Williams, *J. Chem. Soc., Sect. B*, 785 (1966).
(10) H. M. Fales and K. S. Warren, *J. Org. Chem.*, **32**, 501 (1967).
(11) J. Ronayne and D. H. Williams, *Chem. Commun.*, 712 (1966); *J. Chem. Soc. Sect. B*, 540 (1967).
(12) M. Honda, Y. Kawasaki, and T. Tanaka, *Tetrahedron Lett.*, 3313 (1967).
(13) Y. Kawasaki, *Mol. Phys.*, **12**, 287 (1967).
(14) D. J. Barraclough, P. W. Hickmott, and O. Meth-Cohn, *Tetrahedron Lett.*, 4289 (1967).
(15) N. S. Bhacca and D. H. Williams, *ibid.*, 3127 (1964).

TABLE I

SOLVENT SHIFTS AND FREQUENCIES OF CENTERS OF RESONANCE FOR FIVE-MEMBERED RINGS[a]

Compound	$\gamma_{CCl_4}^{\alpha}$	$\gamma_{C_6D_6}^{\alpha}$	Δ^{α}	$\gamma_{CCl_4}^{\beta}$	$\gamma_{C_6D_6}^{\beta}$	Δ^{β}	$\mu_{C_6H_6}$[b]
Cyclopentane	150.9	145.6	5.3	...	...	...	0
Tetrahydrofuran	362.1	357.7	4.4	179.6	142.1	37.5	1.69
Tetrahydrothiophene	275.5	254.2	21.3	191.8	146.5	45.3	1.89
Tetrahydroselenophene	340.5	274.1	66.4	204.0	140.2	63.8	1.81
Tetrahydrotellurophene	311.8	283.8	28.0	204.1	161.5	42.6	...
Cyclopentanone	205.4[c]	170.4[c]	35.0	192.2[c]	130.2[c]	62.0	2.93
Tetramethylenesulfone	291.0	227.2	63.8	218.7	119.0	99.7	4.69
Methylenecyclopentane[d]	222.8	217.9	4.9	165.2	148.0	17.2	...
Tetrahydrotellurophene dibromide	387.1	288.7	98.4	292.1	202.0	90.1	...

[a] All γ and Δ values are in units of cycles per second and the dipole moments (μ) are in Debye units. Measurements were made at 100 Mc. [b] Taken from A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963. [c] The α and β chemical shifts were very similar. The Δ values, therefore, were derived by following individual lines rather than centers of resonance. [d] The olefinic protons are deshielded by 18.2 cycles.

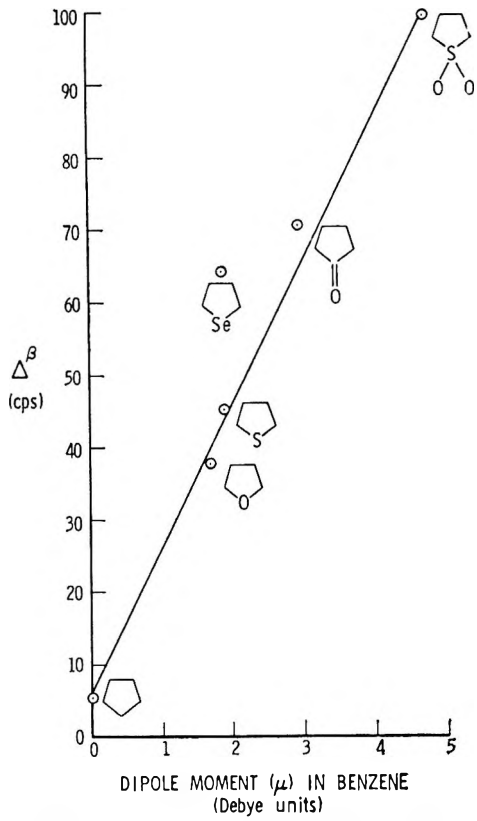

Figure 1.—Plot of dipole moments *vs.* solvent shifts of β protons.

As benzene is believed[11] to solvate electron-deficient sites preferentially, the molecule with the highest dipole moment should show the greatest solvent shift. Steric hindrance will modify this simple picture; and perhaps cause the anomaly in the β-proton shift of tetrahydroselenophene, as well as the nonlinearity of the α-proton shifts.

In order to test independently the validity of the postulated benzene–solute "complexes," the dipole moments of tetrahydrofuran, tetrahydrothiophene, and tetrahydroselenophene were measured in carbon tetrachloride. If an association of the type described above actually exists, the dipole moments of each of these solute molecules in carbon tetrachloride should be changed with respect to benzene. Intuitively, one might expect that the dipole moments should be greater in carbon tetrachloride, for the π electrons of benzene should act to neutralize the dipole. Our results in carbon tetrachloride, together with redeterminations of two results in benzene, are shown in Table II. In

TABLE II

DIPOLE MOMENTS

Compound	$\mu_{CCl_4}^{25°}$	$\mu_{C_6H_6}$[a]	$\mu_{C_6H_6}^{25°}$[b]
Tetrahydrofuran	1.82 ± 0.02	1.69	1.66 ± 0.02
Tetrahydrothiophene	1.98 ± 0.02	1.89	1.85 ± 0.02
Tetrahydroselenophene	1.64 ± 0.02	1.81	...

[a] At 20°, H. de v. Robles, *Rec. Trav. Chim.*, **58**, 111 (1939), taken from Table I, footnote *b*. [b] This work.

accordance with expectation, the dipole moments of tetrahydrofuran and tetrahydrothiophene are indeed greater in carbon tetrachloride. Tetrahydroselenophene is anomalous; however, steric effects of the heteroatom must be greatest in this case.

Experimental Section

Nmr Measurements.—A 5% solution was prepared for each solute in both carbon tetrachloride and deuteriobenzene. TMS was employed as an internal reference. All spectra were taken on a Varian HA 100 nmr spectrometer. Frequencies of all prominent lines were measured with a Hewlett-Packard 522-B electronic counter which has a precision of ±0.1 cps. The solutions were repeatedly diluted by 50% until there were no line shifts between successive dilutions.

Materials.—The following commercially available chemicals were measured without further purification: cyclopentane (Aldrich), tetrahydrofuran (J. T. Baker, boiling range 65.5–65.9°), tetrahydrothiophene (Eastman), cyclopentanone (Eastman), tetramethylene sulfone (Aldrich Chemical Co.), and methylene cyclopentane (K & K).

Tetrahydroselenophene was synthesized by the procedure of Morgan and Burstall.[16] The product was doubly distilled under nitrogen before use. Tetrahydrotellurophene dibromide was formed by the method of Farrar and Gullend,[17] mp 127.5–130.5° (lit.[17] mp 128–131°). Tetrhydrotellurophene was synthesized from the dibromide by the procedure of Morgan and Burstall[18] and was distilled under nitrogen just before use. The carbon tetrachloride (Eastman Technical grade) was also distilled before use and found to contain less than 0.1 mg/ml of impurities after distillation. Deuteriobenzene (99.7%) was obtained from Merck Sharp and Dohme. The purity of tetrahydrothiophene, used for dipole moment measurements, was checked by gas phase chromatography and the compound found to be free of impurities. The tetrahydrofuran was distilled from sodium just prior to being used. Thiophene-free benzene (Baker Analyzed) was distilled from sodium before use in dipole moment studies.

Dipole Moments.—Dielectric constants were measured for a series of carbon tetrachloride and benzene solutions of each compound. All measurements were made in an oil bath at 25° and at a frequency of 1 MHz by means of a Wayne–Kerr transformer ratio arm bridge, Model B601. The capacity of the dielectric cell was measured by a substitution method, using a General Radio Type 1422D variable capacitor. The cell is of a type

(16) G. T. Morgan and F. H. Burstall, *J. Chem. Soc.*, 1096 (1929).
(17) W. V. Farrar and J. M. Gullend, *ibid.*, 11 (1945).
(18) G. T. Morgan and F. H. Burstall, *ibid.*, 180 (1931).

TABLE III

Compound	ϵ_1	V_1, ml/g	α	β, ml/g	P_2, cc	MR_D, cc	μ, D
Tetrahydrofuran[a,b]	2.2280	0.63085	8.59	0.4667	88.59	20.08	1.82
Tetrahydrothiophene[b]	2.2267	0.63078	8.90	0.3344	107.80	26.41	1.98
Tetrahydroselenophene[b]	2.2268	0.63085	3.98	0.1069	85.86	29.19	1.64
Tetrahydrofuran[c]	2.2725	1.14445	4.02	−0.0243	77.62	20.08	1.66
Tetrahydrothiophene[c]	2.2725	1.14445	4.34	−0.1542	97.94	26.41	1.85

[a] ϵ = dielectric constant, V_1 = specific volume, $\alpha = (\epsilon_{12} - \epsilon_1)/W_2$, $\beta = (V_{12} - V_1)/W_2$, W = weight fraction, P = polarization, MR_D = molar refraction. Subscripts: 1, solvent; 2, solute; 12, solution. [b] Measurements carried out in carbon tetrachloride. [c] Measurements carried out in benzene.

designed by Sayce and Briscoe;[19] the air capacitance is 25.99 pF. The cell constant, C_0, was determined from the capacitance, C_a, of the cell containing dry air and the capacitance, C_x, of the cell containing a liquid of known dielectric constant, ϵ, such as benzene or carbon tetrachloride.[20] The cell constant is given by $C_0 = (C_a\epsilon - C_x)/(\epsilon - 1)$.

Solution densities were measured at 25° with a pycnometer that had been calibrated with pure benzene, bp 79.6° (746 mm) (lit.[21] bp 79.6° (746 mm)).

The method of Halverstadt and Kumler[22] was used to calculate the dipole moments. The advantages of this method of treating solution data have been evaluated by Smyth.[23] The electronic polarization is taken as equal to the molar refraction of the solute. The atomic polarization may be assumed, with negligible error,[23] equal to 5% of the electronic polarization. The molar refractions are calculated from electron group refractions.[24] The dipole moments are calculated as

$$\mu = 0.22125(\infty P_2 - 1.05MR_D)^{1/2}$$

In this case, dielectric constants and specific volumes of the carbon tetrachloride and benzene solutions are found to be linear functions of the solute weight fraction over the range studied. The experimental and calculated quantities used to compute the dipole moment are given in Table III.

Registry No.—Benzene, 71-43-2; cyclopentane, 287-92-3; tetrahydrofuran, 109-99-9; tetrahydrothiophene, 110-01-0; tetrahydroselenophene, 3465-98-3; tetrahydrotellurophene, 3465-99-4; cyclopentanone, 120-92-3; tetramethylenesulfone, 126-33-0; methylenecyclopentane, 1528-30-9.

Acknowledgments.—The authors wish to thank L. E. Nelson for making the nmr measurements and Mobil Research and Development Corp. for permission to publish this work.

(19) L. A. Sayce and H. V. A. Briscoe, *J. Chem. Soc.*, 315 (1925).
(20) R. J. W. LeFevre, "Dipole Moments," Methuen and Co., Ltd., London, 1953, p 53.
(21) "Handbook of Chemistry and Physics," K. C. Weast, Ed., The Chemical Rubber Publishing Co., Cleveland, 1964, p D-124.
(22) I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, **64**, 2988 (1942).
(23) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N.Y. 1955, p 224.
(24) See ref 23, p 409.

Acid-Catalyzed Ring Opening of 6,8-Dinitro-1,3-benzodioxane

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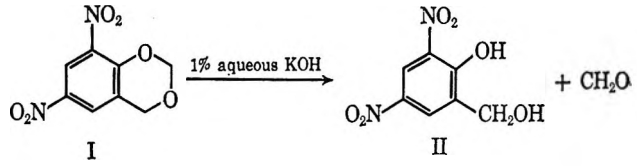
The preparation of 6,8-dinitro-1,3-benzodioxane (I) by the nitration of 6-nitro-1,3-benzodioxane was first described by Chattaway and Irving.[1] Their subsequent investigation[2] revealed that the 6,8-dinitro-1,3-benzodioxane was easily cleaved by dilute alkali to give 2-hydroxy-3,5-dinitrobenzyl alcohol (II).



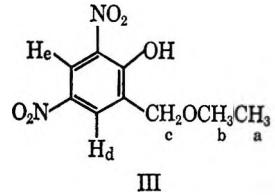
I II

In contrast to this, 6-nitro-1,3-benzodioxane was stable to boiling 25% aqueous alkali or alcoholic potassium ethoxide. Chattaway and Irving then postulated that the stability of this dioxane system toward alkali was decreased by electron-withdrawing groups in the 8 position.

The present investigation has led to the discovery of an acid-catalyzed ring cleavage of 6,8-dinitro-1,3-benzodioxane.

Results and Discussion

The yield of expected product from the nitration of 6-nitro-1,3-benzodioxane was dependent upon the reaction conditions employed. After 20 min at 0° the nitration gave good yields. Prolonged acid treatment at 40–50° led to oxidation and formation of dinitrosalicylic acid as well as the expected product. At intermediate temperatures (10–20°) small quantities of another by-product were formed. This acidic compound (NE 240 ± 2) was precipitated by the addition of water to the ethanolic mother liquor of recrystallization of crude 6,8-dinitro-1,3-benzodioxane and was shown to be 2,4-dinitro-6-ethoxymethylphenol (III) by synthesis using a previously described[3] procedure.



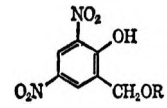
III

Nmr, δ
a, 1.33 (t)
b, 3.71 (q)
c, 4.66 (t, J = 0.7 Hz)
d, 8.62 (d, J = 3.0 Hz)
e, 8.97 (d, J = 3.0 Hz)

The ethoxy compound III and the corresponding methyl ether were found to arise from the dioxane I on treatment with the respective alcohols containing nitric acid. To avoid complications caused by the oxidative properties of nitric acid, the reaction was then performed using an aprotic Lewis acid. A butanol solution of 6,8-dinitro-1,3-benzodioxane containing 1 ml of boron

(1) F. D. Chattaway and H. Irving, *J. Chem. Soc.*, **1931**, 2492.
(2) F. D. Chattaway and H. Irving, *ibid.*, **1934**, 325.
(3) (a) Indian Patent 91,371 (June 1965); (b) French Patent 1,403,658 (Oct 1965).

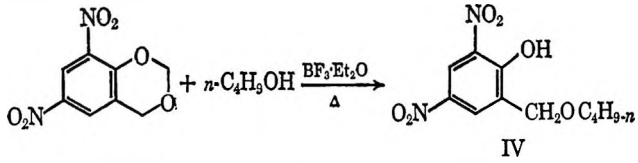
TABLE I
2-ALKOXYMETHYL-4,6-DINITROPHENOLS



No.[i]	R	Reacn conditions: Time, hr	Reacn conditions: Temp, °C	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	CH_3	3	140[a]	84	64[b]	$C_8H_8N_2O_6$	42.11	3.53	12.28	42.18	3.55	12.41
2	C_2H_5	9	130[a]	67	66[c]	$C_9H_{10}N_2O_6$	44.60	4.16	11.62	44.48	4.39	11.88
3	$(CH_3)_2CH$	3	140[a]	99	87[d]	$C_{10}H_{12}N_2O_6$	46.88	4.72	10.93	46.78	4.91	11.26
4	$H_2C{=}CHCH_2$	3	140[a]	55	46	$C_{10}H_{10}N_2O_6$	47.25	3.96	11.02	47.30	4.17	11.03
5	n-C_4H_9	24	118	83	51[e]	$C_{11}H_{14}N_2O_6$	48.86	5.22	10.41	48.80	5.26	10.68
6	sec-C_4H_9	68	100	83	82[f]	$C_{11}H_{14}N_2O_6$	48.86	5.22	10.41	49.19	5.23	10.65
7	i-C_5H_{11}	24	130	88	51	$C_{12}H_{16}N_2O_6$	50.67	5.67	9.90	50.97	5.75	9.80
8	n-C_5H_{11}	4	135	46	47[g]	$C_{12}H_{16}N_2O_6$	50.67	5.67	9.90	50.95	5.63	10.21
9	n-C_6H_{13}	20	140	39	46	$C_{13}H_{18}N_2O_6$	52.34	6.08	9.39	52.61	6.15	9.34
10	$(C_2H_5)_2CHCH_2$	10	140	36	44	$C_{13}H_{18}N_2O_6$	52.34	6.08	9.39	52.55	6.15	9.49
11	$C_6H_5CH_2$	48	108	54	90	$C_{14}H_{12}N_2O_6$	55.24	3.97	9.25	55.42	4.06	9.14
12	$CH_2(CH_2)_4CH-$	6.5	130	70	91[h]	$C_{13}H_{16}N_2O_6$	52.67	5.44	9.50	52.93	5.46	9.52
13	$(CH_3)_2CCH(OH)C(CH_3)_2CH-$	6	110	15	107	$C_{13}H_{20}N_2O_7$	52.96	5.88	8.24	53.15	6.02	8.65

[a] Reaction performed in an autoclave. [b] Lit.[3a] mp 60–61°. [c] Lit.[3a] mp 84–85°. [e] Lit.[3a] mp 49–51°. [f] Lit.[3b] mp 81.5°. [g] Lit.[3a] mp 47–49°. [h] Lit.[3b] mp 87–89°. [i] Registry no.: 1, 2534-05-6; 3, 2542-34-9; 4, 16607-33-3; 6, 2634-04-0; 7, 16607-35-5; 8, 16607-36-6; 9, 16607-37-7; 10, 16607-38-8; 11, 16607-39-9; 12, 2633-96-7; 13, 16607-41-3.

trifluoride etherate was heated to reflux for 24 hr. The product isolated from this reaction was 2-butoxymethyl-4,6-dinitrophenol (IV).



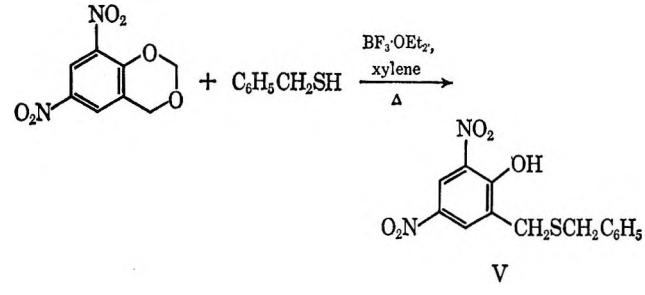
IV

This type of reaction was then extended to other alcohols and the products which were obtained are described in Table I. The reaction required prolonged heating whenever the temperature was maintained below 110°. This required reaction time was dramatically shortened when volatile alcohols were heated under pressure to effect the dioxane cleavage. For example, ethanol was converted in 67% yield into the ethoxymethyl derivative after 9 hr at 130° in an autoclave (41 psig), whereas only a 4% conversion into product was realized after 48 hr at normal reflux temperatures. Several other volatile alcohols were converted into the corresponding benzyl ethers in this fashion.

The scope of this reaction was partially defined when a variety of alcohols were employed as reagents. Formation of 2-alkoxymethyl-4,6-dinitrophenols by this method is apparently limited to the use of sterically unhindered alcohols. Attempted reactions of *t*-butyl alcohol, *t*-pentyl alcohol, diisobutylcarbinol, 4-methyl-2-pentanol, neohexanol and neooctanol all failed to give the desired benzyl ethers. One relatively hindered secondary alcohol, 2,2,4,4-tetramethylcyclobutane-1,3-diol, gave a 15% yield of the 1:1 benzylic ether adduct. In this case, the cyclobutane ring dictated the geometry of the system and minimized the interaction of the hydroxyl with the β-methyl groups. This reaction also proved that a diol could be converted into a 1:1 adduct in spite of the possibility of reaction at each hydroxyl. No attempt was made to isolate any other product.

The products described in Table I had very characteristic infrared spectra. The phenolic O–H stretch absorbed at 3.04–3.08 μ. This assignment was verified by comparison of the spectrum of 2-butoxymethyl-4,6-dinitrophenyl acetate with that of its phenol precursor. A sharp band at 3.05 μ from the phenol was significantly absent after formation of the acetate. Each product exhibited a strong absorption near 6.2 (C=C stretch) as well as a sharp band at 8.2–8.3 μ (OH deformation). The C–O stretch of the ether linkage appeared at 8.8–9.05 μ. In addition to the bands already mentioned, the infrared spectrum of the product from the cyclobutanediol had two sharp bands at 2.78 and 2.85 μ (presumably O–H stretch of *cis* and *trans* isomers).

The preparation of 2-benzylthiomethyl-4,6-dinitrophenol (V) demonstrated that the reaction could be extended to mercaptansm as well as alcohols.

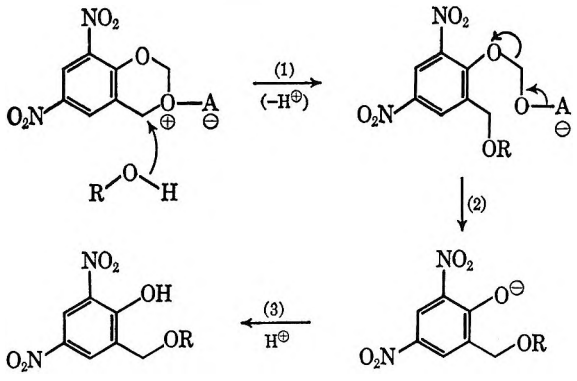


V

A variety of Lewis acids were successfully utilized as catalysts for this reaction. Butanol and 6,8-dinitro-1,3-benzodioxane were maintained at reflux temperature for 24 hr in each case. The catalysts with their corresponding yields of 2-butoxymethyl-4,6-dinitrophenol were as follows: zinc chloride (83%), sulfuric acid (78%), stannic chloride (74%), boric acid (72%), zinc iodide (72%), aluminum chloride (70%), mercuric chloride (70%), boron trifluoride etherate (68%), ferric chloride (59%), and bismuth chloride (41%).

Additional information concerning the scope and limitations of this reaction was obtained by the attempted reaction of 6-nitro-1,3-benzodioxane with butanol. After heating the solution for 24 hr in the presence of boron trifluoride etherate, starting material was quantitatively recovered. The requisite presence of the two nitro groups, in this reaction, led to the postulation of the mechanism in Scheme I where A is a

SCHEME I



Lewis acid. Elimination of formaldehyde from this system (step 2) is evidently dependent upon the formation of the dinitrophenoxide anion. In the absence of the second nitro group, the corresponding *p*-nitrophenoxide anion is considerably less stable as reflected by the fact that 4-nitrophenol is over a 1000-fold less acidic than 2,4-dinitrophenol. This difference in anion stability is so significant that step 2 of the mechanistic pathway is precluded in the mononitro case, and the reverse of step 1 occurs. The proposed mechanism also accounts for the lack of reactivity of sterically hindered alcohols; such attack would perforce create a severe 1,2 interaction with the Lewis acid.

Experimental Section[4]

The 6,8-dinitro-1,3-benzodioxane used as a starting material for this work was prepared according to the method of Chattaway and Irving.[1]

Procedure A is typical of that used to prepare the 2-alkoxymethyl-4,6-dinitrophenols at atmospheric pressure and was also used in the examination of the various Lewis acids as catalysts. Those reactions which were performed under pressure are typified by procedure B.

2-Butoxymethyl-4,6-dinitrophenol. A.—A mixture of 4.5 g (0.02 mol) of 6,8-dinitro-1,3-benzodioxane and 0.2 g of zinc chloride in 40 ml of butanol was stirred and heated to reflux for 24 hr. The resulting solution was chilled (ice bath) and treated with a few drops of water. The yellow platelets which crystallized were collected by suction filtration. Additional product was obtained from the filtrate by the addition of 20 ml of methanol followed by sufficient water to induce crystallization. The combined solids weighed 4.5 g (83% yield) and had mp 48–49°. Recrystallization from aqueous methanol gave an analytical sample.

2,4-Dinitro-6-isopropoxymethylphenol. B.—A 300-ml stainless steel microshaker autoclave was charged with 22.6 g (0.10 mol) of 6,8-dinitro-1,3-benzodioxane, 200 ml of isopropyl alcohol, and 1.0 ml of boron trifluoride etherate. The vessel was purged with nitrogen, then shaken, and heated to 140° for 3 hr. When the vessel had cooled to room temperature, the solution was collected and chilled (ice bath). The resulting tan solid was washed with water and had mp 86–87°. This product was dissolved in boiling methanol and the hot solution was decolorized with charcoal. Treatment of the yellow solution with a few drops of water induced crystallization and gave 25.3 g (99% yield) of analytically pure yellow platelets.

2-Benzylthiomethyl-4,6-dinitrophenol.—A mixture of 22.6 g (0.10 mol) of 6,8-dinitro-1,3-benzodioxane, 24.8 g (0.20 mol) of benzyl mercaptan, 1.0 ml of boron trifluoride etherate, and 225 ml of xylene was stirred and heated to 140° for 24 hr. The reaction mixture was cooled to precipitate 5.0 g of unreacted benzodioxane. The solution was then extracted with three 100-ml portions of 1 *M* sodium hydroxide and the combined aqueous extracts were chilled and acidified to pH 2 with 6 *N* hydrochloric acid. A black oil formed which was dissolved in boiling methanol and the solution was decolorized with charcoal. Chilling the red solution followed by the addition of water gave 2.8 g (11% yield) of yellow product, mp 127–129°. Two recrystallizations (first from aqueous ethanol, then from aqueous methanol) failed to change the melting point of the product.

Anal. Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.47; H, 3.77; N, 8.79; S, 10.01. Found: C, 52.95; H, 4.00; N, 8.94; S, 10.31.

2,4-Dinitro-6-ethoxymethylphenol. A.—Boron trifluoride etherate catalysis and 48 hr at 78° gave a 4% conversion into product. The same procedure with sulfuric acid catalysis and 168 hr at reflux gave a 54% yield of product.

B.—After 9 hr at 130° in an autoclave a 67% yield of product was realized.

C.—A well-stirred solution of 11.3 g (0.05 mol) of 6,8-dinitro-1,3-benzodioxane, 50 ml of ethanol, and 0.5 ml of sulfuric acid in 50 ml of *p*-dioxane was heated to reflux for 30 hr. The solution was chilled and treated with 50 ml of water to give 5.0 g (41% yield) of product.

Registry No.—I, 16607-27-5; III, 2544-94-7; IV, 16607-29-7; V, 16607-30-0.

Acknowledgement.—The authors express their thanks to Dr. R. C. Rittner and his staff for the analytical data, to W. W. Harple and his staff for the infrared spectra, and to G. D. Vickers for his nmr work.

(4) All melting points are uncorrected. Melting points were determined on a Mel-Temp capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer; the nmr spectrum was run in deuteriochloroform solution with tetramethylsilane as an internal standard on a Varian A-60 spectrometer.

Ring-Fused *meso* Ionic *s*-Triazole Derivatives[1]

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In a recent communication,[2] a series of *meso* ionic compounds containing the *s*-triazole nucleus was described. One synthetic procedure used in this earlier study has now been found to be of a general nature for the synthesis of *meso* ionic *s*-triazole derivatives. This paper describes the synthesis of several representative ring-fused systems and the route used here should be useful for the synthesis of numerous heterocyclic systems of unusual structure.

Reaction of the appropriate 2-halo heterocycle with methylhydrazine gave the corresponding 1-methyl-1-(2-heteryl)hydrazine, which underwent ready reaction with phosgene, thiophosgene, or cyanogen bromide to give the appropriate *meso* ionic product. Application of these reactions to the pyridine, quinoxaline, and benzothiazole ring systems gave the products described in Table I. As in our earlier work, analytical and spectral data clearly showed that ring closure to the fused ring system had occurred.

Rearrangement of the substitution pattern in the heterocyclic hydrazine, *e.g.*, replacement of 1-methyl-1-(2-pyridyl)hydrazine (**1**) with 1-amino-2-methylimino-

(1) (a) 1,2,4-Triazoles. Part XIX. (b) Support of this work by U. S. Public Health Service Research Grant CA 08495-01, National Cancer Institute, is gratefully acknowledged.

(2) K. T. Potts, S. K. Roy, and D. P. Jones, *J. Org. Chem.*, **32**, 2245 (1967).

TABLE I

SOME *meso* IONIC RING-FUSED *s*-TRIAZOLE DERIVATIVES

Formula no.	R	Exocyclic atom X	Mp, °C	Crystn solvent[a]	Formula[c]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\nu_{C=O}$, cm^{-1}	$\lambda_{max}^{CH_3OH}$, mμ (log ε)
2		O	219–220[b]	C	$C_7H_7N_3O$	56.4	4.7	28.2	56.2	4.7	28.1	1660	234 (3.97), 285 (3.17)
4		O	212–213	A	$C_7H_7N_3O \cdot H_2O$	50.3	5.4	25.1	50.3	5.2	24.9	1666	235[d] (3.97), 270 (3.84), 308 (3.65)
2		S	311–312	C	$C_7H_7N_3S$	50.9	4.3	25.4	51.2	4.2	25.4		248 (4.24), 291 (3.69)
4		S	262–263	B	$C_7H_7N_3S$	50.9	4.3	25.4	50.7	4.2	25.6		243[d] (4.39), 251 (4.46), 276[d] (3.70), 330 (3.82)
2		NH[e]	247	E	$C_7H_9BrN_4$	36.7	4.0	24.45	36.6	4.0	24.3		
5	H	O	312–313	D	$C_{10}H_8N_4O$	60.0	4.0	28.0	59.8	4.3	28.1	1645	260 (3.80), 262[d] (3.76), 258[d] (3.76), 224 (3.99)
5	H	S	283	D	$C_{10}H_8N_4S$	55.55	3.7	25.9	55.8	3.85	26.0		225 (3.91), 232[d] (3.72), 272[d] (3.72), 289 (3.70)
5	H	NH[e]	292	E	$C_{10}H_{10}BrN_5$	42.8	3.6	25.0	43.05	3.8	25.3		218[d] (4.34), 252 (4.27), 280[d] (3.85).
5	CH_3	O	276	D	$C_{11}H_{10}N_4O$	61.7	4.7	26.2	61.6	4.9	26.45	1637	225 (4.12), 254[d] (3.79), 358 (3.88), 264[d] (3.78)
5	CH_3	NH[e]	299	E	$C_{11}H_{12}BrN_5$	45.0	4.1	23.85	45.2	4.2	23.9		219[d] (4.26), 252 (4.14), 280[d] (3.59), 342 (3.90)
5	Ph	O	292–293	D	$C_{16}H_{12}N_4O$	69.55	4.4	20.3	69.3	4.4	20.3	1653	225 (4.38), 260[d] (4.09), 272 (4.14), 300[d] (3.98)
5	Ph	S	263–265	D	$C_{16}H_{12}N_4S$	65.75	4.1	19.2	65.8	4.0	19.0		225 (4.35), 250[d] (3.80), 285[d] (4.16), 291 (4.18)
5	Ph	NH[e]	321–323	E	$C_{16}H_{14}BrN_5$	54.0	3.9	19.65	53.7	3.9	19.8		257 (4.20), 301 (3.87)
6		O	201	B	$C_9H_7N_3OS \cdot H_2O$	48.5	4.05	18.85	48.5	4.1	19.2	1631	254 (3.92), 270 (4.12), 292 (3.89)
6		S	263	F	$C_9H_7N_3S_2$	48.8	3.2	19.0	49.0	3.3	19.2		230 (4.07), 305 (3.87), 362 (3.80)
6		NH[e]	309	B	$C_9H_9BrN_4S$	38.0	3.2	19.7	38.0	3.2	19.9		225[d] (3.82), 247 (3.62), 280 (3.44), 288 (3.49)

[a] A = acetone; B = methanol; C = acetic acid; D = acetic acid ether; E = methanol ether; F = methanol–ethyl acetate. [b] Lit. mp 216–217°: G. Pallazo and L. Baiochhi [*Ann. Chim.* (Rome), **55**, 935 (1965)] described the synthesis of this product by the same route after the completion of our study. [c] Shoulder. [d] These products, analogous to the sydnone imines can only be isolated as their hydrobromides or other salts. [e] Respective registry numbers are 16621-66-2, 16621-68-4, 16622-03-0, 16622-04-1, 4922-80-9, 16622-05-2, 16622-06-3, 16622-07-4, 16622-08-5, 16622-09-6,16612-10-9, 16622-11-0, 16622-15-4, 16622-12-1, 16622-13-2, 16622-16-5.

1,2-dihydropyridine (**3**), provides a means of obtaining an isomeric *meso* ionic product. This is illustrated by the formation of anhydro-3-mercapto-1-methyl-*s*-triazolo[4,3-*a*]pyridinium hydroxide (**2**) from **1** and thiophosgene, and the formation of anhydro-2-mercapto-3-methyl-*s*-triazolo[1,5-*a*]pyridinium hydroxide (**4**) from **3** and thiophosgene. The dihydropyridine

3 was readily prepared by amination of 2-methylaminopyridine with hydroxylamine-O-sulfonic acid and treatment of the resulting salt with base. An experimental procedure for the preparation of 2-methylaminopyridine that offers several advantages over those reported in the literature is described below.

In the *s*-triazole series, *meso* ionic compounds with an exocyclic sulfur atom reacted readily with methyl iodide to form the corresponding *s*-triazolium salt. A similar nucleophilic behavior of the exocyclic sulfur atom was observed with the fused *s*-triazole systems, *e.g.*, the conversion of anhydro-1-mercapto-3-methyl-4-phenyl-*s*-triazolo[4,3-*a*]quinoxalinium hydroxide (**5**, R = Ph; X = S) into 1-methylthio-3-methyl-4-phenyl-*s*-triazolo[4,3-*a*]quinoxalinium iodide described in the Experimental Section.

Experimental Section[3]

1-Methyl-1-(2-heteryl)hydrazines.—The general procedure used is illustrated by the preparation of the 1-methyl-1-(3-substituted 2-quinoxalinyl)hydrazines. The corresponding 2-chloroquinoxaline (0.5 mol) was dissolved in methanol (200 ml), and methylhydrazine (2.0 mol) was added slowly. After the exothermic reaction had subsided, the resulting solution was refluxed on a steam bath for 5 min and then concentrated under reduced pressure until the product crystallized.

1-Methyl-1-(2-quinoxalinyl)hydrazine was obtained as yellow prisms (80%) from methanol or benzene, or could be purified by sublimation under vacuum: mp 108–110°; ir ($CHCl_3$), 3175, 1610 cm^{-1}.

(3) All evaporations were done under reduced pressure on Rotovap and melting points were taken in capillaries. Infrared spectra were measured on a Perkin-Elmer Model 421 infrared spectrophotometer and on a Baird Model IR-2 spectrophotometer. Ultraviolet absorption spectral data were obtained on a Beckman DK2 spectrophotometer. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.8; N, 32.2. Found: C, 62.2, H, 5.95; N, 32.4.

The picrate was isolated from benzene as yellow needles, mp 157°.

Anal. Calcd for $C_{15}H_{13}N_7O_7$: N, 24.3. Found: N, 24.1.

The *p*-nitrobenzalhydrazone crystallized from benzene as yellow plates, mp 245–247°.

Anal. Calcd for $C_{16}H_{13}N_5O_2$: N, 22.8. Found: N, 23.0.

1-Methyl-1-(3-methyl-2-quinoxalinyl)hydrazine was obtained as yellow needles (45%) from aqueous ethanol, or by sublimation under vacuum: mp 65–67°; ir ($CHCl_3$), 3226, 2890, 1600 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.8; H, 6.4; N, 29.8. Found: C, 64.0; H, 6.4; N, 29.7.

The picrate was isolated from benzene as yellow prisms, mp 167–168°.

Anal. Calcd for $C_{16}H_{15}N_7O_7$: N, 23.5. Found: N, 23.2.

The *p*-nitrobenzalhydrazone crystallized from ethanol as yellow plates, mp 254–256°.

Anal. Calcd for $C_{17}H_{15}N_5O_2$: N, 21.8. Found: N, 21.6.

1-Methyl-1-(3-phenyl-2-quinoxalinyl)hydrazine was obtained as yellow needles (45%) from methanol: mp 103–105°; ir ($CHCl_3$), 3175–2985, 1575 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_4$: C, 72.0; H, 5.6; N, 22.4. Found: C, 71.7; H, 5.7; N, 22.5.

The picrate was obtained from tetrahydrofuran as yellow prisms, mp 225° dec.

Anal. Calcd for $C_{21}H_{17}N_7O_7$: N, 20.55. Found: N, 20.4.

The *p*-nitrobenzalhydrazone crystallized from aqueous methanol as orange needles, mp 174–175°.

Anal. Calcd for $C_{22}H_{17}N_5O_2$: N, 18.3. Found: N, 18.15.

1-Methyl-1-(2-benzothiazolyl)hydrazine crystallized from aqueous ethanol as colorless plates (91%): mp 140°; ir ($CHCl_3$), 3067, 2809, 1642, 1595 cm^{-1}.

Anal. Calcd for $C_8H_9N_3S$: C, 53.6; H, 5.1; N, 23.4. Found: C, 53.8; H, 5.3; N, 23.3.

1-Methyl-1-(2-pyridyl)hydrazine was obtained as a colorless oil (83%): bp 53–54° (0.1 mm) [lit.[4] bp 116–122° (18 mm)]. It was characterized as its picrate which formed yellow needles from ethanol: mp 165–166° (lit.[4] mp 166–167°).

Anal. Calcd for $C_{12}H_{12}N_6O_7$: C, 40.9; H, 3.4; N, 23.9. Found: C, 41.3; H, 3.4; N, 24.1.

2-Methylaminopyridine.—2-Formamidopyridine[5] (71.0 g) in dimethylformamide (100 ml) was added slowly to an ice-cold suspension of sodium hydride (24.0 g, 53.6% in oil suspension) in dimethylformamide (70 ml) with vigorous stirring. Copious evolution of hydrogen took place. After the addition, the mixture was stirred for 30 min and the brown solution was treated with dry benzene (100 ml) and then methyl iodide (27 ml) was added dropwise. After heating on the steam bath for 2 hr, the reaction mixture was extracted with chloroform (300 ml), washed with water, and dried (K_2CO_3) and the extracts were concentrated under reduced pressure. The residual brown oil was distilled under reduced pressure and 2-(N-methylformamido)pyridine was distilled as a colorless oil (59.0 g), bp 160–163° (35 mm). It was then refluxed with aqueous hydrochloric acid (160 ml, 1:1) for 1 hr and the acidic solution was extracted with chloroform (50 ml) and concentrated under reduced pressure. The residue was strongly basified with aqueous sodium hydroxide solution (30%) and extracted with chloroform (150 ml). The chloroform solution was dried (K_2CO_3) and concentrated. Upon distillation of the residual oil, 2-methylaminopyridine (31.0 g) distilled at 205–206° as a colorless oil which soon turned yellow on exposure to air (lit.[6] bp 200–201°).

The picrate crystallized from methanol as yellow needles, mp 192–193° (lit.[6] mp 190°).

Anal. Calcd for $C_{12}H_{11}N_5O_7$: N, 20.8. Found: N, 20.7.

1-Amino-2-methylaminopyridinium Bromide.—A solution of potassium hydroxylamine-O-sulfonate, prepared from hydroxylamine-O-sulfonic acid (5.6 g) in water (40 ml), was added to a mixture of 2-methylaminopyridine (5.4 g) and water (3 ml) and the whole was warmed at 70° for 45 min, cooled, and treated with an aqueous solution of potassium carbonate (3.25 g in 10 ml). The water was removed under reduced pressure at 40–50° and the residue was extracted with absolute ethanol (60 ml). The brown ethanolic solution was treated with aqueous hydrobromic acid (48%) (pH 2–3), cooled in a Dry Ice bath, and diluted carefully with ether when a gummy residue separated. This upon trituration with absolute ethanol (10 ml) gave a yellowish white solid (5.5 g) that crystallized from absolute ethanol as colorless needles, mp 151–153° with previous sintering at 145°.

Anal. Calcd for $C_6H_{10}BrN_3$: C, 35.3; H, 4.9; N, 20.6. Found: C, 35.05; H, 5.0; N, 20.4.

The picrate, prepared by treatment of the hydrobromide in methanol with picric acid, crystallized from methanol (charcoal) as yellow needles, mp 160–161°.

Anal. Calcd for $C_{12}H_{12}N_6O_7$: C, 40.9; H, 3.4; N, 23.9. Found: C, 41.0; H, 3.1; N, 23.8.

The following procedures illustrate the reaction conditions used for the synthesis of the *meso* ionic compounds described in Table I.

***anhydro*-1-Hydroxy-3-methyl-4-Substituted *s*-Triazolo[4,3-*a*]-quinoxalinium Hydroxide.**—The methylhydrazine (0.1 mol) was dissolved in benzene (100 ml) and warmed on a steam bath. With constant stirring, phosgene was bubbled into the solution for 5 min. After 1 hr of reflux on the steam bath, the resulting crystals were filtered and recrystallized from the solvent shown in Table I.

***anhydro*-1-Mercapto-3-methyl-4-Substituted *s*-Triazolo[4,3-*a*]-quinoxalinium Hydroxide.**—The hydrazine (0.05 mol) was dissolved in benzene, followed by the slow addition of thiophosgene. The reaction mixture was refluxed for 1 hr or until the desired product precipitated. Recrystallization was effected from the solvents listed in Table I.

1-Amino-3-methyl-4-Substituted *s*-Triazolo[4,3-*a*]quinoxalinium Bromide.—Equal molar amounts of the appropriate hydrazine and cyanogen bromide were refluxed in methanol (200 ml) for 3 hr. The reaction mixture was evaporated to dryness and the residue recrystallized from the solvent indicated in Table I.

Reaction of 1-Amino-1,2-dihydro-2-methyliminopyridine with Thiophosgene.—The base obtained by filtering a methanolic solution of 1-amino-2-methylaminopyridinium bromide (2.8 g) through an ion exchange column (IRA-400) was freed from methanol under reduced pressure and then dissolved successively in dry chloroform (100 ml) and in dry benzene (100 ml) with the solvents being removed under reduced pressure. The brown residue was dissolved in dry chloroform (100 ml) and added to a solution of thiophosgene (4.0 g) in chloroform (50 ml) and refluxed for 3.5 hr. The solvent was removed completely and the residue was treated with methanol when a pale yellow solid (0.35 g) was obtained. It crystallized from methanol (charcoal) as colorless plates, mp 262–263°.

1-Methylthio-3-methyl-4-phenyl-*s*-triazolo[4,3-*a*]quinoxalinium Iodide.—*anhydro*-1-Mercapto-3-methyl-4-phenyl-*s*-triazolo[4,3-*a*]quinoxalinium hydroxide (0.2 g) and methyl iodide (2 ml) in methanol (2 ml) were warmed on a steam bath for 15 min. Upon cooling, ether was added and the resulting product was recrystallized from methanol–ether, forming yellow plates (45%): mp 215°; ir (Nujol), 2941 (N-CH_3), 1351 (S-CH_3) cm^{-1}.

Anal. Calcd for $C_{17}H_{15}IN_4S$: C, 47.0; H, 3.5; N, 12.9. Found: C, 47.1; H, 3.7; N, 12.8.

Registry No.—1-Methyl-1-(2-quinoxalinyl)hydrazine, 16621-55-9; 1-methyl-1-(2-quinoxalinyl)hydrazine picrate, 16621-67-3; 1-methyl-1-(2-quinoxalinyl)hydrazine *p*-nitrobenzalhydrazone, 16622-19-8; 1-methyl-1-(3-methyl-2-quinoxalinyl)hydrazine, 16621-56-0; 1-methyl-1-(3-methyl-2-quinoxalinyl)hydrazine picrate, 16621-57-1; 1-methyl-1-(3-methyl-2-quinoxalinyl)hydrazine *p*-nitrobenzaldehydrazone, 16621-58-2; 1-methyl-1-(3-phenyl-2-quinoxalinyl)hydrazine, 16621-59-3; 1-methyl-1-(3-phenyl-2-quinoxalinyl)hydrazine picrate, 16621-60-6; 1-methyl-1-(3-phenyl-2-quinoxalinyl)-hydrazine *p*-nitrobenzalhydrazone, 1057-22-3; 1-methyl-1-(2-benzothiazolyl)hydrazine, 16621-62-8; 2-methylamino-1-aminopyridinium bromide, 16621-63-9; 2-methylamino-1-aminopyridine picrate, 16621-64-0; 1-methylthio-3-methyl-4-phenyl-*s*-triazolo[4,3-*a*]quinoxalinium iodide, 16621-65-1.

(4) G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959).

(5) A. E. Tschitschibabin and I. L. Knunjanz, *Ber.*, **64**, 2841 (1931).

(6) A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *ibid.*, **54**, 814 (1921).

Aroylations of N,N-Dimethylglycinonitrile to Form α-Dimethylamino-β-ketonitriles. Cyclizations with Acetophenone to Give 3-Dimethylamino-2-pyridones[1]

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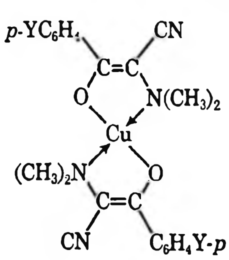
Similar to the earlier benzoylation of acetonitrile to form benzoylacetonitrile,[2] aroylations of dimethylaminoacetonitrile (**1**)[3] have now been accomplished with methyl benzoate, methyl anisate, and methyl *p*-chlorobenzoate by means of sodium amide in liquid ammonia to form aroyl N,N-dimethylglycinonitriles **2a–c**, respectively (eq **1**) (Table I).

$$CH_2(CN)N(CH_3)_2 \xrightarrow[\text{liquid } NH_3]{NaNH_2} NaCH(CN)N(CH_3)_2 \xrightarrow[2.\ NH_4Cl]{1.\ p\text{-}YC_6H_4COOCH_3} p\text{-}YC_6H_4COCH(CN)N(CH_3)_2 \quad (1)$$

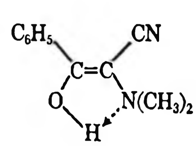
2a, Y = H
b, Y = OCH_3
c, Y = Cl

These new examples of the Claisen type of aroylation were effected in the presence of an extra equivalent of sodium amide,[4] and the products **2a–c** were isolated through their hydrochloride salts. The yield of **2a** was 65% when isolated in this manner but only 40% when isolated by direct recrystallization of the crude reaction product.

In contrast to benzoylacetonitrile, the corresponding α-dimethylamino compound **2a** evidently exists mainly in its enol form. Whereas benzoylacetonitrile gave a negative enol test and failed to form a copper chelate, **2a** produced a strong, positive enol test with ethanolic ferric chloride and readily yielded the copper chelate **3a**. The infrared spectrum of benzoylacetonitrile



3a, Y = H
b, Y = Cl



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showed a strong carbonyl peak but that of **2a** exhibited only a slight shoulder in this region. The nmr spectrum of **2a** showed an enol proton at 8.5 and a methinyl proton at 5.2 ppm, the intensities of which were, by integration, in the ratio of 3:2. These results suggest

(1) Supported by the National Science Foundation and by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute.

(2) C. J. Eby and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 723 (1957).

(3) This compound is readily prepared from formaldehyde, dimethylamine, and sodium cyanide: A. Lespangnol, E. Cuingnet, and M. Derbaert, *Bull. Soc. Chim. Fr.*, **2**, 383 (1960).

(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 114, 122 (1954).

TABLE I

AROYL N,N-DIMETHYLGLYCINONITRILES AND THEIR COPPER CHELATES

Compd	Mp, °C	Yield, %	Infrared spectrum, μ	Empirical formula	Calcd, % C	H	N	Found, % C	H	N
2a	85–86	65	3.3 (s) broad, 3.5 (s) broad, 4.6 (s), 6.0 (w) sh, 6.15 (m) Sh, 6.3 (s)	$C_{11}H_{12}N_2O$	70.2	6.43	14.9	70.26	6.50	14.87
2b	69–70	45	2.9 (w) broad, 3.35 (m), 3.5 (m) 4.5 (m), 5.9 (s), 6.2 (s), 6.35 (s)	$C_{12}H_{14}N_2O_2$	66.1	6.47	12.83	66.06	6.43	12.82
2c	84–85	60	3.1 (s) broad, 3.6 (s) broad, 4.55 (s), 5.95 (m) Sh, 6.25 (s) broad	$C_{11}H_{11}N_2OCl$	59.3	4.98	12.58	59.12	5.12	12.36
3a	181	48	3.4 (w) broad, 4.55 (s), 6.3 (m), 6.5 (s)	$C_{22}H_{22}N_4O_2Cu$	60.25	5.06	12.78	60.34	5.01	12.65
3b	184–185	53	3.4 (w) broad, 4.6 (s), 6.3 (m), 6.5 (s)	$C_{22}H_{20}N_4O_2Cl_2Cu$	52.15	3.97	11.05	52.07	4.32	10.84

TABLE II
3-DIMETHYLAMINO-4-*para*-SUBSTITUTED 6-PHENYL-2(1H)-PYRIDONES

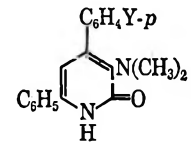
Compd	Mp, °C	Yield, %	Infrared spectrum, μ	Empirical formula	Calcd, % C	Calcd, % N	Found, % C	Found, % H	Found, % N
5a	231–234 dec	37	2.9 (w), 3.4 (s) broad, 6.1 (s), 6.35 (m), 6.5 (m), 12.9 (s), 13.1 (s), 14.3 (s)	$C_{19}H_{18}N_2O$	78.6	6.35	78.55	6.42	9.32
5b	259–262 dec	35[a]	2.9 (w), 3.5 (s) broad, 6.1 (s), 6.35 (m), 6.5 (m), 12.0 (s), 12.2 (m), 13.0 (s) doublet, 14.4 (s)	$C_{20}H_{20}N_2O_2$	75.0	6.3	74.89	6.26	8.56
5c	272–275 dec	30	2.9 (w), 3.4 (s) broad, 6.15 (s), 6.3 (m), 6.5 (m), 11.9 (s), 12.3 (m) 12.9 (s), 14.4 (s)	$C_{19}H_{17}N_2OCl$	70.20	5.35	70.36	5.23	8.53

[a] Also amide **6b**, mp 135–136°, was isolated in 35% yield. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 61.0; H, 6.83; N, 11.86. Found: C, 61.22; H, 6.78; N, 12.10.

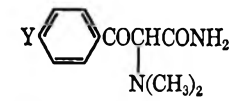
that about two-thirds of **2a** exists in the enol form which, in spite of distortion of the normal bond angles of the ethylene system, appears to be stabilized by hydrogen bonding as indicated in **4**. Such distortion may be mitigated somewhat by conjugation of the ethylniec double bond with both the phenyl and cyanide groups. Another possibility for stabilization of the enol form might arise through the enamine type of resonance. Molecular weight determinations by the Rast method in camphor and by the freezing point method in benzene indicated that the enol form did not exist as a dimer.

Although **2a** gave a strong enol test, the *p*-methoxy and *p*-chloro compounds **2b–c** produced weakly positive enol tests and their infrared spectra showed strong and medium peaks, respectively, for the carbonyl group. These results suggest predominance of the keto form; **2c** afforded copper chelate **3b**, but this may have arisen through shift in equilibrium to the side of the enol as the reaction proceeded.

Similar to the earlier cyclization of benzoylacetonitrile or benzoylacetamide with acetophenone to form a substituted 2-pyridone,[5] the ketoaminonitriles **2a–c** were cyclized with this ketone by means of polyphosphoric acid (PPA) to give the amino-2-pyridones **5a–c**, respectively (Table II). Presumably, the corresponding amides such as **6a–b** or PPA derivatives of them were intermediates; actually, amide **6b** was isolated from the reaction mixture (see note *a*, Table II). Moreover, nitrile **2a** was converted into amide **6a** by sulfuric acid, and subsequently cyclized with acetophenone to form pyridone **5a** by PPA. Benzoylacetonitrile has previously been converted into benzoylacetamide by PPA.[6]



5a, Y = H
b, Y = OCH_3
c, Y = Cl



6a, Y = H
b, Y = OCH_3

All of the products described above are new. Their structures are supported by analyses and infrared spectra (see Tables I and II and Experimental Section). The yields of the ketoaminonitriles **2a–c** were good (45–65%), but those of the amino pyridones **5a–c** were only fair (30–37%); these yields are probably not the maximum obtainable.

Experimental Section[7]

Aroyl N,N-Dimethylglycinonitriles (Table I).—Sodium amide was prepared by dissolving 10.7 g (0.466 mol) of sodium in approximately 350 ml of liquid ammonia containing a trace of ferric nitrate hexahydrate. To the stirred suspension of sodium amide in liquid ammonia was added N,N-dimethylglycinonitrile[3] (19.6 g, 0.233 mol). A yellow color developed. After stirring

(5) C. R. Hauser and C. J. Eby, *J. Amer. Chem. Soc.*, **79**, 728 (1957).
(6) C. R. Hauser and C. J. Eby, *ibid.*, **79**, 725 (1957).
(7) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord in potassium bromide pellets. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform solutions and tetramethylsilane as an internal standard. Elemental analyses were performed by Janssen Pharmaceutical Research Laboratories, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich.

for 15 min, 0.233 mol of the appropriate ester was added in 75 ml of ether. The reaction mixture was stirred for 20 min; then an excess of ammonium chloride was added. The ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was stirred with water to dissolve the inorganic salts. The layers were separated, and the aqueous layer was extracted twice with small portions of ether. The combined ethereal solution was dried over anhydrous sodium sulfate and saturated with anhydrous hydrogen chloride. The resulting precipitate was collected and dried to give the crude hydrochloride salts of the aroyl N,N-dimethylglycinonoitriles 2a–c in yields of 80, 70, and 75%, respectively. The salts were neutralized with aqueous sodium bicarbonate to liberate the free base. Extraction of the aqueous mixture with ether, removal of the ether under reduced pressure, and recrystallization of the solid residue from hexane provided 2a–c in the yields given in Table I.

To a solution of the aryl N,N-dimethylglycinonitrile in ethanol was added an excess of aqueous copper acetate solution with stirring. The mixture was stirred for about 20 min; then the precipitate was collected and recrystallized from 95% ethanol to give the copper chelate (see Table I).

Benzoyl N,N-Dimethylglycinamide (6a).—Benzoyl N,N-dimethylglycinonitrile (2a) (1 g) was dissolved in 5 g of concentrated sulfuric acid and heated on the steam bath for 30 min. The reaction mixture was poured onto crushed ice and the solution was neutralized with solid sodium bicarbonate. The mixture was extracted several times with ether; the combined ethereal extract was dried over anhydrous potassium carbonate and the ether was removed under reduced pressure. The residue was recrystallized from a benzene–hexane mixture giving 0.9 g (85%) of the amide 6a: mp 93–94°; ir, 3.0 (s), 3.15 (s), 3.5 (m), 3.55 (m), 5.9 (s), 6.1 (w), and 6.25 (m) μ.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.84; N, 13.59. Found: C, 64.38; H, 6.75; N, 13.33.

3-Dimethylamino-4-*para*-Substituted 6-Phenyl-2(1H)-pyridones (Table II).—The aroyl N,N-dimethylglycinonitrile was stirred into five times its weight of polyphosphoric acid, and then an equivalent of acetophenone was added. The reaction mixture was placed in an oil bath and heated at 80–90° until a homogeneous solution was obtained. An additional equivalent of acetophenone was added and the temperature was raised to 140° and maintained at this temperature for 25 min. Upon addition of the solution to crushed ice, a precipitate formed. The resulting mixture was made basic with ammonium hydroxide and the precipitate was collected. Recrystallization of the product from benzene–ethanol gave the pyridone.

In a similar manner, N,N-dimethylbenzoylglycinamide (6a) was cyclized to give pyridone 5a in 35% yield.

Registry No.—**1**, 926-64-7; acetophenone, 98-86-2; **2a**, 16607-55-9; **2b**, 16607-56-0; **2c**, 16607-57-1; **3a**, 16591-65-4; **3b**, 16591-66-5; **5a**, 16607-58-2; **5b**, 16607-18-4; **5c**, 16607-19-5; **6a**, 16622-18-7; **6b**, 16607-20-8.

A Convenient Preparation of Dimethyl Cyclohexa-1,3-diene-1,4-dicarboxylate. A Bicyclo[2.2.2]octane Precursor

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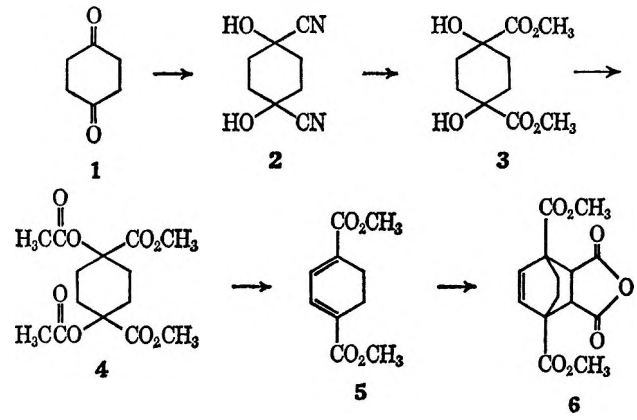
We wish to report a convenient synthesis of dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate (5; see Chart I), a bicyclo[2.2.2]octane precursor. Bridgehead substituted bicyclo[2.2.2]octanes have been a subject of intensive study.[1] A time-consuming synthesis of these

(1) See H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **87**, 2404 (1965), and references cited therein.

CHART I



compounds was developed by Kauer and coworkers[2] which involves the dehydrohalogenation of dimethyl 1,4-dibromocyclohexane-1,4-dicarboxylate followed by addition of ethylene to the resulting 1,3-diene.

Although 1,4-cyclohexanedione is available by other routes,[3] we found the oxidation of 1,4-cyclohexanediol with chromium trioxide to be a convenient source of this dione. Compound 1 reacts readily with acetone cyanohydrin to yield compound 2. This material, in turn, is then converted in two steps into dimethyl 1,4-diacetoxy-1,4-dicarboxylate (4). Pyrolysis of this diacetate at 400° affords the desired diene (5) in 75% yield. The other major product, formed in 18% yield, is dimethyl terephthalate. The crude pyrolysate reacted readily with maleic anhydride to give 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-*endo*-2,3-dicarboxylic anhydride (6). It is of interest to note the remarkable selectivity of the pyrolysis reaction under the conditions studied, especially since previous work strongly suggests that dimethyl cyclohexa-1,4-diene-1-4-dicarboxylate is the most stable of the methyl esters of the dihydroterephthalic acids.[4]

Experimental Section[5]

1,4-Cyclohexanediol.—This alcohol was prepared in 93% yield by the hydrogenation of hydroquinone according to the procedure of Owen and Robins.[6]

1,4-Cyclohexanedione (1)[3,7] was prepared by adding a solution of CrO_3 (9.1 g) and concentrated sulfuric acid (7.7 ml) in water (33.8-ml total volume)[8] to 1,4-cyclohexanediol (5.0 g, 0.043 mol) in acetone (300 ml) at 10°. After addition was completed (1 hr, voluminous precipitate), stirring for 0.5 hr, pouring into ice water, neutralizing with Na_2CO_3, continuous extraction with CH_2Cl_2, drying ($MgSO_4$), evaporating, and sublimation of the residue gave 4.1 g (84%) of 1.

1,4-Dihydroxy-1,4-dicyanocyclohexane (2).—1,4-Cyclohexanedione (56 g, 0.5 mol) was mixed with acetone cyanohydrin[9] (750 ml, Matheson Coleman and Bell, practical grade) and heated to

(2) J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431 (1965). These authors discuss the synthetic difficulties of previously reported approaches toward these compounds.

(3) A. T. Nielsen and W. R. Carpenter, *Org. Syn.*, **45**, 25 (1965).

(4) See ref 2, footnote 17.

(5) Melting points are corrected and were recorded on a Fisher–Johns apparatus. Microanalyses were done by H. C. Jones of this laboratory. Ultraviolet spectra were recorded on a Perkin-Elmer Spectracord Model 4000A. Infrared spectra were taken as KBr pellets using a Perkin-Elmer Infracord Model 137 spectrophotometer. Gas chromatographic analyses were done using an F & M Model 700 chromatograph. Recrystallizations were done in ethyl acetate.

(6) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

(7) J. R. Vincent, A. F. Thompson, Jr., and L. I. Smith, *J. Org. Chem.*, **3**, 603 (1939).

(8) C. Djerassi, R. R. Engle, and A. Bowers, *ibid.*, **21**, 1547 (1956).

(9) H. J. Ringold, *J. Amer. Chem. Soc.*, **82**, 961 (1960).

40°; 10% NaOH (20 ml) was added; and this temperature was kept for 0.5 hr. The mixture was cooled and poured into 1500 ml of ice water containing 10 ml of glacial HOAc. The white precipitate after drying and recrystallizing weighed 56 g (67%), mp 167–168°. The yield of cyanohydrin can be raised to 85% of theoretical by running the reaction overnight at room temperature. An infrared spectrum of this solid exhibited absorptions *inter alia* at 3400 (OH stretching vibration) and at 2265 cm^{-1} (C≡N stretching vibration).

Anal. Calcd for $C_8H_{10}O_2N_2$: C, 57.85; H, 6.07; N, 16.85. Found: C, 57.54; H, 6.14; N, 16.97.

Dimethyl 1,4-dihydroxy-1,4-cyclohexanedicarboxylate (3) was prepared by slowly adding HCl (Matheson, reagent grade) to a solution of **2** (8.4 g, 0.05 mol) in methanol (100 ml) until no more gas was absorbed. The mixture was stirred for an additional 2 hr and the resulting precipitate was collected and reacted with water (200 ml) overnight. The recrystallized white solid weighed 9.1 g (81% yield), mp 162–175°. An infrared spectrum of this material exhibited absorptions *inter alia* at 3510 (OH stretching vibration) and at 1730 cm^{-1} (C=O stretching vibration). The diester (2.0 g) was saponified under usual conditions[10] and the white crystals collected after acidification were recrystallized to obtain 1.5 g of 1,4-dihydroxy-1,4-cyclohexanedicarboxylic acid, mp 224–237°. An infrared spectrum of this solid (KBr pellet) exhibited absorptions *inter alia* at 3415 and 1720 cm^{-1}.

Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.93. Found: C, 46.92; H, 5.81.

Dimethyl 1,4-Diacetoxy-1,4-cyclohexanedicarboxylate (4).—To acetic anhydride (16.4 g, 0.16 mol) at 80° was slowly added a solution of compound **3** (9.2 g, 0.04 mol) in HOAc (80 ml). The reaction mixture was refluxed overnight, cooled, and poured into ice water. After drying and recrystallization 11.4 g (90% yield) of a white solid was obtained, mp 168–182°.

An infrared spectrum of this solid exhibited an absorption, *inter alia*, at 1750 cm^{-1} (acetate C=O stretching vibration).

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.38. Found: C, 53.14; H, 6.27.

Dimethyl Cyclohexa-1,3-diene-1,4-dicarboxylate (5).—Pyrolyses[11] were conducted in a 0.75 × 18 in. quartz column, filled with 0.25-in.-diameter glass beads, mounted vertically and surrounded by an electric heating oven. A slow stream of nitrogen was passed through the column during the pyrolysis. The temperature was controlled by means of a "Pyro-O-Vane" temperature controller. The temperature inside the column was measured with a thermocouple inserted in a well near the center of the column. The pyrolysate was collected in two traps connected in series and immersed in a Dry Ice–perchloroethylene mixture.

In a typical run, 5.0 g of dimethyl 1,4-diacetoxy-1,4-cyclohexanedicarboxylate was dissolved in 300 ml of methyl acetate at 50°, maintained at this temperature throughout the reaction by means of flexible heating tape, and was dropped through the column at 400° and at a rate of *ca.* 2.5 ml/min. When the addition was complete, the column was allowed to cool and was washed with additional methyl acetate.

Removal of the solvent afforded 3.8 g of a slightly yellow product. Vapor phase chromatographic analysis[12] revealed that 95% of the starting material had been converted into two major products with retention times of 5.8 and 6.2 min. The first peak accounted for 18% of the pyrolysate, whereas the latter represented a 75% yield. Samples of both materials were collected from the gas chromatograph. The product with a retention time of 5.8 min melted at 139–141°, identical with the melting point of dimethyl terephthalate.[13] Comparison of the infrared spectrum and vpc retention time with an authentic sample[14] completed the identification. The 6.2-min product melted at 83.5–84.2° (lit.[2] mp 83.1–84.6°). Comparison of the infrared and ultraviolet spectra with those of authentic samples helped confirm the identification.[15] To complete the identification, the adduct of the pyrolysate with maleic anhydride was prepared by a previously described procedure.[16] The adduct melted at 185–192° (lit. mp 188.0–188.6°,[16] 191.5°[17]) and its infrared spectrum, as a KBr pellet, exhibited absorptions at 1865, 1780, 1745, and 1620 cm^{-1} identical with the published spectrum[17] of 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-*endo*-2,3-dicarboxylic anhydride.

Registry No.—**2**, 16273-48-6; **3**, 16273-49-7; **3**, free acid, 16273-50-0; **4**, 16273-51-1; **5**, 1659-95-6.

Acknowledgment.—The author is grateful to Dr. J. W. Way for many valuable discussions.

(10) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1950, p 83.

(11) W. J. Bailey, R. Barclay, and R. A. Baylouney, *J. Org. Chem.*, **27**, 1851 (1962).

(12) A 6 ft. × 0.25 in. diameter 10% XE-60 on 60/80 mesh Chromosorb W column was used. No corrections were made for differences in thermal conductivities.

(13) I. Heilbron, "Dictionary of Organic Compounds," Vol. 5, Oxford University Press, New York, N. Y., 1965, p 2,949.

(14) Du Pont dimethyl terephthalate, refined grade.

(15) The author is grateful to Dr. J. C. Kauer for supplying these spectra.

(16) J. C. Kauer, U. S. Patent 3,071,597 (Jan 1, 1963).

(17) G. Smith, C. L. Warren, and W. R. Vaughan, *J. Org. Chem.*, **28**, 3323 (1963).

Synthesis of α-Hydroxyarylacetic Acids from Bromoform, Arylaldehydes, and Potassium Hydroxide, with Lithium Chloride Catalyst

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Received December 5, 1967

A one-step preparation of α-methoxyarylacetic acids from arylaldehydes, bromoform (or chloroform), and potassium hydroxide in methanol has been described.[1] The preparative method for the α-hydroxyarylacetic acids given here is a modification of that procedure, differing in that lithium chloride serves as an additional catalyst along with the potassium hydroxide,[2] and a 50:50 mixture of water and 1,4-dioxane acts as solvent, instead of methanol. The yields in these α-hydroxy compound syntheses (quantitative) are decidedly better than those obtained in the preparations of α-methoxy compounds (1–80%).

There are a number of articles in the literature wherein others have reported preparation of trihalomethyl carbinols (a proposed intermediate in this reaction) in heterogeneous media, and/or treated trihalomethylcarbinols with nucleophilic reagents to obtain α-substituted acids, but none of these procedures[2,3] produces a quantitative yield of product.

In some of these cases[2] the yields are less because side reactions, such as the Cannizzaro, are occurring simultaneously or exclusively. In fact, when the preparations of the α-hydroxyarylacetic acids were attempted in pure 1,4-dioxane and with lithium hydroxide as a base catalyst (a heterogeneous mixture), with six different aryl aldehydes only the corresponding arylcarboxylic acids were isolated.

(1) W. Reeve and C. W. Woods, *J. Amer. Chem. Soc.*, **82**, 4062 (1960); W. Reeve and E. L. Compere, Jr., *ibid.*, **83**, 2755 (1961).

(2) The potassium hydroxide is a reagent as well as a catalyst; see E. D. Bergmann, D. Ginsburg, and D. Lavie, *ibid.*, **72**, 5012 (1950).

(3) (a) P. Hebert, *Bul. Soc. Chim. Fr.*, **27**, 45 (1920); (b) J. W. Howard, *J. Amer. Chem. Soc.*, **47**, 455 (1925); (c) J. W. Howard, *ibid.*, **52**, 5059 (1930); (d) J. Jocicz, *Zh. Russ. Fiz. Khim. Obshchest.*, **29**, 100 (1897); *Chem. Zentr.*, **1**, 1013 (1897).

TABLE I

SPECIFIC DATA ON THE α-HYDROXYARYLACETIC ACID SYNTHESES

Compd[a]	Mp, °C Obsd	Mp, °C Lit.	Quantity of starting aldehydes	Crude yields of hydroxy acids[c]	Recrystn solvent	Analytical data: Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Neut equiv Calcd	Neut equiv Found
α-Hydroxyphenylacetic acid	118–119.5	118–119[d]	26.5 g (0.25 mol), benzaldehyde	34.2–35.1 g or 90.0–92.3% 28.5 g of 75.0%[b]	5:1 Chloroform–ligroin (60–90°)	63.16	63.12	5.29	5.37	152	153
2-Chloro-α-hydroxyphenylacetic acid	82–83	85–85.5[e]	35.1 g (0.25 mol), 2-chlorobenzaldehyde	45.9–47.2 g or 98.3–100%	Chloroform	51.49	51.71	3.78	3.97	186.5	188
3-Chloro-α-hydroxyphenylacetic acid	106.5–107	115–115.5[e]	10 g (0.07 mol), 3-chlorobenzaldehyde	13.2–13.7 g or 99.5–100%	Chloroform	51.49	51.63	3.78	3.70	186.5	186
4-Chloro-α-hydroxyphenylacetic acid	119–120	120.5–121[e]	35.1 g (0.25 mol), 4-chlorobenzaldehyde	45.1–46.8 g or 96.8–100%	Chloroform–ligroin (60–90°)	51.49	51.36	3.78	3.94	186.5	187
2-Fluoro-α-hydroxyphenylacetic acid	114–115	116.5[f]	10 g (0.08 mol), 2-fluorobenzaldehyde	12.5–13.7 g or 91.3–100% 7.6 g of 60.8%	Chloroform	56.48	56.46	4.15	4.27	170	171
3-Fluoro-α-hydroxyphenylacetic acid	98–99	101[f]	10 g (0.08 mol), 3-fluorobenzaldehyde	12.2–14.5 g or 89.0–100% 12.2 g of 89.0%	Chloroform	56.48	56.50	4.15	4.17	170	168
4-Fluoro-α-hydroxyphenylacetic acid	138–139.5	133[f]	10 g (0.08 mol), 4-fluorobenzaldehyde	12.7–14.1 g or 92.7–100% 10.2 g of 74.5%[b]	Chloroform	56.48	56.51	4.15	4.16	170	171
4-Methoxy-α-hydroxyphenylacetic acid	100–101	108–109[g]	17 g (0.125 mol), 4-methoxybenzaldehyde	10.3–10.8 g or 44.3–47.5%	Chloroform	59.34	59.39	5.53	5.51	182	181
α-Hydroxy-α-(1-naphthalene)acetic acid	87–88	91–93[h]	25 g (0.16 mol), 1-naphthaldehyde	25.2–26.6 g or 77.8–82.2%	5:1 Chloroform–ligroin (60–90°)	71.28	71.36	4.93	5.12	202	203
α-Hydroxy-α-(2-naphthalene)acetic acid	155–156	158[i]	10 g (0.07 mol), 2-naphthaldehyde	10.7–12.3 g or 82.6–95.2% 8.7 g of 67.2%[b]	5:1 Chloroform–ligroin (60–90°)	71.28	71.36	4.93	4.86	202	202

[a] Analyses (C–H) were by Spang Microanalytical Laboratory, Ann Arbor, Mich. 48109. [b] Yields obtained when the reaction systems were diluted twofold with solvent. [c] Infrared spectra of the "crudes" are identical with those of the analytical samples. [d] G. Dorner, *Chem. Zentr.*, 4901 (1959). [e] S. S. Jenkins, *J. Amer. Chem. Soc.*, **53**, 2341 (1931). [f] R. Belcher, A. Sykes, and J. C. Tatlow, *Anal. Chim. Acta*, **10**, 34 (1954). [g] R. Quelet and J. Gavarret, *Bull. Soc. Chim. Fr.*, 1075 (1950). [h] A. McKenzie and W. S. Dennler, *J. Chem. Soc.*, 1599 (1926). [i] R. Quelet, C. Borgel, and R. Durand, *Compt. Rend.*, **240**, 1900 (1955). [j] The respective registry numbers are 90-64-2, 10421-85-9, 16273-37-3, 492-86-4, 389-31-1, 395-05-1, 395-33-5, 10502-44-0, 6341-54-4, 14289-44-2.

Certain other variations in the reaction conditions were shown to affect the product yields. In six cases (see Table I), when a twofold dilution of the reactants was made by adding more solvent, the yields were reduced to 55–89% instead of being quantitative. In the case of mandelic acid preparation, if the lithium chloride was excluded, the yields in three trials were less (62% average) even than in the cases above where the twofold dilutions were made without the exclusion of this catalyst. These data suggest that the lithium chloride exerts a significant catalyzing effect, presumably by a loose attachment of the lithium ion to the carbonyl oxygen.

Aside from the utility of this method of preparation, the products were of interest because it was thought that they might have the ability to form relative insoluble crystalline sodium[1] and cesium[4] acid salts from aqueous solution, a property which mandelic acid and α-methoxyarylacetic acids share.[5,6]

(4) Only the α-methoxyarylacetic acids do this: E. L. Compere, Jr., unpublished results.

(5) Many alkali acid salts of monobasic acids have been known for over a century [N. V. Sidgwick, *J. Chem. Soc.*, **127**, 2379 (1925)], but a survey of the literature [J. C. Speakman, *ibid.*, 3357 (1949), and references therein] shows that, excepting those referred to above, most are easily dissolved in water.

(6) All of the α-hydroxyarylacetic acids form initially soluble sodium acid salts, excepting the 1-naphthyl derivative; the two least soluble sodium acid salts were the 2-naphthyl (0.12 g/100 g of H_2O) and the *p*-chlorophenyl (0.37 g/100 g of H_2O) derivatives, whose solubilities were determined after the salts had been kept dry for 6 months. Other alkali-metal acid salts are not easily formed, just as in the case of those of mandelic acid: A. McKenzie and N. Walker, *ibid.*, 356 (1922).

Experimental Section

General Procedure for Preparing α-Hydroxyarylacetic Acids.—In a 600–800-ml erlenmeyer flask were placed 0.5 mol of lithium chloride, 1.0 mol of potassium hydroxide, and 200 g of ice. To this mixture were added 200 ml of 1,4-dioxane, 0.25 mol of arylaldehyde, and 0.25 mol of bromoform. The mixture (containing some undissolved solids) was placed in a refrigerator (5–10°) and was stirred magnetically for 24 hr. If the pH was then below 12, 0.125 mol potassium hydroxide was added. Then the mixture was allowed to stir outside the refrigerator at 30–35° for another 24 hr.

The solution was then transferred to an 800-ml beaker, diluted to 600-ml volume with water. This solution was extracted three times with 50-ml portions of ether.[7] The aqueous layer was then acidified to a pH of 1 and extracted four times with 50-ml portions of ether. The combined ether extract was dried over magnesium sulfate, filtered, and evaporated to obtain the crude acid (usually a colored oil which solidified over several days time). These crude materials were recrystallized in an appropriate solvent; see Table I.

Registry No.—Bromoform, 75-25-2; potassium hydroxide, 1310-58-3; lithium chloride, 7447-41-8.

Acknowledgment.—The author is grateful to the American Chemical Society for a grant from the Petroleum Research Fund (PRF No. 1328B) which helped support this work.

(7) In several of the preparations, notably the cases of *p*-methoxy-α-hydroxyphenylacetic and mandelic acids, a precipitate occurred which is presumed to be a normal lithium salt of the respective acid. In these cases the reaction mixture was acidified and extracted with ether, and the ether extract was extracted twice with 5% sodium hydroxide, to remove the acid. This basic solution was then treated according to the general procedure. In the *p*-methoxy case, the precipitate may be the cause of the lower yield.

Carbonium Ion Salts. XI. Convenient Preparations of Hydroxytropenylium Salts, Ditropenyl Ether, and Tropone[1]

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In the course of thermodynamic and infrared spectral studies,[3-5] we have prepared and characterized a number of anhydrous and hydrated hydroxytropenylium ion salts. Previous reports of the chloride,[6,7] bromide,[8-11] and iodide[12,13] have contained either no or inconvenient synthetic directions, and, of the salts discussed herein, only the perchlorate[14] has previously been satisfactorily characterized. The preparations given here use the single starting material tropone, are simple to carry out, and give good yields of stoichiometric salts.

At first we used tropone prepared by the acid-catalyzed disproportionation of ditropenyl ether after the method of ter Borg.[15] We found this distillative disproportionation to give considerable polymerization in the still, and the product tropone usually needed redistillation; however, the method is satisfactory for obtaining a sample of tropone quickly.

In the course of this work we have developed a convenient, large-scale preparation for the ditropenyl ether necessary for the synthesis of tropone. When methylene chloride solutions of either ditropenyl ether or tropenyl methyl ether were stored over molecular sieve drying agent, we observed the formation of tropone in the solutions; this suggested that the sieve acted as a mild acid catalyst to initiate disproportion. To test this a solution of ditropenyl ether in methylene chloride was stored in the cold over Linde 4A molecular sieve; aliquots of this solution were withdrawn at intervals and extracted with 50% sulfuric acid. Spectral analysis[16] of these acid extracts showed a steady increase in tropone content, and a concurrent decrease in tropenylium ion arising from extraction of ditropenyl ether into sulfuric acid. At the conclusion of the reaction, the nearly water-white methylene chloride solution contained quantitative yields of tropone and cycloheptatriene. We have found this reaction to be an excellent source of tropone; the solution can be concentrated and treated with acids to yield hydroxytropenylium salts, or tropone can be obtained in a pure state by concentration and distillation. The reaction is quite slow, however; a number of weeks are required for completion. We find it convenient to keep a large quantity of solution on hand at all times, stored in the refrigerator over molecular sieve.

Experimental Section

Cycloheptatriene,[17] cyclohexane,[17] acetonitrile,[16] methylene chloride,[16] ether,[18] and boron bromide[17] were prepared as previously described. Mallinckrodt reagent grade benzene, carbon tetrachloride, and ethyl acetate were dried over Linde 4A molecular sieve. U. S. I. absolute alcohol, Baker and Adamson reagent grade 71% perchloric acid, 48% hydrobromic acid, 47% hydriodic acid, and phosphorus pentachloride, Volk Radiochemical 99.8% deuterium oxide, and Matheson anhydrous hydrogen bromide were used without further treatment. Ultraviolet spectra were taken on the Cary 13 spectrophotometer; Baker and Adamson reagent grade 96% sulfuric acid was used for analytical spectra. Melting points were taken on a Fisher–Johns block and are corrected.

Tropone.—Tropone was prepared by a method adapted from that of ter Borg.[15] Ditropenyl ether was placed in a modified Hickman[19] still with a portion of a moist mixture of alumina and phosphorus pentoxide; the temperature was held at 56° at 150 torr until distillation of cycloheptatriene ceased, then was raised to 90° at 15 torr to effect distillation of tropone. Yields ranged between 60 and 70%. Tropone is extremely sensitive to oxygen and light and care must be taken to protect the product from both. Redistillation of the tropone fraction afforded a water-white liquid with an infrared spectrum identical with that reported[20] for tropone.

Hydroxytropenylium Perchlorate.[21]—Tropone (0.20 g, 1.89 mmol) was dissolved in acetonitrile (15 ml) and 71% perchloric acid (0.5 ml) was added. Ether (60 ml) was added slowly to afford a white precipitate. This material was recrystallized twice from acetonitrile by slow addition of ethyl acetate and dried *in vacuo* to yield 47.7% hydroxytropenylium perchorate (0.185 g 0.90 mmol) as white plates, mp 187° (lit.[14] mp 186°).

Anal. Calcd for $C_7H_7O_5Cl$: $HClO_4$, 48.87. Found: $HClO_4$, 48.94.

The ultraviolet spectrum of this compound was carefully determined in 96% sulfuric acid showing absorptions at λ_{max} 229 mμ (ε 41,700), 306 (10,300), and 312 (sh).

Hydroxytropenylium Chloride.—Tropone (0.26 g, 2.45 mmol) was dissolved in absolute ethanol (5 ml) and 38% hydrochloric acid (0.30 ml, 3.8 mmol) was added. Ether (150 ml) was added and the flask was stored at −10° overnight. The solvent was decanted while cold from a crop of fine white needles; these were washed with two 25-ml portions of ether, dried *in vacuo*, and sublimed to yield 71.8% hydroxytropenylium chloride (0.251 g, 1.76 mmol) as white needles, mp 78–82° dec.

Anal. Calcd for C_7H_7OCl: $C_7H_6OH^+$, 75.13; Cl^-, 24.87. Found: $C_7H_6OH^+$, 75.2;[22] Cl^-, 25.18.

(1) Work supported by the National Science Foundation and the Petroleum Research Fund.

(2) Petroleum Research Fund Scholar, 1964–1965.

(3) K. M. Harmon and T. T. Coburn, *J. Amer. Chem. Soc.*, **87**, 2499 (1965).

(4) K. M. Harmon, T. T. Coburn, and J. M. Fisk, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p L50.

(5) K. M. Harmon and T. T. Coburn, *J. Phys. Chem.*, in press.

(6) The chloride was reported by Dauben and Ringold[7] as a deliquescent salt which was not characterized.

(7) H. J. Dauben, Jr., and H. J. Ringold, *J. Amer. Chem. Soc.*, **73**, 876 (1951).

(8) The bromide has been reported by Doering and Detert[9] from bromination of methoxycycloheptatriene (no analysis), by Dauben and Harmon[10] from solvolysis of halotropenylium salts, and by Zaitsev, *et al.*,[11] from addition of hydrogen bromide to tropone (no analysis).

(9) W. von E. Doering and F. L. Detert, *ibid.*, **73**, 876 (1951).

(10) H. J. Dauben, Jr., and K. M. Harmon, Abstracts, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958, p 35P; unpublished work in Ph.D. Thesis of K. M. H., University of Washington, Seattle, Wash., 1958; *Dissertation Abstr.*, **19**, 1563 (1959).

(11) B. E. Zaitsev, Yu. D. Koreshkov, M. E. Vol'pin, and Yu. N. Sheinker, *Dokl. Akad. Nauk SSSR*, **139**, 1007 (1961).

(12) The iodide has been reported by Harmon, *et al.*,[13] by reaction of tropone with anhydrous hydrogen iodide; this yields material of good quality, but the reaction presents significant manipulative difficulty.

(13) K. M. Harmon, A. B. Harmon, S. D. Alderman, L. L. Hesse, and P. A. Gebauer, *J. Org. Chem.*, **32**, 2012 (1967).

(14) T. Nozoe, T. Mukai, and K. Takase, *Sci. Rep. Res. Inst., Tohoku Univ., Ser. A*, **39**, 172 (1956).

(15) A. P. ter Borg, *et al.*, *Helv. Chim. Acta*, **43**, 457 (1960).

(16) K. M. Harmon, F. E. Cummings, D. A. Davis, and D. J. Diestler, *J. Amer. Chem. Soc.*, **84**, 3349 (1962).

(17) K. M. Harmon, A. B. Harmon, and F. E. Cummings, *ibid.*, **86**, 5511 (1964).

(18) K. M. Harmon, *et al.*, *ibid.*, **87**, 1700 (1965).

(19) K. C. D. Hickman, *Chem. Rev.*, **34**, 51 (1944).

(20) Y. Ikegami, *Bull. Chem. Soc. Jap.*, **35**, 967 (1962).

(21) Carbonium ion perchlorates should be prepared only in small amounts and handled with caution; detonation can occur on shock or ignition.

(22) Quantitative ultraviolet spectral analysis in 96% sulfuric acid affords the best technique for estimating carbonium ions: K. M. Harmon and A. B. Harmon, *J. Amer. Chem. Soc.*, **83**, 865 (1961).

Hydroxytropenylium Bromide.—Tropone (0.44 g, 4.15 mmol) was dissolved in absolute ethanol (10 ml) and 48% hydrobromic acid (1.18 g, 7.0 mmol) was added. Ether was added until turbidity persisted and the reaction was chilled at −10° overnight to afford a mass of white needles. The solvent was decanted and the crystals were washed with ether, dried *in vacuo*, and sublimed (80°, 1 torr) to yield 76.1% hydroxytropenylium bromide (0.59 g, 3.16 mmol) as pale yellow prisms. These crystals turn brilliant yellow at 125° and decompose above 170°.

Anal. Calcd for C_7H_7OBr: $C_7H_6OH^+$, 57.27; Br^-, 42.72. Found: $C_7H_6OH^+$, 56.9; Br^-, 42.91.

Hydroxytropenylium Bromide Monohydrate.—A freshly sublimed portion of hydroxytropenylium bromide was dissolved in oxygen-free water; this solution was allowed to evaporate to dryness in an oxygen-free glove box in which the vapor pressure of water was maintained at about 8 torr by a saturated solution of calcium chloride hexahydrate. This process affords hydroxytropenylium monohydrate as a mass of colorless, brittle spars and plates.

Anal. Calcd for $C_7H_9O_2Br$: $C_7H_6OH^+$, 52.20; Br^-, 38.95. Found: $C_7H_6OH^+$, 52.2; Br^-, 38.80.

Hydroxytropenylium Iodide.—Tropone (0.45 g, 4.25 mmol) was dissolved under nitrogen in deoxygenated absolute ethanol (10 ml) and 47% hydriodic acid (1.18 g, 4.4 mmol) was added. Anhydrous ether (80 ml) was added to precipitate a mixture of red and yellow crystals; these were washed with three 10-ml portions of ether, dried *in vacuo*, and sublimed (55°, 1 torr) to yield 86.0% hydroxytropenylium iodide (0.855 g, 3.66 mmol) as dark red prisms, mp 151–152° (lit.[13] mp 151°).

Hydroxytropenylium Iodide Monohydrate.—This material was prepared in the same manner as hydroxytropenylium bromide monohydrate, with the additional precaution that the preparation was carried out under red light. Evaporation of solvent water yielded hydroxytropenylium iodide monohydrate as orange spars which crush to a brilliant yellow powder.

Anal. Calcd for $C_7H_9O_2I$: $C_7H_6OH^+$, 42.50; I^-, 50.75. Found: $C_7H_6OH^+$, 42.4; I^-, 50.71.

Deuterioxytropenylium Bromide.—Boron bromide (1.06 g, 4.24 mmol) was placed in a small flask connected by a gas delivery tube to a second flask containing tropone (0.2 g, 1.9 mmol) in benzene (10 ml). Deuterium oxide (2 ml) was injected slowly into the boron bromide (*caution*) at a rate which maintained vigorous bubbling of deuterium bromide into the benzene solution. When the reaction was complete, the benzene was decanted from precipitated solids; these were washed with three 5-ml portions of benzene and dried *in vacuo* to yield deuterioxytropenylium bromide as a white microcrystalline powder. The infrared spectrum of this material was identical with that of hydroxytropenylium bromide with the exception of displacement of the O–H absorption.[3] This spectrum showed the sample to be contaminated with some hydroxytropenylium ion, even though the procedure had been carried out in a carefully dried glove box; this was shown to arise from residual water which is tenaciously retained by tropone, even on vacuum drying.[7,20]

Modified Preparation of Tropone. A. Ditropenyl Ether.[23–25]—Phosphorus pentachloride (108 g, 0.52 mol) was dissolved at reflux in carbon tetrachloride (800 ml) and a solution of cycloheptatriene (20 g, 0.22 mol) in carbon tetrachloride (400 ml) was added dropwise to this refluxing, vigorously stirred solution. The mixture was refluxed for 1 hr, then cooled, and allowed to stand overnight with protection from moisture; after this time, the flask was chilled in an efficient ice bath and distilled water (500 ml) added cautiously with stirring. The water layer was separated and retained; the carbon tetrachloride layer was discarded.

A 4-l., globe-shaped separatory funnel (Corning 6340) was clamped horizontally with the deep part in an ice bath on a magnetic stirrer; the neck of the funnel was fitted with a gas dispersion tube and a 60° funnel, both bent so as to reach the deepest part of the globe. A solution of 20% sodium hydroxide (500 g) was added and was deoxygenated by a stream of nitrogen; then the aqueous extract of tropenylium ion from the phosphorus pentachloride reaction was added slowly through the 60° funnel to the stirred, chilled base solution with continued bubbling of nitrogen. When addition was complete, the separatory funnel contained a snow-white emulsion of ditropenyl ether; this was extracted with three 200-ml portions of deoxygenated methylene chloride; magnesium sulfate was added to dry the methylene chloride extract; and this was again deoxygenated with a stream of nitrogen to remove air entrapped in the sulfate powder. The methylene chloride solution was brought to volume and an aliquot was extracted with 50% sulfuric acid; spectral analysis[16] of the acid extract showed the yield to be 77.8% ditropenyl ether (16.7 g, 0.084 mol) with a trace (less than 1%) of tropone.

B. Tropone and Cycloheptatriene.—The methylene chloride solution from the above preparation was placed over Linde 4A molecular sieve ($^1/_{16}$-in. pellets) and bubbled with nitrogen to remove air entrapped in the sieve. The flask was tightly stoppered, wrapped in foil, and stored in the refrigerator for 8 weeks. An aliquot was withdrawn and extracted with 50% sulfuric acid; spectral analysis[16] of this extract showed a yield of 97.5% tropone (8.69 g, 0.082 mol). Spectral analysis[16] of the methylene chloride remaining after acid extraction showed a yield of 97.2% cycloheptatriene (7.50 g, 0.0815 mol).

C. Hydroxytropenylium Ion Salts.—A portion of a methylene chloride solution prepared as above (100 ml) containing tropone (0.737 g, 6.9 mmol) and cycloheptatriene was concentrated to a volume of 20 ml, and hydrogen bromide passed over the surface of the stirred solution until precipitation ceased. Cyclohexane (50 ml) was added, the combined solvents were decanted, and the solid was washed with cyclohexane (50 ml) and dried *in vacuo* to yield 99.3% hydroxytropenylium bromide (1.28 g, 6.83 mmol) as a yellow powder.

Anal. Found: $C_7H_6OH^+$, 57.3.

A similar portion of the methylene chloride solution was concentrated at the rotary evaporator and the material not volatile at room temperature was taken up in deoxygenated absolute ethanol (15 ml) and 48% hydriodic acid (1.1 ml) was added. Dry ether (500 ml) was added and the mixed precipitate of red and yellow crystals was dried *in vacuo* to yield 67% hydroxytropenylium iodide (0.99 g, 4.2 mmol) as red crystals, mp 151°.

Registry No.—Hydroxytropenylium perchlorate, 16273-43-1; hydroxytropenylium chloride, 16273-44-2; hydroxytropenylium bromide, 16273-45-3; hydroxytropenylium iodide, 16273-46-4; ditropenyl ether, 16273-47-5; tropone, 539-80-0.

Acknowledgment.—We wish to thank Lee Louise Hesse, Catherine H. Burke, and Janice R. McMahon for technical assistance.

(23) The preparation of tropenylium hexachlorophosphate is adapted from Kursanov,[24] and that of ditropenyl ether is adapted from Doering and Knox.[25] The specific procedures reported herein are designed to prevent losses from transfer operations, and discoloration and contamination from facile air oxidation.

(24) D. N. Kursanov and M. E. Vol'pin, *Dokl. Akad. Nauk SSSR*, **113**, 339 (1957).

(25) W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3203 (1954).

Lithium Aluminum Hydride Reduction of Benzoyldiferrocenylphenylmethane[1]

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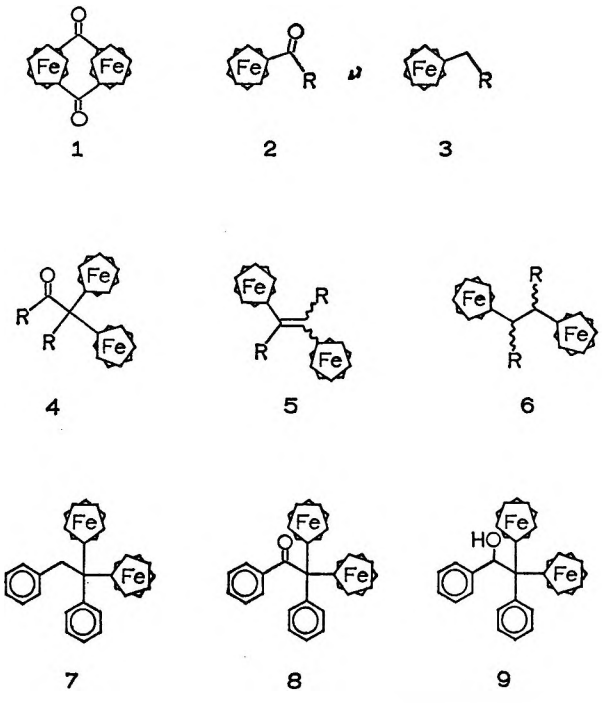
In connection with our synthesis work on the diketone (1) we were led to investigate the products of Clemmensen reductions of several ferrocenyl ketones (2) including benzoylferrocene (2, R = Ph). We established that products corresponding to **5** and **6** were formed along with the previously recognized products corresponding to **3** and **4**. Isolation of the former pair raised intriguing questions as to their mode of formation, and we have continued investigations into

(1) Presented at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, Abstracts, p 308.



these questions. In the meantime, the independent work of Rausch and Adams[2] has confirmed the presence of **5** and **6** (R = Ph) among the Clemmensen reduction products of benzoylferrocene with evidence similar to that gathered during that phase of our work.[3] The account by Rausch and Adams,[2] however, leaves unanswered an interesting point upon which we should like to comment.

Rausch, Vogel, and Rosenberg[4] first reported the isolation of a red-orange solid which decomposed when heated above 250°. Subsequently, Nesmeyanov and Kritskaya[5] suggested that this material was benzyldiferrocenylphenylmethane (**7**) formed by reduction of benzoyldiferrocenylphenylmethane (**8**) which they had also found among the products of Clemmensen reduction of benzoylferrocene. It is clear, however, from our own work, and now from the work of Rausch and Adams[2] as well, that the unknown material was **5** (R = Ph) and not **7**. Since Nesmeyanov and Kritskaya[5] had reported that the product of lithium aluminum hydride treatment of **8** in a separate experiment was identical with their Clemmensen reduction product (actually **5**), it was of interest to repeat the experiment in order to learn the source of the difficulty.

Lithium aluminum hydride reductions of ferrocenoyl compounds (**2**) in the presence of aluminum trihalide proceed to complete reduction, that is to say, formation of the corresponding ferrocenylmethyl compounds (**3**).[6] The same transformation also appears to be general for ordinary aryl ketones as well as for arylcarbinols;[7] the presence or absence of aluminum trihalide in the reported[5] reduction of **8** is problematical since the account of the work is devoid of experimental detail and previous claims of similar complete reductions[8] were later explained as probably due to the presence of aluminum trihalide.[9] We, however, elected to carry out the reduction in the presence of aluminum chloride.

Two products were found: the major one exhibited properties consistent with the expected alcohol (**9**), whereas the minor product was shown to be the olefin (**5**, R = Ph). Isolation of the red-orange olefin provided the basis of a reasonable explanation for the observation made by Nesmeyanov and Kritskaya,[5] for the red-orange solid of their Clemmensen reduction and their lithium aluminum hydride reduction was in fact the same, although it was not **7** as claimed by these authors but rather the recently established olefin (**5**, R = Ph).

The formation of **5** may easily be envisioned through formation of the benzylic carbonium ion from the benzilic alcohol (**9**). Ferrocenyl group migration in the former followed by deprotonation readily and reasonably accounts for the olefin. In the present work it is not clear whether the rearrangement took place during reaction work-up or during chromatography of the reaction product. In any case the point is of minor importance, for the absence of any experimental account for the original reduction[5] obviated an exact repetition of that experiment. The important point is that the isolation of the red-orange olefin in the present work suggests a rational explanation for what was clearly in contradistinction to the results obtained in this laboratory and to those obtained by Rausch and Adams[2] which established **5** (R = Ph) as the red-orange product of the Clemmensen reduction of benzoylferrocene.

Experimental Section

Reduction of Benzoyldiferrocenylphenylmethane (8) with Lithium Aluminum Hydride in the Presence of Aluminum Trichloride.—A sample of the pinacolone (**8**)[5] was carefully purified by two column chromatographies over alumina (Merck, acid washed). The compound was then shown to be pure to the limits of thin layer chromatography. Samples of 2, 5, 10, and 20 μg on silica gel were developed with 1:1 (v/v) benzene–hexane to show only one spot (**8**) with no trace of any spot corresponding to **5** (R = Ph).

A solution of the purified material (193 mg, 0.342 mmol) in 5 ml of anhydrous ether was added to a rapidly stirred slurry of lithium aluminum hydride (2.0 g, 53 mmol) in 25 ml of ether. This was then followed by addition of aluminum trichloride (3.5 g, 26 mmol) in 10 ml of ether. After the reaction mixture was stirred at room temperature during 4 hr, the excess hydride was carefully destroyed by dropwise addition of 2 ml of water and 4 ml of 20% aqueous sodium hydroxide solution. The material obtained from the ethereal phase and from several small ether extracts of the aqueous residue was combined and chromatographed on alumina. Only two bands developed during elution with the usual elutropic series of solvents. Benzene caused a small orange band to develop. The red-orange material obtained from this elution was shown to be **1,2-diferrocenyl-1,2-diphenylethene** (**5**, R = Ph) by direct comparison with authentic material where both were spotted together and in parallel on thin layer plates and developed with two different solvent systems, ether and 1:1 (v/v) benzene–hexane. This identity was confirmed by the identical electronic spectra determined from the two substances. Continued elution of the alumina column through the elutropic series of solvents did not produce any

(2) M. D. Rausch and D. L. Adams, *J. Org. Chem.*, **32**, 4144 (1967).

(3) Structural assignments were aided materially by mass spectral studies carried out in collaboration with Henry M. Fales, National Heart Institute.

(4) M. D. Rausch, M. Vogel, and H. Rosenberg, *ibid.*, **22**, 903 (1957).

(5) A. N. Nesmeyanov and I. I. Kritskaya, *Izv. Akad. Nauk, SSSR, Otd. Khim. Nauk*, 352 (1962).

(6) See, for example, E. A. Hill and J. H. Richards, *J. Amer. Chem. Soc.*, **83**, 4216 (1961).

(7) For example see the work (as well as additional references) cited by B. R. Brown and A. M. S. White [*J. Chem. Soc.*, 3755 (1957)] and by R. F. Nystrom and R. A. Berger [*J. Amer. Chem. Soc.*, **80**, 2896 (1958)].

(8) A. N. Nesmeyanov, E. G. Perevalova, and Z. A. Bienoravichute, *Dokl. Akad. Nauk SSSR*, **112**, 439 (1959).

(9) M. Rosenblum, "Chemistry of the Iron Group Metallocenes: Ferrocene, Ruthenocene, Osmocene," John Wiley and Sons, Inc., New York, N. Y., 1965, p 147.

further development until methanol was used. In that solvent all of the remaining colored material was eluted, and the spectral data determined from the yellow solid (mp 78–80°) obtained on evaporation of the eluate were consistent with the alcohol, 2,2-diferrocenyl-1,2-diphenylethanol (9): ir (CH_2Cl_2), 3590, 3510, 3420 (O–H), 3090, 3045, 3025 (aromatic C–H), 1600, 1575, 1500, 1450 (phenyl), 1100, 995 cm^{-1} (ferrocenyl); nmr ($CDCl_3$), δ 7.5–6.9 (complex multiplet, two, phenyl), 5.23 (s, one, CH–O or OH), 4.10 (s, ten, unsubstituted ferrocenyl rings), 4.18–3.70 (complex multiplet, nine, α and β ferrocenyl and CH–O or OH).

Registry No.—Lithium aluminum hydride, 1302-30-3; **8**, 12258-13-8; **9**, 12258-14-9.

Metal–Ammonia Reduction. II. Apparent Inhibition by Ferrous Metals[1]

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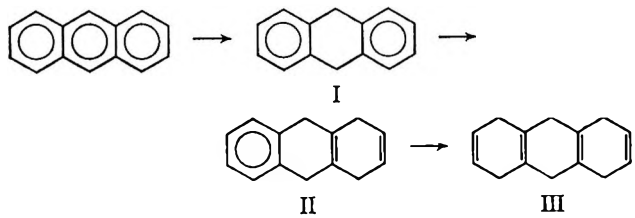
Received October 3, 1967

Conditions have recently been devised in this laboratory permitting the controlled, stepwise reduction of polycyclic aromatic hydrocarbons[2] by alkali metals dissolved in liquid ammonia.[3,4] A preliminary report[5] described procedures for the efficient conversion of 9,10-dihydroanthracene (I) into either 1,4,9,10-tetrahydroanthracene or 1,4,5,8,9,10-hexahydroanthracene (III), and also reported inhibition of this reduction by impurities in commercial ammonia or by iron salts. The essential features of the method are utilization of low lithium/hydrocarbon ratios and addition of the necessary proton source (*i.e.*, alcohol) late in the reaction period.



I II III

The inhibitory effects of trace metals and their salts which have been noted in scattered reports throughout the literature[4,6,7] have been the subject of speculation. However, aside from a study of the effect of colloidal iron on the Birch reduction of estradiol methyl ether,[8] the nature of the phenomenon has not been investigated. Dryden, Webber, Burtner, and Cella[8] conclude that iron interferes mainly by catalysis of the reaction between alcohol and alkali metal. Although this mechanism is probably valid when normal Birch conditions are employed (*i.e.*, alcohol present initially, generally in excess), it appears less certain for reactions conducted under other conditions.

TABLE I

REDUCTION OF ANTHRACENE (A) BY LITHIUM IN AMMONIA[a]

Expt no.	Lithium, equiv	Metal salt added (1 equiv)	Product Composition,[b] % A	I	II	III
1	2.5	...	0	90	10	0
2	5.0	...	0	15	68	17
3	10.0	...	0	0	32	68
4	2.5	$FeCl_3$	0	100	0	0
5	5.0	$FeCl_3$	0	100	0	0
6	10.0	$FeCl_3$	0	100	0	0
7	5.0	$CoCl_2$	0	100	0	0
8	5.0	Nickel acetyl acetonate	0	100	0	0
9	2.5	Commercial ammonia	0	100	0	0
10	5.0	Commercial ammonia	0	85	15	0
11	10.0	$FeCl_3$[c]	0	0	41	59
12	10.0	$FeCl_3$[d]	0	100	0	0
13	10.0	$FeCl_3$[e]	100	0	0	0

[a] Lithium wire was added to a solution of 900 mg of the hydrocarbon in 75 ml of dry THF and 150 ml of distilled ammonia, and the solution was maintained at reflux (−33°) for 2 hr, then quenched by rapid addition of alcohol. [b] Percentages were determined from the integrated peak values in the proton nmr spectra of the product.[5] [c] Ferric chloride was added 2 hr after lithium, and 5 min before alcohol. [d] Ferric chloride was added 2 hr after lithium, and 2 hr before alcohol. [e] Anthracene was added 2 hr after other components, and 2 hr before alcohol.

A series of experiments with anthracene carried out under our standard conditions[5] (Table I) provides new insight into inhibition by metallic salts. In the absence of added salts, I–III are the sole products, and their ratio is highly dependent upon the number of equivalents of lithium present (expt 1–3). Ferric chloride, cobaltous chloride, nickel acetylacetonate, or impurities in ammonia powerfully inhibit reduction beyond the dihydro stage (expt 4–9), and relatively large excesses of lithium are insufficient to counteract this effect. In contrast, transformation of anthracene itself to I remains entirely unaffected. This apparent relative rapidity of anthracene 9,10-dianion formation is supported by additional experiments. Thus, rapidly quenched reactions (1–2 min) analogous to expt 3 and 6 exhibited essentially the same product distribution as the former experiment. That ammonia ($pK_a \sim 34$)[4] is ineffective as a protonating agent compared to alcohol ($pK_a = 16$–18) may be deduced from the failure of conversion of I into II or III, despite a 2-hr delay before addition of ferric chloride (expt 3 *vs.* 12).

Salts of ferrous metals are readily reduced to the metallic state by alkali metals in liquid ammonia,[9] and the free metals are catalysts for reaction of lithium with both ammonia[9,10] (eq 1) and alcohol[7] (eq 2).

$$e^- + NH_3 \longrightarrow NH_2^- + {}^1/_2H_2 \quad (1)$$

$$e^- + ROH \longrightarrow RO^- + {}^1/_2H_2 \quad (2)$$

(1) This investigation was supported in part by Public Health Service Research Grant CA-08674 from the National Cancer Institute.

(2) Stepwise reduction of benz[*a*]anthracene through the dodecahydro stage is reported in paper III: R. G. Harvey and K. Urberg, *J. Org. Chem.*, **33**, 2206 (1968). Efficient single-stage transformation of a large number of polycyclic aromatic compounds will be reported shortly.

(3) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

(4) H. Smith, "Organic Reactions in Liquid Ammonia," John Wiley and Sons, Inc., New York, N. Y., 1963.

(5) R. G. Harvey, *J. Org. Chem.*, **32**, 238 (1967).

(6) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(7) W. Hückel, B. Graf, and D. Münkner, *Ann.*, **614**, 47 (1958).

(8) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(9) K. W. Greenlee and A. L. Henne, *Inorg. Syn.*, **2**, 128 (1946), and references therein.

(10) W. L. Jolly, University of California Radiation Laboratory Report UCRL-16046, 1965; W. L. Jolly and C. J. Hallada in "Solvent Systems," T. C. Waddington, Ed., Academic Press Inc., New York, N. Y., 1965; E. J. Kirschke and W. L. Jolly, *Science*, **147**, 45 (1965).

That the iron-catalyzed[11] side reaction of importance is with ammonia rather than with alcohol is clear from the dramatic difference between a 5-min delay and a 2-hr delay before addition of alcohol (expt 11 *vs.* 12). This view is also supported by an experiment in which anthracene added to a solution of lithium in ammonia 2 hr after addition of ferric chloride was recovered unchanged (expt 13).

The experimental findings suggest the following interpretation: (1) initial rapid transfer of two electrons to anthracene with formation of its 9,10 dianion, further transformation of which fails to take place in the absence of an added proton source; (2) slower iron-catalyzed consumption of lithium by interaction with ammonia, complete in less than 2 hr; then (3) rapid protonation of dianion I on addition of alcohol, followed by further reduction by alternate acquisition of single electrons and protons until excess lithium is consumed. Failure of I to undergo further transformation in the absence of an added proton source is in accord with the results of kinetic studies on simple benzenoid compounds.[12]

The colloidal metal effect has already found useful application in this laboratory for selective single-stage reduction of compounds capable of forming stable dianions in liquid ammonia.[2]

Registry No.—Anthracene, 120-12-7; lithium, 7439-93-2; ammonia, 7664-41-7.

(11) Less finely divided iron than that prepared *in situ* (*i.e.*, commercial iron powder) is ineffective as a catalyst.

(12) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959); O. J. Jacobus and J. F. Eastham, *ibid.*, **87**, 5799 (1965).

Reactions of *cis*- and *trans*-1,4-Dichloro-2-butene with Sodium Amide

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Recently it has been shown that cyclopropene[1] and 1-methylcyclopropene[2] can be synthesized by addition of the appropriate allylic chloride to a suspension of sodium amide in an inert solvent. A carbene intermediate seems to be involved in these reactions. We were interested in determining whether this procedure might be applicable to the synthesis of 3-chloromethylcyclopropene from *trans*- and/or *cis*-1,4-dichloro-2-butene and sodium amide. We recognized that both *cis*- and *trans*-1,4-dichloro-2-butene might react with sodium amide to give mainly 1-chloro-1,3-butadiene by 1,4 elimination, inasmuch as it has already been shown that *trans*-1,4-dichloro-2-butene reacts with potassium hydroxide to give 1-chloro-1,3-butadiene.[3] In the case of *cis*-1,4-dichloro-2-butene, additional reactions are possible, such as insertion on the 4-carbon atom to give 3-chlorocyclobutene, or attack of a carbanion precursor to the carbene on the 4-carbon atom to eliminate chloride and gave 3-chlorocyclobutene. Finally, unless 3-chloromethylcyclopropene were removed rapidly, further reaction with base could occur.

(1) G. L. Closs and K. D. Krantz, *J. Org. Chem.*, **31**, 638 (1966).

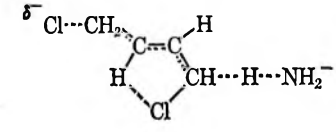
(2) F. Fisher and D. E. Applequist, *ibid.*, **30**, 2089 (1965).

(3) A. A. Petrov and N. P. Sopov, *J. Gen. Chem. USSR*, **15**, 981 (1945). These authors do not state that they used the *trans* isomer, but the method of synthesis is known to give only 3,4-dichloro-1-butene and *trans*-1,4-dichloro-2-butene.

Results and Discussion

The allylic dichlorides were added to sodium amide in mineral oil through which a slow stream of nitrogen was passed, carrying any products to a Dry Ice trap. The products from *cis*- and *trans*-1,4-dichloro-2-butene were studied by nmr, ultraviolet, and infrared spectroscopy and vapor phase chromatography. The nmr spectra showed only vinyl hydrogen peaks (τ 5.2–4.9),[4] and thus suggested that *cis*- and *trans*-1,4-dichloro-2-butene both gave only 1-chloro-1,3-butadiene.[5] However, the nmr spectra of the two products were not identical, the spectrum of the compound from *trans*-1,4-dichloro-2-butene being more complex and shifted downfield. The infrared spectra were also very similar, but not identical. Using the vapor phase chromatographic method of Viehe[6] for the separation of *cis*- and *trans*-1-chloro-1,3-butadiene, the interesting observation was made that the product from *trans*-1,4-dichloro-2-butene consisted of mainly *cis*-1-chloro-1,3-butadiene, whereas the product from *cis*-1,4-dichloro-2-butene was primarily *trans*-1-chloro-1,3-butadiene.[7,8] The data for the *cis*- and *trans*-1-chloro-1,3-butadienes are listed in Table I.

To account for the differences in the direction of elimination for *cis*- and *trans*-1,4-dichloro-2-butene, we would like to suggest the following explanation. Viehe[9] has proposed that the higher concentration of *cis*-1-chloro-1,3-butadiene over *trans*-1-chloro-1,3-butadiene at equilibrium results from bonding between the chlorine atom and the 3-hydrogen atom in *cis*-1-chloro-1,3-butadiene. Perhaps this stabilizing, hydrogen–chlorine bonding, which would lead to *cis*-diene, is operative in the transition state in the elimination with *trans*-1,4-dichloro-2-butene, as shown.



(4) For a discussion on the position of absorption of vinyl hydrogens in the nmr spectrum, see J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. Y., 1965, pp 84, 85.

(5) The absence of all but some insignificant peaks in the neighborhood of τ 8.3–8.8 indicated that neither 3-chloromethylcyclopropene nor 3-chlorocyclobutene was formed. For a discussion on the postion of absorption of the methylene hydrogens of these compounds, see K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961). Although 3-chloromethylcyclopropene could have decomposed during isolation of the product, and, hence, nmr analysis would have failed to indicate its formation, this seems unlikely since a negligible amount of residue remained after distillation.

(6) H. G. Viehe, *Ber.*, **97**, 598 (1964).

(7) For the exact compositions of the diene products, see Table I. Vpc analysis also indicated the presence of a small amount of an unidentified impurity.

(8) As far as we can determined, this is both the first report on the formation of 1-chloro-1,3-butadiene from *cis*-1,4-dichloro-2-butene, and the first report on the synthesis of reasonably high purity *trans*-1-chloro-1,3-butadiene.

(9) H. G. Viehe, *Angew. Chem.*, **75**, 793 (1963).

TABLE I

DATA FOR *cis*- AND *trans*-1-CHLORO-1,3-BUTADIENE

Chloride	$n^{20}D$	Ultraviolet[a] λ_{max}, mμ (ε)	Retention times,[b] min	Bp, °C	Yield, %
cis-1-Chloro-1,3-butadiene[c]	1.4707	233 (26,900)	136	66.5–68	72
trans-1-Chloro-1,3-butadiene[d]	1.4696	228 (18,700)	141	66–67.5	52

[a] The solvent was cyclohexane. [b] The flow rate (He) was 213 ml/min. [c] Contained 10% *trans* isomer. [d] Contained 15% *cis* isomer.

On the other hand, in the elimination with *cis*-1,4-dichloro-2-butene, hydrogen–chlorine bonding, leading to *cis*-diene, would be impossible since the extended π bonding in this transition state would prevent rotation of the 2,3-carbon bond. Steric hindrance between the chlorine atoms in the transition state would cause these atoms to lie away from each other and, hence, elimination would lead to the *trans* diene.

Experimental Section[10]

Reaction of *cis*- and *trans*-1,4-Dichloro-2-butene with Sodium Amide.—To a 500-ml, five-neck, round-bottom flask, equipped with a dropping funnel, fritted-glass nitrogen inlet, thermometer, mechanical stirrer, and outlet to a Dry Ice trap, and containing 20 g (0.51 mol) of sodium amide in 250 ml of mineral oil at 80°, was added, dropwise, 25 g (0.20 mol) of the dichloride in 135 ml of mineral oil. When the addition was complete, the trap was removed from the Dry Ice bath, and the ammonia was allowed to evaporate. The remaining liquid was distilled.

Identification and Analysis of the Products.—*cis*-1-Chloro-1,3-butadiene was confirmed as the principal product from *trans*-1,4-dichloro-2-butene on the basis of its boiling point, and infrared, ultraviolet, and nmr spectra. These spectra were all essentially identical with those of commercial 1-chloro-1,3-butadiene, obtained from Aldrich Chemical Co., Inc. Vpc analysis indicated that the commercial 1-chloro-1,3-butadiene contained approximately 85% *cis* isomer and 15% *trans* isomer.

trans-1-Chloro-1,3-butadiene was confirmed as the principal product from *cis*-1,4-dichloro-2-butene on the basis of the following observations: its nmr spectra showed only vinyl hydrogen absorption, the boiling point and the nmr, infrared, and ultraviolet spectra were very similar to those of *cis*-1-chloro-1,3-butadiene, and *trans*-1-chloro-1,3-butadiene rearranged with iodine to a *cis*–*trans* mixture, as described by Viehe.[6,11]

The 1-chloro-1,3-butadienes were analyzed by vpc according to the procedure of Viehe.[6] Peak enhancement studies confirmed that the products from *cis*- and *trans*-1,4-dichloro-2-butene were composed of the same compounds, but in different quantities.

Preparations and Purities of *cis*- and *trans*-1,4-Dichloro-2-butene.—*cis*-1,4-Dichloro-2-butene was synthesized according to the procedure of Babbit, Amundsen, and Steiner.[12] *trans*-1,4-Dichloro-2-butene was obtained from Eastman Organic Chemicals Department. Vpc analysis showed that the *cis* isomer was contaminated with approximately 5% of an unknown impurity, and a trace of the *trans* isomer. *trans*-1,4-Dichloro-2-butene contained only a trace of the *cis* isomer and no other impurities. The conditions for analysis on an Aerograph 90 P-3 chromatograph were as follows: flow rate (He), 323 ml/min; column length and diameter, 6 ft × 0.25 in.; column temperature, 29°; column composition, 2.5% SE-30 on 60–80 mesh DMCS Chromosorb W. Under these conditions the retention times of *cis*- and *trans*-1,4-dichloro-2-butene, are, respectively, 3.2 and 4.0 min.

(10) Boiling points are uncorrected.

(11) Viehe reports that heating a mixture of *cis*-1-chloro-1,3-butadiene and a solution of 1% iodine in benzene at 100° gives an equilibrium mixture of 70 ± 5% *cis* isomer and 30 ± 5% *trans* isomer. We confirmed this using the *cis*-1-chloro-1,3-butadiene from *trans*-1,4-dichloro-2-butene. Heating the *trans*-1-chloro-1,3-butadiene with iodine–benzene solution gave a mixture of 60% *cis* isomer and 40% *trans* isomer. The rearrangment undoubtedly would have gone to equilibrium if the decomposition products had been removed and the iodine replenished. We found that disappearance of iodine was rapid, and if more iodine was added, the rearrangement continued.

(12) J. Babbit, L. Amundsen, and R. Steiner, *J. Org. Chem.*, **25**, 2231 (1960).

Registry No.—*cis*-1,4-Dichloro-2-butene, 1476-11-5: *trans*-1,4-dichloro-2-butene, 110-57-6; sodium amide, 12125-45-0; *cis*-1-chloro-1,3-butadiene, 10033-99-5; *trans*-1-chloro-1,3-butadiene, 16503-25-6.

Acknowledgment.—Acknowledgment is made to the Research Corporation for support of this research. We are indebted to Mr. Gerald Oliver of the Jet Propulsion Laboratory, Pasadena, Calif., for the nmr spectra.

A Conformational Analysis of Some 2-Alkoxytetrahydropyrans

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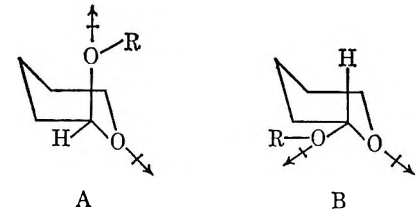
Received January 11, 1968

Oxane rings substituted in the 2 position by electronegative groups are generally more stable with the 2 substituent in an axial conformation. The interactions which cause the observed destabilization of the equatorial conformation in these compounds are commonly referred to as the anomeric effect, a term first used by Lemieux and Chu.[1] Examples of the anomeric effect are to be found in certain 1-substituted D-glucopyranosides,[2] 2-substituted tetrahydropyrans,[3,4] and substituted dioxanes.[5] Edward[6] has explained the anomeric effect in terms of a dipole–dipole interaction between the lone electron pairs of the ring oxygen and the substituent bond. Because of the angles between the dipoles, this interaction would be much smaller for an axial substituent (A) than for an equatorial substituent (B).



A B

As would be expected in a dipole–dipole interaction, the magnitude of the anomeric effect is dependent on the dielectric constant of the solvent. A solvent of high

(1) R. U. Lemieux and N. J. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p 31N.

(2) For examples, see E. L. Eliel, N. J. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 375–377.

(3) G. E. Booth and R. J. Ouelette, *J. Org. Chem.*, **31**, 544 (1966).

(4) C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964).

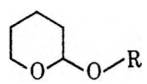
(5) C. Altona, C. Romers, and E. Havinga, *Tetrahedron Lett.*, No. 10, 16 (1959).

(6) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

dielectric constant would be expected to stabilize the equatorial conformer by reducing the strength of the dipole interaction. The actual strength observed for the anomeric effect varies considerably with changing solvent polarity. For example, Rowley and Bailey[7] have obtained values for the anomeric effect in glucose of 0.35 kcal/mol in water and 0.90 kcal/mol in methanol, while Levene and Hill[8] obtained a value for mannose of 1.15 kcal/mol in pyridine. Booth and Ouellette[3] have estimated the value for the anomeric effect in 2-halotetrahydropyrans to be greater than 2.3 kcal/mol in a series of nonpolar and slightly polar solvents.

The conformational equilibrium of compounds exhibiting the anomeric effect would be expected to be altered by both the polar and steric nature of the substituent groups. Increasing the substituent polarity would increase the strength of the substituent dipole. Such an increase in dipole strength would greatly increase the interaction in the equatorial conformer (B) where the dipoles are nearly parallel. The same increase in dipole strength would be expected to have a much smaller effect on the axial conformer (A) where the dipoles are at widely divergent angles. Thus increasing the polarity of the substituent would be expected to shift the equilibrium toward the axial conformation by increasing the magnitude of the dipole interaction. The steric requirement of a substituent should also have an effect on the conformational equilibrium. Since the axial conformer is more stericly crowded due to diaxial interactions, an increase in substituent size would be expected to favor the equatorial conformer.

This paper describes a conformational study of several 2-alkoxytetrahydropyrans (**1**–**10**) in which the steric and polar nature of the substituents vary over a



1, R = H	**6**, R = CH_2CF_3
2, R = CH_3	**7**, R = CH_2CCl_3
3, R = C_2H_5	**8**, R = $CH(CH_3)_2$
4, R = $(CH_2)_2Cl$	**9**, R = $C(CH_3)_3$
5, R = CH_2CHCl_2	**10**, R = C_6H_5

fairly wide range. The particular compounds were chosen in an attempt to discern the dependency of the conformational equilibrium upon the steric and polar requirements of the alkoxy substituent. The conformational equilibrium was determined *via* nmr techniques. Since the spin–spin coupling constants are related to the dihedral angle between the C–H bonds by a $\cos^2\theta$ function, it is often possible to determine conformational equilibria from the magnitude of these coupling constants.[3,9] To obtain reasonably quantitative results, the coupling constants for the reference proton in both of its conformations must be known. These coupling constants can be obtained from suitably chosen model compounds which are conformationally homogeneous and closely analogous to the system being studied. In the study of the 2-alkoxytetrahydropyran system the C-2 proton resonance was observed. The model compound used to obtain the coupling constant for a totally axial substituent was methyl 2-deoxy-α-D-glucopyranoside. This compound is assumed to be a completely axial conformer because of the two separate 1,3 diaxial interactions which would occur in the equatorial conformer. The model compound used to obtain the coupling constants for the equatorial conformer was *cis*-4-methyl-2-methoxytetrahydropyran;[4] this compound is believed to exist entirely as the equatorial conformer because of the strong 1,3 diaxial interactions between the methyl and methoxy groups which would occur in the axial conformer.

(7) H. H. Rowley and S. D. Bailey, *J. Amer. Chem. Soc.*, **62**, 2562, (1940).
(8) P. A. Levene and D. W. Hill, *J. Biol. Chem.*, **102**, 536 (1933).
(9) Edgar W. Garbish, Jr., *J. Amer. Chem. Soc.*, **86**, 1780 (1964).

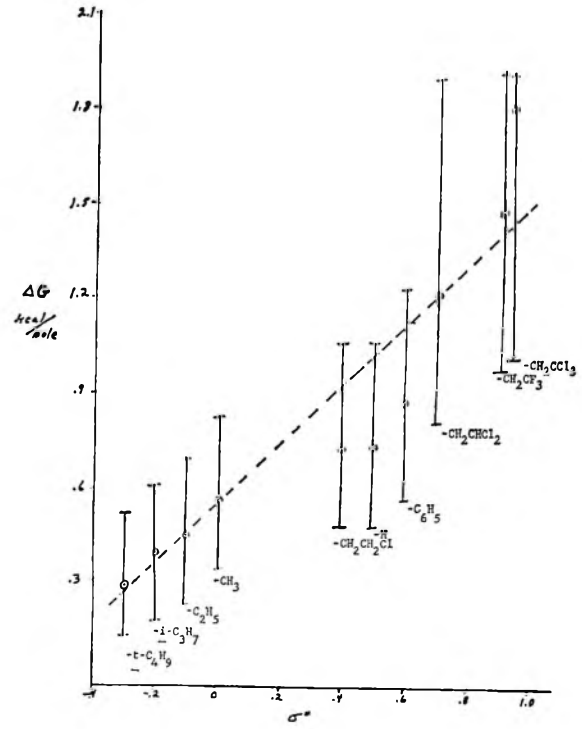


Figure 1.—The relationship between substituent Taft constant and conformational free-energy difference of 2-alkoxytetrahydropyrans.

Results and Discussion

The observed coupling constant of a rapidly equilibrating system is a time average of the components of the system. The equilibrium constant between conformers A and B of the 2-alkoxytetrahydropyran sys-

A B

tem can be estimated from the distance between the two outside peaks of the C-2 proton resonance provided $J_{2,3a}$ and $J_{2,3e}$ are known for both conformers. The C-2 proton resonance is a part of an ABX system with the C-2 absorption well downfield of the C-3 protons. If weak transition states are ignored, the distance between the two outside peaks of the C-2 absorption can be approximated as equal to $J_{2,3a} + J_{2,3e}$. This sum shall be referred to as J_A and J_B for conformers A and B, respectively. The observed distance between the two outside peaks, J^0, is equal to $J_AN_A + J_BN_B$ where N_A and N_B are the percentages of the two conformers. Values for J_A (4.7 cps) and J_B (10.5 cps) were obtained

TABLE I

COUPLING CONSTANTS OF SOME SUBSTITUTED TETRAHYDROPYRANS

No.	Compounds	Source	$J_{1,2}$, cps			
			$J_{a,a}$	$J_{a,e}$	$J_{e,e}$	$J_{e,a}$
1	*cis*-4-Methyl-2-methoxytetrahydropyran	*a*	8.3	2.2		
2	*cis*-4-Methyl-2-butoxytetrahydropyran	*a*	8.5	2.0		
3	Methyl 2-deoxy-2-D-glucose	*b*			3.5	1.2
4	Acetylated sugars	*c*	5–8 (av 6.9)	2–6.2 (av 3.3)	3.0	
5	α-D-Glucopyranosides	*d*		3.0–3.5		
6	α-D-Manopyranosides	*d*			1.0–1.5	
7	Acetylated mannose derivatives	*e*	6.5–8.7 (av 7.5)		1.0	

[a] C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964). [b] This paper. [c] R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. C. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958). [d] R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, **42**, 532 (1964). [e] K. Onedera, S. Hirano, F. Masuda, and N. Kashimura, *J. Org. Chem.*, **31**, 2403 (1966).

TABLE II

CONFORMATIONAL PERCENTAGES AND FREE ENERGIES OF 2-ALKOXYTETRAHYDROPYRANS

R	Shift	J^0, cps	N_A, %	ΔG, kcal mol
H	5.1	6.0	77	0.75 ± 0.3
CH_3	5.6	6.3	72	0.58 ± 0.3
C_2H_5	5.45	6.5	68	0.47 ± 0.3
$(CH_2)_2Cl$	5.3	6.0	77	0.75 ± 0.3
CH_2CHCl_2	5.4	5.5	88	1.2 ± 0.6
CH_2CF_3	5.2	5.2	92	1.5
CH_2CCl_3	5.05	5.0	95	1.8
$CH(CH_3)_2$	5.35	6.7	66	0.42 ± 0.3
$C(CH_3)_3$	5.2	6.9	62	0.31 ± 0.3
C_6H_5	4.8	5.8	81	0.90 ± 0.4

from coupling constants observed for methyl 2-deoxy-α-D-glucopyranoside and *cis*-4-methyl-2-methoxytetrahydropyran, respectively. Coupling constants observed for several carbohydrate derivatives of known configuration (see Table I) are consistent with the values chosen for J_A and J_B. The value of N_A can be calculated from the equation

$$N_A = \frac{J_B - J^0}{J_B - J_A}$$

The free-energy difference between the two conformers can be obtained from

$$\Delta G = RT \ln \frac{N_A}{1 - N_A}$$

Table II lists the J^0 values and chemical shifts observed for the compounds studied. The values calculated for N_A and ΔG are also included. Since the J^0 values could only be estimated to ±0.5 cps the values given for N_A and ΔG are subject to considerable error. The relationship between the observed free-energy difference and the Taft polar constants for the R groups is given in Figure 1. The slope of the line given in Figure 1 is consistent with the expected increase in dipole interaction with increasing substituent polarity (higher Taft values). The linearity of the graph seems to indicate that the steric size of the substituent has little or no effect on the conformational free energy.

A value for the anomeric effect which can be compared to values previously reported may be obtained by adding 0.9–1.0 kcal/mol[10] to the free energies listed in Table II to account for diaxial interactions. Thus, the anomeric effect for this series of 2-alkoxytetrahydropyrans varies from 1.3 to 2.8 kcal/mol. Since these results were obtained in nonpolar solvents, the values are consistent with those of earlier workers.[3,7,8]

TABLE III

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR 2-ALKOXYTETRAHYDROPYRANS NOT PREVIOUSLY REPORTED

R	Bp, °C (mm)	$n^{20}D$	Calcd, %		Found, %	
			C	H	C	H
$CH(CH_3)_2$	159–160	1.4242	66.63	11.18	66.80	11.39
$C(CH_3)_3$	169–170	1.4290	68.31	11.47	68.40	11.75
CH_2CHCl_2	84–86 (10)	1.4724	42.23	6.08	44.17[a]	6.08
CH_2CF_3	141–143	1.3784	45.65	6.02	46.10	5.48
CH_2CCl_3	88–89 (10)	1.4796	36.00	4.75	37.56[a]	4.86

[a] These compounds were purified by chromatography only since they tended to decompose on distillation. The infrared and nmr spectra were in complete agreement with the proposed structures.

Experimental Section

All compounds, with the two exceptions noted below, were prepared according to the procedure of Woods and Kramer[11] and purified by distillation. Physical constants and analytic data for compounds not previously reported in the literature are listed in Table III. The 2-hydroxytetrahydropyran was prepared by the procedure of Schniep and Geller,[12] and the 2-(2-chloroethoxy)tetrahydropyran was purchased from Aldrich Chemicals. All spectra were run as neat samples on a Varian A-60A spectrometer operating at 38°. Coupling constants were reproducible to 0.5 cps.

Registry No.—**1**, 694-54-2; **2**, 931-60-2; **3**, 4819-83-4; **4**, 5631-96-9; **5**, 16408-82-5; **6**, 16408-83-6; **7**, 16408-84-7; **8**, 1927-70-4; **9**, 1927-69-1; **10**, 4203-50-3.

(10) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 236.

(11) G. F. Woods and D. N. Kramer, *J. Amer. Chem. Soc.*, **69**, 2246 (1947).

(12) L. E. Schniep and H. H. Geller, *ibid.*, **68**, 1646 (1946).

The Base-Catalyzed Reaction of Fluorene and Indene with Lactones and Hydroxy Acids

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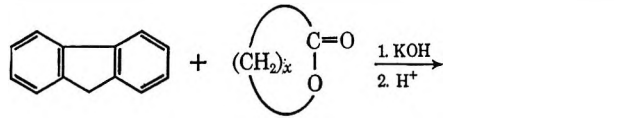
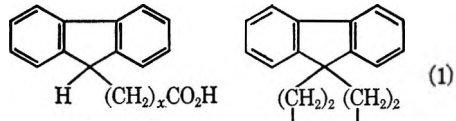
The alkylation of fluorene and indene[2] with alcohols gives 9-alkylfluorenes and 1,3-dialkylindenes in high yield. The reaction has been extended to cover reactions of hydroxy acid salts with indole[3] to form 3-indolealkanoic acids. This Note reports the base-catalyzed reaction of hydroxy acid salts with fluorene to give 9-fluorenylalkanoic acids and with indene to give 3-indenylalkanoic acids and 1,3-indenedialkanoic acids. The hydroxy acid salts were normally generated *in situ* by the reaction of strong base, such as potassium hydroxide, with lactones. Most of the compounds synthesized by this technique were unreported prior to this work.

Treatment of fluorene with γ-butyrolactone, δ-valerolactone, and ε-caprolactone in the presence of potassium hydroxide at 200–220° produced 9-fluorenylalkanoic acids 1a–c in yields of 33, 83, and 96%, respectively (eq 1). Similarly, reaction of fluorene with propiolactone gave diacid 2, while glycolic acid afforded





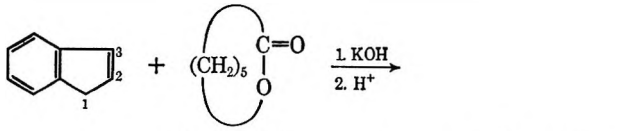
(1)

1a, $x = 3$
b, $x = 4$
c, $x = 5$

2

9-fluorenylacetic acid in 10% yield. Bachmann and Sheehan[4] have previously synthesized 9-fluorenylacetic acid using a four-step process. The acid products from these reactions were normally isolated as the methyl esters for analytical evaluation. A summary of these reactions is found in Table I and the properties of the products are found in Table II.

Indene also reacted with ε-caprolactone in the presence of excess potassium hydroxide to give about equal



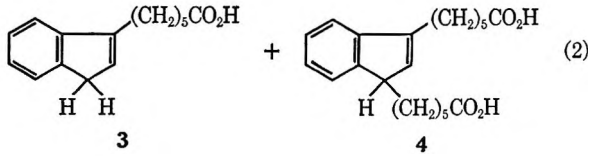


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TABLE I

BASE-CATALYZED REACTIONS OF FLUORENE WITH LACTONES AND HYDROXY ACIDS[a]

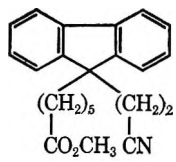
Lactone, x	Temp, °C	Time, hr	Yield of 1, %	Efficiency on fluorene, %
2[b]	220	20	18	67
3	220	22	33	67
4	220	20	83	91
5[c]	220	20	96	100
1[d]	250	20	10	20

[a] All runs in stainless steel rocker autoclave unless otherwise noted. [b] Product was the diacid 9,9-bis(carboxyethyl)fluorene, 2. [c] Run at atmospheric pressure at reflux of reaction mixture. [d] Glycolic acid used as starting material.

amounts of 6-(3-indenyl)caproic acid, 3, and 1,3-bis(carboxypentyl)indene, 4. These products were isolated and identified as their methyl esters.

Other substrates which were tried in this general reaction of hydroxy acid salts with active methylene-containing compounds were diphenylmethane, 9,10-dihydroanthracene, 9,10-dihydrophenanthrene, and 9-methylfluorene. Only 9,10-dihydroanthracene gave a product and that was only a 5% yield of acidic material containing an anthracene, rather than dihydroanthracene, nucleus. The failure of these compounds to react can be rationalized on mechanistic grounds which will be discussed below.

The structure proof of the fluorene and indene derivatives was provided by a combination of nmr, infrared, and ultraviolet spectroscopy along with elemental analysis, and comparison of properties with those of identical compounds in the literature, when available. For example, the nmr spectrum of fluorene contains a sharp singlet of δ 3.8 representing the methylene protons of carbon 9. The fluorene compounds which were disubstituted on the 9 position showed no resonance in this area. The eight protons of the aromatic rings were observed in a complex multiplet between δ 7.0 and 7.8. Fluorene derivatives singly substituted at carbon 9, such as 9-fluorenylacetic acid and methyl 6-(9-fluorenylcaproate), gave triplets representing single protons centered at δ 4.38 and 3.80, respectively. When methyl 6-(9-fluorenyl)caproate was cyanoethylated by the method of Bruson[5] to form 5 this triplet disappeared.



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In all cases, the number of aromatic protons stayed constant at eight.

The nmr spectrum of indene showed peaks centered at δ 3.20 for the two protons of the carbon 1 methylene groups and peaks centered at δ 6.35 and 6.75, representing one proton each, for the 2 and 3 position protons, respectively. The nmr spectrum of methyl 6-(3-indenyl)caproate, 6, showed no proton at carbon 3 and absorption at δ 6.07 for the carbon 2 proton and a quartet at δ 3.2 representing two protons. The disubstituted indene showed a single proton at carbon 1 (δ 3.2) as well as a single proton at carbon 2 (δ 6.10). In both cases,

(1) To whom inquiries should be addressed.

(2) (a) H. E. Fritz, D. W. Peck, M. A. Eccles, and K. E. Atkins, *J. Org. Chem.*, **30**, 2540 (1965); (b) K. L. Schoen and E. I. Becker, *J. Amer. Chem. Soc.*, **77**, 6030 (1955).

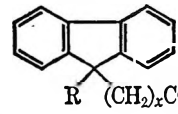
(3) (a) H. E. Fritz, *J. Org. Chem.*, **28**, 1384 (1963); (b) H. E. Johnson and D. G. Crosby, *ibid.*, **28**, 1246 (1963).

(4) W. E. Bachmann and J. C. Sheehan, *J. Amer. Chem. Soc.*, **62**, 2687 (1940).

(5) H. A. Bruson, *ibid.*, **64**, 2457 (1942).

TABLE II

PROPERTIES OF 9-FLUORENYL ACIDS AND METHYL ESTERS[a]

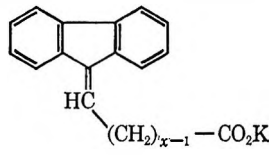


	x	Acid or ester mp, °C	Methyl ester bp (mm), °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Sapon equiv Calcd	Sapon equiv Found
Acid[b]	2	282–284[c]	...	73.53	5.85	73.72	6.05	...	...
Ester	2	83–84[d]	196–200 (0.4)	74.50	6.60	74.50	6.60	169	170
Acid	3	133–133.5[d]	...	80.92	6.39	81.10	6.48	...	...
Ester	3	52[c]	166–170 (0.4)	81.21	6.78	81.29	6.95	266	263
Acid[e]	4	...	...	...	...	...	...	...	...
Ester	4	39[f]	212 (3)	81.43	7.14	81.52	7.41	280	277
Ester[g]	4	...	270 (10)	82.49	9.06	82.46	8.91	378	377
Acid	5	66[d]	...	81.40	7.19	81.61	7.25	...	...
Ester	5	43–44[c]	195–197 (1)	81.60	7.70	81.66	7.53	284	294
Acid[h]	1	131–132[i]	...	80.30	5.40	80.20	5.50	...	...

[a] R = H except where $x = 2$, then it is $-(CH_2)_2CO_2H(CH_3)$. [b] Neut equiv, 153 (calcd 155). [c] Recrystallized from methanol. [d] Recrystallized from cyclohexane. [e] Acid only isolated as methyl ester. [f] Recrystallized from hexane. [g] 2,2,4-Trimethylpentyl ester. [h] Neut equiv, 229 (calcd 224). [i] Lit.[4] mp 131–132°.

the aromatic pattern remained consistent with that of indene and represented four protons.

The proposed mechanism for the reaction of both fluorene and indene with lactones is analogous to that relayed by Schoen and Becker[2] for the alkylation of fluorene with alcohols. The first step is the reaction of lactone with potassium hydroxide to yield the salt of the hydroxy acid. Next the alcohol function is oxidized or dehydrogenates to the corresponding aldehyde and this aldehyde condenses with a fluorenyl anion to form an alkylidene compound, **7**, which is reduced either by



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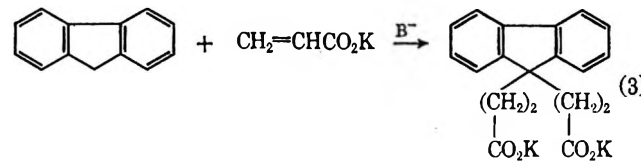
hydrogen present from dehydrogenation of the alcohol group or by alkoxide to yield product.

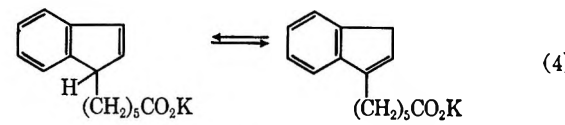
This mechanism explains why no product is formed when 9-substituted fluorenes are used as substrates since both methylene hydrogens are needed to yield the intermediate alkylidene compound. The failure of diphenylmethane to react can be rationalized by the fact that its pK_a is 35[6] while those of indene[5] and fluorene[5] are 21 and 25, respectively. The acidity of these methylene protons could determine whether an anion would be formed under the reaction conditions.

This mechanism also explains why only monosubstituted fluorenes are obtained, except in the case of propiolactone. When this lactone is opened with potassium hydroxide it forms a hydroxy acid salt which upon dehydration could yield an acrylate salt. Acrylate esters[7] are known to condense with compounds containing activated methylene groups under basic catalysis (Michael reaction), but the use of acrylate salts is not reported. It is thought that this sequence is followed in the propiolactone experiments to yield 9,9-disubstituted fluorenes just as occurs when fluorene is cyanoethylated[5] with acrylonitrile under basic catalysis. The use of acrylate salts in the Michael reaction has been studied and will be reported in the following communication.



(3)

The reaction of indene with ϵ-caprolactone also fits this mechanistic sequence. Indene would first be attacked at the methylene group and then the double bond isomerized to provide another methylene group for reaction, thus explaining the disubstituted product observed (eq 4 and 5).



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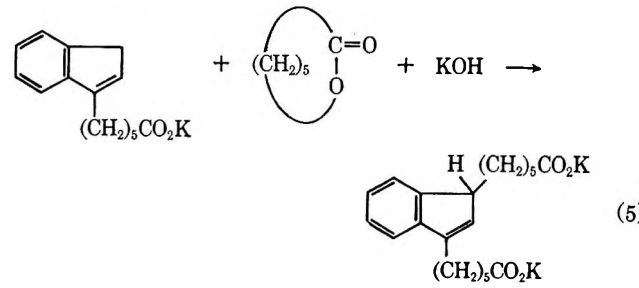


(5)

(6) W. K. McEwen, *J. Amer. Chem. Soc.*, **58**, 1124 (1936).

(7) E. B. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

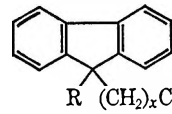
Experimental Section

Melting points were obtained on a Fisher-Johns melting point block. Infrared spectra were recorded by a Beckman IR-4, ultraviolet spectra by a Cary Model 21 spectrophotometer, and nuclear magnetic resonance spectra by a Varian Associates Model A-60 spectrometer. Elemental analysis was performed by the UCC Chemicals and Plastics Division R and D analytical group.

General Procedure for the Reaction of Lactones with Fluorene. Autoclave Preparation.—To a stainless steel rocker autoclave were charged fluorene (1.0 mol), lactone or hydroxy acid (1.1 mol), and potassium hydroxide (1.3 mol). In the case of propiolactone, a higher yield was obtained if 2.1 mol were used. This mixture was heated to 220° and held for 20 hr. The cooled reaction mixture was treated with water and extracted with isopropyl ether to remove any unreacted fluorene. The aqueous layer was acidified with concentrated hydrochloric acid to release

TABLE III

INFRARED SPECTRA[a] OF 9-FLUORENYLALKANOIC ACIDS AND METHYL ESTERS



R $(CH_2)_xCO_2R'$

R	R′	x	Primary absorption bands,[b] μ									
H	H	1	3.0–3.9 (b)	5.84 (s)	6.9, 7.0, 7.1 (t)	7.82 (m)	8.10 (m)	10.70 (m)	13.52 (s)			
H	H	3	3.0–4.0 (b)	5.85 (s)	6.9–7.09 (d)	7.75 (m)	8.05 (m)	10.70 (m)	13.53 (s)			
H	H	4	3.0–4.0 (b)	5.84 (s)	6.9–7.05 (d)	7.80 (m)	8.10 (m)	10.70 (m)	13.54 (s)			
H	H	5	3.0–4.0 (b)	5.88 (s)	6.9–7.08 (d)	7.80 (m)	8.18 (m)	10.75 (m)	13.60 (s)			
$(CH_2)_2$ | CO_2H	H	2[c]	3.0–4.0 (b)	5.80 (s)	6.91–6.99 (d)	7.72 (m)	8.22 (m)	10.70 (m) 10.90	13.65 (s)			
H	CH_3	3	3.25	3.39	3.45	5.71 (s)	8.10 (m)	8.35 (m)	8.55 (m)	8.71 (m)	13.0 (w)	13.50 (s)
H	CH_3	4	3.22	3.42	3.51	5.78 (s)	8.05 (m)	8.20 (m)	8.41 (m)	8.58 (m)	13.05 (w)	13.54 (s)
H	CH_3	5	3.29	3.42	3.51	5.79 (s)	8.03 (m)	8.41 (m)	8.60 (s)	8.88 (w)	13.09 (w)	13.60 (s)
$(CH_2)_2$ | CO_2CH_3	CH_3	2	3.30	3.40	3.50	5.72 (s)	8.02 (m)	8.39 (s)	8.55 (s)		13.15 (m)	13.55 (s)

[a] Unless otherwise designated, spectra were recorded in CCl_4 from 2.0 to 7.5 μ and in CS_2 from 7.5 to 15.0 μ. [b] b = broad, s = strong, m = medium, w = weak, d = doublet, t = triplet. [c] KBr pellet.

the organic acid product. The carboxylic acid was either recrystallized or converted into the methyl ester by refluxing in excess methanol with a catalytic amount of *p*-toluenesulfonic acid. The ester was then distilled under reduced pressure and, if the cuts solidified, was recrystallized.

Atmospheric Pressure Procedure.—The same molar ratios as used above were employed in these reactions. A stainless steel flask rather than a glass flask was used because of the deleterious effect of alkali hydroxides on glassware at high temperatures. The reaction mixture was stirred and heated at reflux and the water formed in the reaction collected in a trap. Some exothermicity was observed during the reaction and care was taken to leave plenty of empty space in the reaction flask. The work-up technique used was the same as that outlined above.

The structures of the products from the above reactions were elucidated by nmr, ir, and uv spectroscopy, elemental analysis, neutralization equivalents, and saponification equivalents. Most of these properties are found in Tables II and III and in the discussion section. The uv spectra of these materials are very similar to that of fluorene with about the only significant change being a bathochromic shift of 2–3 mμ for each additional substituent in the 9 position.

9-Carbmethoxypentyl-9-cyanoethylfluorene (5).—A solution of 109 g (0.37 mol) of methyl 6-(9-fluorenyl)caproate and 1000 ml of dioxane was charged to a reaction flask and 10 g of 32% Triton B (benzyltrimethylammonium hydroxide) in methanol was added. Acrylonitrile, 50 g (0.94 mol), was added over 5 min without any sign of reaction; therefore, the mixture was heated to reflux and stirred for 6 hr. About halfway through an additional 10 g of Triton B was added. After cooling to room temperature, the reaction mixture was treated with 2 l. of water and extracted twice with 500-ml portions of benzene. The benzene layers were combined and washed with water several times. After removal of the solvent, the solid product was recrystallized once from cyclohexane and once from methanol to yield 42 g of the methyl ester of 9-carboxypentyl-9-cyanoethylfluorene, **5** (mp 95–96°). The ir spectrum (CS_2 and CCl_4) exhibited primary absorption at 3.28, 3.41, 3.50, 4.43 (C≡N), 5.76 (C=O), 6.9, 7.45, 8.35, 8.58, 12.9, 13.2, and 13.60 μ (fluorene ring); nmr ($CDCl_3$), δ 4.58 for the methyl group, δ 7.32 and 7.70 for the ring protons, and two groups from δ 1.20 to 1.70 and from 1.85 to 2.55 representing the other protons. The integrated areas were consistent with the structure assignments.

Anal. Calcd for $C_{23}H_{25}O_2N$: C, 79.50; H, 7.69; N, 4.23. Found: C, 79.70; H, 7.49; N, 4.04.

Methyl 6-(3-Indenyl)caproate (6) and 1,3-Bis(carbomethoxypentyl)indene (8).—There were charged to a 3-l. stainless steel rocker autoclave 129 g (1.1 mol) of indene, 139 g (1.2 mol) of ε-caprolactone, and 100 g (1.5 mol) of 85% potassium hydroxide pellets and this mixture was heated to 200° for 20 hr. The solid reaction product was treated with water and extracted with isopropyl ether to remove any unreacted indene. The aqueous layer was cooled with ice and acidified with concentrated hydrochloric acid releasing 191 g of an oil which became semisolid on standing. This material was esterified by refluxing for 20 hr with 2 l. of methanol and 5 g of *p*-toluenesulfonic acid. The reaction mixture was treated with 1 l. of water and extracted twice with 250-ml portions of isopropyl ether. The combined ether layers were washed once with 100 ml of 5% sodium hydroxide solution and with water until neutral. The ether was removed and the ester mixture distilled under reduced pressure giving 42 g (15.7%) of methyl 6-(3-indenyl)caproate (**6**) [bp 145° (0.45 mm); $n^{20}D$ 1.5327] and 61 g (27%) of the dimethyl ester of 1,3-bis(carboxypentyl)indene (**8**) [bp 222° (0.4 mm); $n^{20}D$ 1.5250]. The ir (CS_2 and CCl_4) of both **6** and **8** exhibited bands at 5.73 μ (C=O); nmr of **6** (CCl_4), δ 1.4–1.85 (m, six protons), 2.1–2.58 (m, four protons), 3.2 (q, two protons), 4.55 (s, three protons), 6.08 (one proton), and 7.05–7.38 (m, four protons).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.36; H, 8.37.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; mol wt, 372.5. Found: C, 74.47; H, 8.51; mol wt (by freezing point depression of benzene), 372.

Registry No.—Fluorene, 86-73-7; indene, 95-13-6; 9-fluorenylacetic acid, 6284-80-6; **1a**, 16425-43-7; **1a** methyl ester, 16425-44-8; **1b**, 16425-45-9; **1b** methyl ester, 16425-46-0; **1b** 2,2,4-trimethylpentyl ester, 16425-47-1; **1c**, 16425-48-2; **1c** methyl ester, 16425-49-3; **2**, 4425-95-0; **2** dimethyl ester, 13098-97-0; **5**, 16605-83-7; **6**, 16425-52-8; **8**, 16452-33-8.

Acknowledgment.—The authors wish to thank Dr. W. T. Pace for the nmr spectra, as well as Mr. A. H. DuVall and Mr. S. B. Gottlieb for elemental analysis and other analytical services and Mr. M. A. Eccles for technical assistance.

The Michael Reaction of Acrylate Salts

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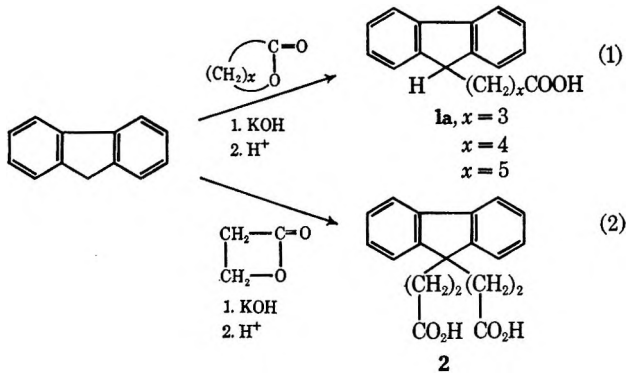
The Michael reaction[2] has been well reviewed and is an important synthetic tool. Briefly, it consists of the reaction of a carbanion with an electron-deficient unsaturated system.

(1) To whom inquiries should be addressed.

(2) E. B. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

During the investigation[3] of the reaction of lactones with fluorene and potassium hydroxide to form ω-(9-fluorenyl)alkanoic acids (**1**), it was observed that all the lactones used gave monosubstituted fluorene derivatives except propiolactone, which gave 9,9-bis-(carboxyethyl)fluorene.[3] Although most lactones were postulated to react with fluorene through a hydroxy acid salt intermediate, the potassium 3-hydroxypropionate which would form from propiolactone could dehydrate to an acrylate under the reaction conditions. Acrylate salts are not reported as acceptors in the Michael reaction, except in the case of the reaction of indole[4] with acrylate and methacrylate salts to form 1- and 3-indolepropionic acid. The mechanism of 3-indole acid formation probably involves a rearrangement of the 1-indolepropionic acid.[5] This communication extends the Michael reaction of acrylate salts to more common hydrocarbon donor systems and reports the synthesis of several unknown compounds. Also, the reaction of potassium phenylacetate with acrylate salts is reported and provides an example of a new class of donor molecules.



Fluorene was treated with potassium or sodium acrylate,[3] formed *in situ* by the reaction of acrylic acid with the alkali metal hydroxide, using excess base as catalyst to give **2** in 50–60% yield and 90–100% efficiency based on fluorene. The normal reaction was conducted either in a rocker autoclave or at atmospheric pressure at 210–235° for about 20 hr. No improvement in the reaction was observed when tetralin, naphthalene, or diphenylmethane were employed as solvents. All of the experiments are outlined in Table I. The diacid (**2**) prepared by this technique had previously been made by Bruson[6] *via* cyanoethylation of fluorene followed by hydrolysis of the corresponding dinitrile derivative.

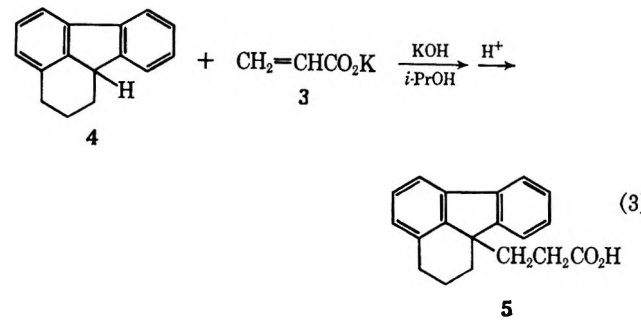
Tetrahydrofluoranthene, **4**, also reacted with potassium acrylate and potassium hydroxide to yield 3-[6a(4H)-5,6-dihydrofluoranthenyl]propionic acid, **5**, in 33% yield and 70% efficiency based on **4**. This product, **5**, has been synthesized[7] *via* cyanoethylation of **4** followed by hydrolysis to the acid.

TABLE I

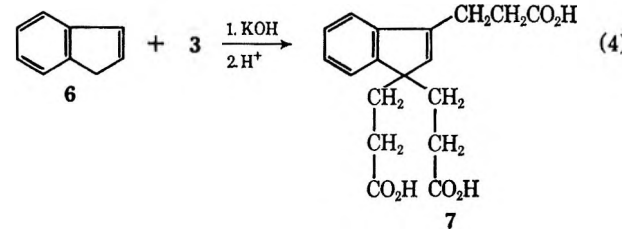
SYNTHESIS OF 9,9-BIS(CARBOXYETHYL)FLUORENE[a]

Run no.	Temp, °C	Time, hr	Yield,[b] %	Efficiency,[b] %
1[c]	230	20	64	98
2[c]	112	20	0	0
3[c]	230	6	49	...
4[c]	225	1	50	100
5[d-f]	228	20	0	0
6[d,e,g]	228	20	32	...
7[d,h,i]	214	14	11	...

[a] Unless otherwise noted, the molar ratio of fluorene–acrylic acid–KOH was 1.0:2.1:2.7. [b] Based on fluorene. [c] Reacted in a 3-l. stainless steel rocker autoclave. [d] Reacted in a stainless steel flask. [e] Molar ratio 1.0:3.0:4.1. [f] Tetralin used as solvent. [g] Naphthalene used as solvent. [h] Molar ratio 1.0:2.1:3.0. [i] Diphenylmethane used as solvent.



Indene, **6**, reacted with acrylate salts to give the trisubstituted product 1,1,3-tris(carboxyethyl)indene, **7**. This material was isolated as its trimethyl ester in about 10% yield. Some material thought to be due to disubstitution was isolated but contained impurities that could not be removed by standard techniques. These results are analogous to the cyanoethylation of indene[6] where 1,1,3-tris(cyanoethyl)indene was the primary product.



Diphenylmethane and 9,10-dihydroanthracene failed to react with potassium or sodium acrylate. Neither of these worked in the reaction of lactones[3] with compounds containing activated methylene groups.

The use of acrylate salts as acceptors in the Michael reaction has been extended to a new class of donors—compounds with active hydrogens also containing an acid salt in the molecule. The specific examples are potassium phenylacetate, **8**, and the potassium salt of ω-substituted (9-fluorenyl)alkanoic acids, **1a** and **1c**.

Phenylacetic acid was treated with acrylic acid and potassium hydroxide to give a 40% yield of 2-phenylglutaric acid, **9**. The acid was identified by conversion to its dimethyl ester, **10**, and to 2-phenylgutaric anhydride, **11**. The best reported synthesis of 2-phenylglutaric acid[8,9] involves cyanoethylation of phenyl-

(3) H. E. Fritz, D. W. Peck, and K. E. Atkins, *J. Org. Chem.*, **33**, 2575 (1968).

(4) (a) H. E. Johnson and D. G. Crosby, *ibid.*, **28**, 2030 (1963); (b) W. Reppe and H. Ufer, U. S. Patent 2,195,974 (1940).

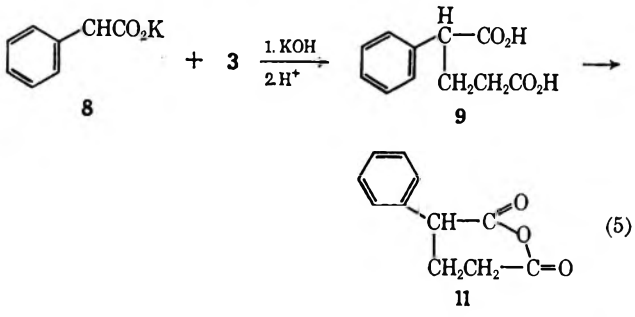
(5) H. E. Fritz, *J. Org. Chem.*, **28**, 1384 (1963).

(6) (a) H. A. Bruson, *J. Amer. Chem. Soc.*, **64**, 2457 (1942); (b) H. A. Bruson, U. S. Patent 2,339,218 (1944); (c) H. A. Bruson, U. S. Patent 2,339,373 (1944).

(7) CIBA Ltd, British Patent 666,713 (1952); *Chem. Abstr.*, **47**, 7547e (1953).

(8) E. C. Horning and A. F. Finelli, *Org. Syn.*, **30**, 81 (1950).

(9) M. F. Ansell and D. H. Hey, *J. Chem. Soc.*, 1683 (1950).



malonic or phenylcyanoacetic esters, followed by hydrolysis with cleavage of one carboxyl group.

The reactivity of potassium phenylacetate in this system was surprising. Since the carboxylate salt does not have good electron-withdrawing properties, it would have been reasonable to predict that the methylene hydrogens would not be acidic enough to form a carbanion that would enter into the Michael reaction. The fact that these reactions were conducted in solid phase, free of solvent, may have changed some of these factors.

Other acids salts which participate as donors are **1a** and **1c** which yield the corresponding unsymmetrical diacids in 40–50% yields when treated with potassium acrylate in the presence of potassium hydroxide. The compounds were previously unknown and no other simple synthesis can be immediately envisioned. The carboxylate salt groups are far enough away from the active hydrogen that they should not affect the initial carbanion formation.

Experimental Section

Melting points were obtained on a Fisher-Johns instrument. Infrared spectra were recorded by Beckman IR-4, ultraviolet spectra by a Cary Model 21 spectrophotometer, and nuclear magnetic resonance spectra by a Varian Associates Model A-60 spectrometer. Elemental analyses were performed by the UCC Chemicals and Plastics R and D analytical group.

9,9-Bis(carboxyethyl)fluorene (2).—Into a 1-l. stainless steel rocker autoclave were charged 166 g (1.0 mol) of fluorene, 80 g (1.1 mol) of acrylic acid, and 100 g (1.5 mol) of 85% potassium hydroxide pellets and this mixture was heated to 220° for 20 hr. The cooled product was treated with 1 l. of water and extracted with 1 l. of isopropyl ether. The ether was removed by distillation and 86 g (0.52 mol) of unreacted fluorene was recovered. Acidification of the aqueous layer with concentrated hydrochloric acid released 128 g of 9,9-bis(carboxyethyl)fluorene, **2**. The infrared, ultraviolet, and nmr spectra were identical with those of an authentic sample[3] and there was no depression of a mixture melting point. This represented a 75% yield of diacid based on the acrylic acid charged and an 85% yield based on reacted fluorene.

3-[6a(4H)-5,6-Dihydrofluoranthenyl]propionic Acid (5).—To a 3-l. stainless steel rocker autoclave were charged 200 g (0.98 mol) of 1,2,3,10b-tetrahydrofluoranthene,[10] **4**, 100 g (1.4 mol) of glacial acrylic acid, 100 g (1.5 mol) of 85% potassium hydroxide pellets, and 500 ml of isopropyl alcohol. This mixture was heated to 240° and held for 20 hr. Water, 1 l., was added to the reaction mixture and the solution was filtered to recover 109 g of unreacted **4**. The filtrate was acidified with concentrated hydrochloric acid, releasing a white solid. After recrystallization from 1 l. of benzene, 92 g of **5** (33%) were obtained. An analytical sample was obtained by a recrystallization from methanol, mp 181–182° (lit.[7] mp 176–176.5°). A mixture melting point with authentic material was not depressed. The ir spectrum of the acid (KBr) showed bands at 3.3, 3.42 (broad), 5.87, 6.95 (doublet), 7.67, 7.94, 10.7, and 13.25 μ. The band at 13.25 μ is consistent with an *ortho*-substituted aromatic ring with four adjacent H atoms.[11] The acid was converted into its methyl ester by refluxing in methanol in the presence of *p*-toluenesulfonic acid catalyst. Upon recrystallization from benzene white crystals, mp 115–117, were obtained.

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52; neut equiv, 278.3. Found: C, 82.10; H, 6.59; neut equiv, 274.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.31; H, 6.84.

1,1,3-Tris(carboxyethyl)indene (7).—To a 3-l. stainless steel rocker autoclave were charged 116 g (1.0 mol) of indene, 230 g (3.2 mol) of glacial acrylic acid, and 280 g (4.2 mol) of 85% potassium hydroxide pellets. This mixture was heated to 240° for 20 hr, then the cooled reaction product was treated with 2 l. of water. The solution was extracted with 1 l. of isopropyl ether to remove unreacted indene. The aqueous layer was acidified with concentrated hydrochloric acid to release 206 g of tan taffylike material which was treated with 500 ml of methanol and 20 g of *p*-toluenesulfonic and refluxed for 10 hr. The methanol solution was treated with water releasing a brown oil which was removed by extraction with 1 l. of isopropyl ether. The ether solution was washed with 100 ml of 10% sodium hydroxide and then with water. The ether was evaporated leaving 189 g of brown oil which was distilled at reduced pressure to yield 37 g of the trimethyl ester of 1,1,3-tris(carboxyethyl)indene (10%). In a similar experiment, the taffylike material obtained upon acidification was recrystallized from benzene to yield the triacid, mp 148–150°.

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.37; H, 7.00; sapon equiv, 125. Found: C, 67.61; H, 7.15; sapon equiv, 130.

Anal. Calcd for $C_{15}H_{20}O_6$: C, 65.05; H, 6.07; neut equiv, Found: C, 65.28; H, 6.27; neut equiv, 110.0.

2-Phenylglutaric Acid (9).—There was charged to a 3-l. stainless steel rocker autoclave 136 g (1.0 mol) of phenylacetic acid, 200 g (2.8 mol) of glacial acrylic acid, and 300 g (4.6 mol) of 85% potassium hydroxide pellets. This mixture was heated to 240° for 20 hr and the product was recovered from the autoclave by dissolving in water. The clear, brown solution was acidified with concentrated hydrochloric acid. The aqueous solution was extracted twice with 500-ml portions of isopropyl ether and, after evaporation of the ether, 134 g of acidic product was obtained. This material was esterified by refluxing with 500 ml of methanol and 5 g of *p*-toluenesulfonic acid for 10 hr. The reaction mixture was diluted with water and worked up in the normal manner. Distillation of the crude product at reduced pressure yielded 80 g of dimethyl 2-phenylglutarate: bp 167–168° (10 mm); $n^{20}D$ 1.5011.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.07; H, 6.83; mol wt, 236.3. Found: C, 66.08; H, 6.90; mol wt (by freezing point depression of benzene method), 237.

2-Phenylglutaric Acid Anhydride (11).—The reaction above was repeated and 152 g of crude acid product was obtained. This material was distilled under reduced pressure and 89 g of **11** was obtained: bp 177–182° (1.0–1.6 mm); afte rrecrystallization from ether, mp 95.0–95.5° [lit.[8] bp 178–188° (0.5–1.0 mm), mp 95–96°]. Infrared spectrum (CS_2) showed a carbonyl doublet centered at 5.56 μ indicative of anhydride.

9-(Carboxyethyl)-9-(carboxypropyl)fluorene (12a).—To a 1-l. stainless steel rocker autoclave was charged 126 g (0.5 mol) of 4-(9-fluorenyl)butyric acid,[12] **1a**, 108 g (1.5 mol) of acrylic acid, and 200 g of 85% potassium hydroxide pellets (3.0 mol). This mixture was heated to 260° and held for 10 hr. The product was recovered by dissolving in 2 l. of water and the aqueous solution was acidified with concentrated hydrochloric acid. Isopropyl ether, 1 l., was used to extract the crude acid product. The ether was evaporated and the resulting solid recrystallized from a benzene–isopropyl alcohol mixture yielding 69 g of **12a**, mp 187–187.5°, representing a 42% yield. There was recovered 47 g of 4-(9-fluorenyl)butyric acid making the efficiency, based on **1a**, 80%. The dimethyl ester of **12a** was prepared by refluxing in methanol containing a catalytic amount of *p*-toluenesulfonic acid. After recrystallization from ether the dimethyl ester melted 70–70.5°.

The ir spectrum of 12a (KBr pellet) showed major bands at 2.90, 3.3, 3.4, 5.82, 6.9, 7.05, 7.7, 8.1, 8.2, 8.62, 12.85, 12.95, and 13.55 μ. The major bands of the dimethyl ester of **12a** (CS_2

(10) Obtained by sodium metal catalyzed hydrogenation of fluoranthene.

(11) E. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., p 77.

(12) Prepared from the base-catalyzed reaction of fluorene with γ-butyrolactone (see ref 3).

and CCl_4) are 3.40, 5.76, 6.90, 6.95, 7.35, 7.79, 8.03, 8.40, 8.60, 13.0, 13.18, and 13.60 μ. The nmr of 12a showed absorption at δ 0.4–3.6 (m, ten protons), 7.3, 7.8 (eight protons), and a broad absorption at 9.9 ppm for acid protons (two protons). The nmr of 12a dimethyl ester (CCl_4) showed absorption at δ 1.4–2.5 (m, ten protons), singlets at 3.40 and 3.53 (six protons), and 7.3 and 7.7 (m, eight protons).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.1, H, 6.3. Found: C, 74.4, H, 6.4.

Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.9; sapon equiv, 176. Found: C, 74.9; H, 7.00; sapon equiv, 176.

9-(Carboxyethyl)-9-(carboxypentyl)fluorene (12b).—A 3-l. stainless steel rocker autoclave was charged with 526 g of methyl 6-(9-fluorenyl)caproate[13] (1.8 mol), 225 g (3.1 mol) of glacial acrylic acid, and 450 g (6.8 mol) of 85% potassium hydroxide pellets. This mixture was heated to 220° for 20 hr. The product was dissolved in 3 l. of water and filtered, and the filtrate was acidified with concentrated hydrochloric acid liberating a white viscous oil. Upon dissolving this crude oil in 2 l. of methanol approximately 110 g was insoluble. This apparently polymeric material was separated by decantation. To the methanol solution was added 15 g of *p*-toluenesulfonic acid; this mixture was refluxed for 24 hr. After the usual work-up 398 g of the dimethyl ester was isolated by distillation [bp 215–218° (0.3 mm), $n^{25}D$ 1.5604]. The ir spectrum of the dimethyl ester of **12b** (CS_2 and CCl_4) showed major bands at 3.3 (w), 3.41 (s), 3.50, 5.75, 6.90, 6.95, 7.31, 7.70, 8.05, 8.40, 8.60, 13.0, 13.17, and 13.62 μ. The infrared spectrum of **12b** (KBr pellet) showed major bands at 3.0, 3.32, 3.48, 4.18, 5.88, 6.93, 7.0, 7.65, 8.0, 8.31, 10.7, 12.86, and 13.58 μ.

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42; sapon equiv, 190. Found: C, 75.95; H, 7.42; sapon equiv, 202.

Registry No.—**5**, 13099-00-8; **7**, 974-60-7; dimethyl 2-phenylglutarate, 10436-86-9; **12a**, 13098-95-8; **12a** dimethyl ester, 13098-96-9; **12b** dimethyl ester, 13098-99-2; **5** methyl ester, 16423-39-5.

Acknowledgment.—The authors wish to thank Dr. W. T. Pace for the nmr analysis as well as Mr. A. H. DuVall and Mr. S. B. Gottlieb for elemental analysis, Mr. B. Romine for saponification equivalents, and Mr. M. A. Eccles for experimental assistance.

(13) Prepared by the base-catalyzed reaction of fluorene with ϵ-caprolactone (see ref 3).

The Mills Nixon Effect. II[1]

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In an earlier paper[1] we reported a quantitative examination of product distributions in bromination and nitration of *o*-xylene, indan, and tetralin. The results revealed a higher *ar*-β/*ar*-α substitution ratio for indan than for tetralin and it was assumed that this order, which is the reverse of that to be expected on steric grounds, and is also inexplicable on any standard electronic basis, could be explained in terms of the strain developed in the five-membered ring system of indan. We now report work on aromatic hydrogen exchange of the three hydrocarbons in anhydrous trifluoroacetic acid. This system was chosen because it has probably the lowest steric requirement of any electrophilic substitution reaction and any steric masking of the effect of ring strain should therefore be minimized. The results are shown in Table I.

(1) Part I: J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, **21**, 1665 (1965).

TABLE I

RATE CONSTANTS FOR HYDROGEN EXCHANGE OF TRITIATED HYDROCARBONS IN ANHYDROUS TRIFLUOROACETIC ACID AT 70°

Hydrocarbon	10^5k, sec^{-1}	Registry No.
3-[^{3}H]-*o*-Xylene	1.10 ± 0.02	16408-68-7
4-[^{3}H]-*o*-Xylene	1.55 ± 0.03	16408-69-8
4-[^{3}H]-Indan	0.82 ± 0.01	16408-70-1
5-[^{3}H]-Indan	3.34 ± 0.04	16408-71-2
5-[^{3}H]-Tetralin	3.10 ± 0.02	16408-72-3
6-[^{3}H]-Tetralin	3.35 ± 0.03	16408-73-4

The rate constants for detritiation of indan confirm that the two aromatic positions have markedly different reactivities. The ratio of the two rate constants *ar*-α/*ar*-β is 0.25, of the same order as the ratios of the percentages of α-bromo and β-bromoindans,[1] which range from 0.19 to 0.28. The two positions in tetralin are almost equally reactive, and again this result is in line with the bromination and nitration studies and with the results for *o*-xylene.[2] It seems clear, therefore, that indan reflects in its electrophilic substitution reactions the strain imposed on the aromatic ring by the fused, five-membered ring. Tetralin does not show this difference in reactivity, and it is probable that the buckled six-membered ring imposes little strain on the aromatic ring.

One further point should be made. In our previous detailed explanation,[1] we assumed that an increase in the double-bond character of the common bond in indan will results in a less stable system. This is undoubtedly a useful practical assumption but in making it we were directly applying a conclusion drawn by Brown from his results on nonaromatic derivatives of cyclopentane and cyclohexane.[3] This we now believe was not justifiable because the kind of interference (involving methylene hydrogens) that allowed Brown to explain his generalization is absent in our compounds. While, therefore, the assumption correlates our results, it does not provide a satisfactory explanation for them.

Experimental Section

Anhydrous trifluoroacetic acid was prepared by fractional distillation of commercial acid from sulfuric acid and then from silver oxide.

Tritiated hydrocarbons were prepared from the corresponding bromo compounds.[1] The bromo compounds were shown to be pure by glpc analysis under conditions known to separate isomeric pairs; the Grignard reagents formed from them were treated with tritiated water (specific activity 10 mCi/ml), and the resulting hydrocarbons were purified by fractional distillation. These showed no impurity on glpc analysis.

Rate Measurements.—These were carried out in anhydrous trifluoroacetic acid solvent at 70° as described previously,[4] using hydrocarbon concentrations of about 0.05 *M*. First-order rate plots of log count rate *vs.* time were linear over at least three half-lives in all cases; rate constants calculated from the equation $k = 2.303 \times$ slope of rate plot, were determined at least twice for each substrate and were reproducible to within ±2%. The rate constants were not converted into partial rate factors because the rate constant obtained for *p*-[^{3}H]-toluene in this study was 7% lower than that previously reported[4] and used as standard.

(2) R. Taylor, G. J. Wright, and A. J. Homes, *J. Chem. Soc., Sect. B*, 780 (1967).

(3) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(4) R. Baker, C. Eaborn, and R. Taylor, *J. Chem. Soc.*, 4927 (1961).

However, since all runs were carried out in the same trifluoroacetic acid and reproducible rate constants were obtained for all the hydrocarbons, the comparison of rate constants within the series studied is valid.

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Solvolysis of 2-(Δ^2-Cyclohexenyl)ethyl System

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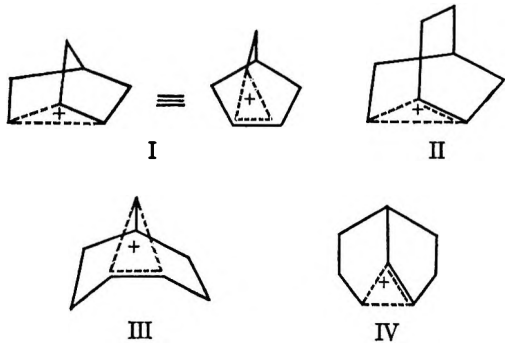
The field of π-electron participation in solvolytic displacement reactions of unsaturated sulfonate esters has grown rapidly in the last decade and has attracted the interest of many chemists both from the theoretical and synthetic point of view.[1]

Recently, it has been commonly accepted that one and the same bridged nonclassical ion can be generated by delocalization of either σ or π electrons. One criterion which has been frequently used to demonstrate the intervention of bridged ions is rate enhancement observed in solvolysis. Examples of this phenomenon include the 2-norbornyl nonclassical ion[2-4] I and the two isomeric nonclassical bicyclo[3.2.1]oct-2-yl cations[5,6] (II and III)[7] as well as the nonclassical bicyclo[3.3.0]oct-2-yl cation[8,9] (IV).



Such rate enhancement is not, however, the general rule for all compounds possessing a nonconjugated double bond. Thus Wilcox and Chibber[10] reported the absence of double bond interaction in the solvolysis of Δ^3-cyclohexenylcarbinyl derivatives. A similar conclusion was reached for 2-(Δ^2-cyclopentenyl)ethyl-,[11] 3-(Δ^1-cyclopentenyl)propyl-,[9] and 3-(Δ^3-cyclopentenyl)-propyl brosylates.[3]

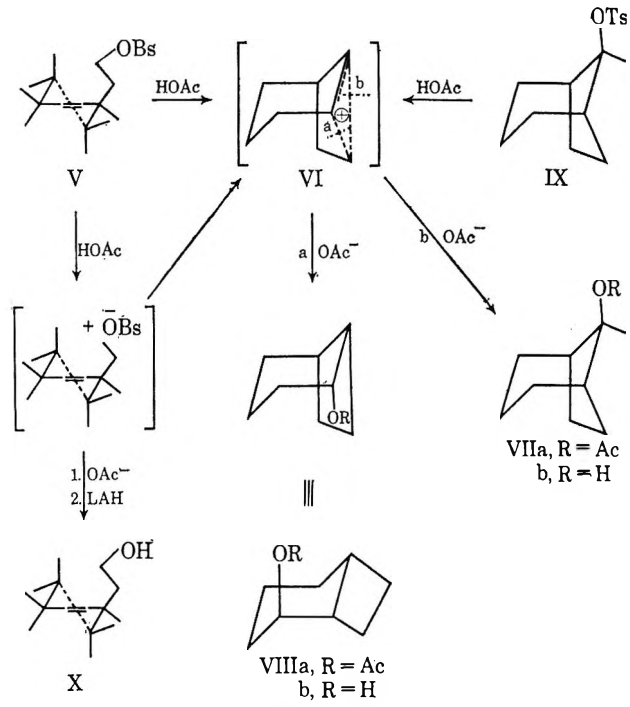


Figure 1.

In view of the general interest of double-bond interactions we wish to report the synthesis of 2-(Δ^2-cyclohexenyl)ethyl brosylate and its acetolysis along with the saturated analog.

Results and Discussion

2-(Δ^2-Cyclohexenyl)ethyl alcohol and the brosylate ester were prepared as outlined in the Experimental Section. The purity of the ester, which is a liquid at room temperature, was estimated from the infinity titer of kinetic runs to be better than 95–96%. The solvolysis was conducted in anhydrous acetic acid at two temperatures, and the first-order reactions were followed to about 60% reaction. The kinetic data are collected in Table I along with pertinent reference rates.

Product Analysis.—Infrared analysis, vapor phase chromatography, and nuclear magnetic resonance techniques were used to determine product composition. Acetolysis products were reduced by lithium aluminum hydride to the corresponding alcohols and analyzed. Possible bicyclic products, *endo*-bicyclo[3.2.1]octanol-8 (VIIb) and *endo*-bicyclo[4.2.0]octanol-2 (VIIIb), which could have been formed if double-bond participation was significant, were looked for carefully and found to be absent within experimental error. Acetolysis of V gave only compound X (See Figure 1).

The slight decrease in the rate of acetolysis of V compared with the saturated analog is attributed to the double bond which destabilizes the transition state for solvolysis by inductively retarding the departure of the incipient anion. The ratio $k_{satd}/k_{unsatd} = 1.73$ agrees with that found by Wilcox[10] for the solvolysis of Δ^3-

(1) For excellent reviews in this field, see (a) D. Bethel and V. Gold, *Quart. Rev.* (London), **12**, 173 (1958); (b) B. Capon, *ibid.*, **18**, 45 (1964); (c) G. D. Sargent, *ibid.*, **20**, 301 (1966).

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TABLE I
SPECIFIC RATE CONSTANTS AND ACTIVATION PARAMETERS[a]

Compd	Temp, °C ±0.05	k_1, sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
2-(Δ^2-Cyclohexenyl)ethyl	75.00	2.02×10^{-6}		
p-bromobenzenesulfonate	95.00	1.71×10^{-5}	26.3	−8.8
2-Cyclohexylethyl	75.00	3.50×10^{-6}		
p-bromobenzenesulfonate[b]	95.00	4.02×10^{-5}	31.4	6.5
endo-Bicyclo[3.2.1]octyl	75.00	1.35×10^{-8}		
8-*p*-toluenesulfonate[c]	120.00	0.30×10^{-6}	31.9	−3.5
exo-Bicyclo[3.2.1]octyl-8-*p*-toluenesulfonate[c]	75.00	3.16×10^{-5}		

[a] All solvolyses were conducted in acetic acid. [b] Winstein reported a value of *ca.* 2×10^{-6} for k_1 at 75°.[2b] [c] Extrapolated: C. S. Foote and R. B. Woodword, *Tetrahedron*, 20, 687 (1964).

cyclohexenyl carbinyl systems (1.68) where double-bond participation was excluded.

This result differs from that observed for 2-(Δ^3-cyclohexenyl)ethyl brosylate where rate enhancement and formation of bicyclic products was reported.[2b] Such difference can be rationalized by considering the interaction of the developing carbonium ion *para* orbital with the *para* orbitals of the double bond.[12] A symmetrical interaction in 2-(Δ^3-cyclohexenyl)ethyl cation can lead to a stabilized nonclassical ion. An unsymmetrical interaction predicted for 2-(Δ^2-cyclohexenyl)-ethyl cation can only lead to a classical ion as actually observed. A similar interaction between the π electrons of the double bond and a polar substituent in the side chain was recently postulated[13] for Δ^3-cyclohexene derivatives resulting from a preferential fixed conformation of the ring.

A bridged ion VI would be comparable to that expected from solvolysis of *endo*-bicyclo[3.2.1]octyl 8-tosylate (IX), resulting from σ delocalization, if it does occur. Fortunately, acetolysis of this system was recently studied[14] and the results excluded intervention of a bridged ion. The absence of σ delocalization in the *endo* isomer, as opposed to the *exo* isomer (see Table I), was attributed to increase in angle strain in formation of a bridged transition state. Consequently, it is not unreasonable to assume that the same argument holds good for acetolysis of V.

Furthermore, the value of k_s/k_Δ, the ratio of solvent to double-bond participation in 2-(Δ^2-cyclohexenyl)-ethyl system, can be roughly estimated following a procedure similar to that suggested by Wilcox.[10] Assuming that the difference in free energies between Δ^3- and Δ^2-cyclohexenylethyl systems equals the free energy difference in the related transition states for solvolysis of bicyclo[2.2.2]octyl-2- and *endo*-bicyclo-[3.2.1]octyl-8-tosylates, respectively, k_s/k_Δ was calculated to be *ca.* 10^5 or no significant double-bond participation in the 2-(Δ^2-cyclohexenyl)ethyl system.

A preliminary study of the kinetics of solvolysis of 1-(Δ^2-cyclohexenyl)-2-chloropropane and its saturated analog in 70% aqueous acetone similarly showed absence of double bond participation ($k_{satd}/k_{unsatd} = 1.3$). These results will be reported later in detail.

It is noteworthy to point out a simple relationship that exists between rate enhancement and the position of the double bond relative to the leaving group. In all cases found in the literature, participation accompanied by rate enhancement is observed when the double bond in the cyclic system is separated from the carbon carrying the leaving group by an odd number of carbon atoms.[2b,3,7,9,11] Participation is, however, insignificant when the separation is by an even number of carbon atoms (see ref 3, 9, 10, 11, and present work).

(12) Kindly suggested by one of the referees.

(13) G. P. Kugatova-Shemyakina, *et al.*, *Tetrahedron*, **23**, 2721, 2987 (1967).

(14) See Table I, footnote *c*.

Experimental Section[15]

Diethyl Δ^2-Cyclohexenylmalonate.—To a solution of sodium (36.8 g, 1.6 g-atom) in absolute ethanol (600 ml) was added, while stirring under a nitrogen atmosphere, diethyl malonate (128 g, 0.8 mol) and then 1,2-dibromocyclohexane (121 g, 0.5 mol). The reaction mixture was heated at reflux for 15 hr and most of the alcohol was then removed. The residue was diluted with water (500 ml), extracted with three 100-ml portions of ether, and dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled *in vacuo* to give a colorless liquid (86 g, 71.5%): bp 136–137° (1 mm) (lit.[16] bp 87° (0.11 mm)).

Δ^2-Cyclohexenylmalonic Acid.—This was obtained in 71% yield by hydrolysis of the ester with methanolic potash. The acid crystallized from benzene in colorless plates: mp 167–169° (lit.[17] mp 165–167°).

Δ^2-Cyclohexenylacetic Acid.—Δ^2-Cyclohexenylmalonic acid (18.6 g, 0.1 mol) was heated in an oil bath up to 190°. The residue in the flask was distilled to give a colorless liquid (10.6 g, 75%): bp 116° (1 mm), n^{26}D 1.4828 (lit.[18] 125–127° (8 mm)).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.56; H, 8.47.

Methyl (Δ^2-Cyclohexenyl)acetate.—This ester was prepared quantitatively by treating the preceding acid with the appropriate amount of diazomethane in ether: bp 67–69° (2 mm), n^{26}D 1.4731.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.12; H, 9.09. Found: C, 70.24; H, 8.94.

2-(Δ^2-Cyclohexenyl)ethyl Alcohol.—Methyl (Δ^2-cyclohexenyl)-acetate (15.4 g) was reduced by lithium aluminum hydride in anhydrous ether (5-hr reflux) according to the usual procedure. The resulting alcohol (11.5 g, 92%), bp 100–101° (6 mm), was converted into the 3,5-dinitrobenzoate and crystallized from petroleum ether: mp 52–53°.

Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.00; N, 8.75. Found: C, 55.91; H, 5.28; N, 8.91.

Pure 2-(Δ^2-cyclohexenyl)ethyl alcohol was regenerated by alkaline hydrolysis of the 3,5-dinitrobenzoate derivative, followed by careful distillation through a 6-in. Vigreux column: bp 95–96° (2 mm); n^{26}D 1.4863.

(15) Melting points and boiling points are uncorrected. Microanalyses were performed by Alfred Bernhardt, West Germany. The infrared spectra were determined with a Unicam SP200 spectrophotometer. The vpc analyses were obtained with an Aerograph A-90 gas chromatograph, using a 10-ft column packed with 1% Carbowax on Chromosorb P, helium was used as a carrier gas. The nmr spectra were obtained with a Varian A-60 spectrometer. The petroleum ether used has bp 50–70°.

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Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.57; H, 10.95.

Vpc analysis showed that the alcohol was more than 99% pure. The infrared spectrum showed absorptions at $\nu_{max}^{CCl_4}$ 3400 (OH), 2960 (CH), 1645 (CH=CH), and 1050 cm^{-1} (CO). The nmr (CCl_4) spectrum showed peaks at τ 9.0–8.1, complex multiplet (9 $C_4H_7CH_2$); 6.47, triplet, J = 6.5 cps (2 $-OCH_2CH_2-$); 5.45, singlet (1 OH); 4.52, (2 CH=CH).

2-(Δ^2-Cyclohexenyl)ethyl *p*-Bromobenzenesulfonate.—Attempts to prepare this brosylate by the common method[19] gave back the alcohol and the acid chloride. Consequently, the alkoxide of the alcohol was prepared (0.69 g of sodium and 3.84 g of alcohol) in anhydrous ether under a nitrogen atmosphere. A solution of *p*-bromobenzenesulfonyl chloride (7.68 g) in anhydrous ether was added dropwise while cooling to −5°. The reaction mixture was stirred for 2 hr at this temperature and then for an additional 6 hr at room temperature. It was then left overnight, the ether solution was filtered, the solvent was removed and the residue was pumped at 0.5 mm for 30 min to remove any volatile products. The crude ester (9.5 g, 91.5%) was purified by several crystallizations, at low temperature, from petroleum ether: mp 10–11°; ir, $\nu_{max}^{CCl_4}$ 2930 (CH_2), 1650 (C=C), 1575 and 1460 (aromatic H), 1395 and 1190 cm^{-1} (OSO_2); nmr ($CDCl_3$), τ 9.0–8.2 (complex multiplet, 9 $C_4H_7CH_2$), 5.87 (triplet, J = 6.5 cps, 2 $-OCH_2CH_2-$), 4.50 (quartet, 2 CH=CH), 2.32 (multiplet, 4 aromatic H).

Ethyl cyclohexylidenecyanoacetate was prepared in 74% yield following Cope's procedure:[20] bp 150–151° (9 mm) (lit.[20] bp 150–151° (9 mm)); $n^{25}D$ 1.4980.

Ethyl cyclohexylcyanoacetate was prepared in 89% yield by catalytic reduction of ethyl cyclohexylidenecyanoacetate in the presence of Pd–C catalyst: bp 144–146° (7 mm); $n^{25}D$ 1.4640.

Cyclohexylacetic acid was prepared in 73% yield by refluxing ethyl cyclohexylcyanoacetate with concentrated hydrochloric acid for 20 hr. Working up the reaction mixture and distillation gave the acid: bp 116–118° (1 mm) (lit.[21] bp 135° (13 mm)); $n^{24}D$ 1.4682.

Ethyl Cyclohexylacetate.—Cyclohexylacetic acid was converted into the ethyl ester according to the usual procedure: bp 82–85° (2 mm) (lit.[21] bp 100° (17 mm)).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.58. Found: C, 70.49; H, 10.59.

2-Cyclohexylethyl alcohol was prepared in 94% yield by lithium aluminum hydride reduction of ethyl cyclohexylacetate according to the usual procedure, bp 100–102° (9 mm). The alcohol was converted into the 3,5-dinitrobenzoate derivative, crystallized from petroleum ether: mp 71° (lit.[22] 71–72°).

Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.59; N, 8.69. Found: C, 55.84; H, 5.53; N, 8.92.

The pure alcohol was regenerated by alkaline hydrolysis of the 3,5-dinitrobenzoate followed by careful distillation through a 6-in. Vigreux column: bp 100–101° (8 mm); $n^{26}D$ 1.4660 (lit.[23] bp 85–87° (6 mm), $n^{20}D$ 1.4670). Vpc analysis showed that the alcohol was homogenous: ir, $\nu_{max}^{CCl_4}$ 3450 (OH), 2975 (CH), and 1055 cm^{-1} (CO); nmr (CCl_4), τ 9.0–8.2 (complex multiplet, 13 $C_6H_{11}CH_2$), 6.5 (triplet, J = 6.5 cps, 2 $-OCH_2CH_2-$), 5.52 (singlet, 1 OH).

2-Cyclohexylethyl *p*-bromobenzenesulfonate was prepared following the procedure employed for the unsaturated ester. The crude product (92% yield) was purified by crystallization from petroleum ether: mp 36° (lit.[2b] mp 37°); ir, $\nu_{max}^{CCl_4}$ 2950 (CH_2), 1645 (C=C), 1580 and 1460 (aromatic H), 1393 and 1190 cm^{-1} (OSO_2); nmr ($CDCl_3$), τ 9–8.2 (complex multiplet, 13 $C_6H_{11}CH_2$), 5.95 (triplet, J = 6.5 cps, 2 $-OCH_2CH_2-$), 2.32 (multiplet, 4 aromatic H).

Product Analysis.—The pure brosylate ester (0.035 mol) was allowed to react in anhydrous acetic acid (500 ml) containing sodium acetate (0.048 mol) for about 14 half-lives. The cooled solution was diluted with 2 l. of water and extracted three times with 200-ml portions of ether. The aqueous layer was diluted again with water, and extracted with ether. The combined ether extract was washed with water, allowed to stand for 2 hr over anhydrous sodium carbonate, and then dried over anhydrous sodium sulfate. The solvent was stripped carefully and the residue was distilled without an attempt at fractionation. The unsaturated ester gave a colorless liquid (91%) with bp 93–102° (2 mm), and the saturated ester gave a colorless liquid (89.5%) with bp 95–103° (3 mm).

Reduction of the Acetolysis Product.—To a slurry of lithium aluminum hydride (1.2 g) in anhydrous ether (30 ml) was added a solution of the solvolysis acetate (0.018 mol) in anhydrous ether. The mixture was refluxed with stirring for 5 hr and left overnight at room temperature. The reaction mixture was decomposed with wet ether and worked up in the usual manner to give the corresponding solvolysis alcohol. The alcohols were purified by distillation without fractionation and subjected to analysis.

Analysis of the Solvolysis Alcohols.—Vpc analysis of the solvolysis alcohol from the unsaturated brosylate showed that it was identical with pure 2-(Δ^2-cyclohexenyl)ethyl alcohol. Similarly the solvolysis alcohol from the saturated brosylate was identical with pure 2-cyclohexylethyl alcohol. Infrared and nmr spectra of the alcohol from the unsaturated brosylate were superimposable upon those of a pure sample: 3,5-dinitrobenzoate, mp 52–53° (from petroleum ether), undepressed when admixed with an authentic sample.

Rate Measurements.—The reagents used were purified and standardized as described in ref 5a. Titrations were carried out with 5-ml microburets using methyl violet indicator (saturated solution in chlorobenzene) and the end point was approached from the acid side. The compound to be solvolyzed was weighed into a volumetric flask and brought up to the mark with sodium acetate solution (0.03–0.04 M). The amount of material used was calculated so that the solution would still contain sodium acetate at the end of the reaction. The ampoule technique was employed throughout the rate measurements.

First-order rate constants k (where $k = 1/t \ln (a/a - x)$, a is the initial concentration in moles per liter of the material, t is the elapsed time, and x is the concentration of consumed base) were calculated. A plot of log $(a - x)$ *vs.* t for the solvolysis of the brosylate esters at different temperatures gave straight lines.

Registry No.— Methyl (Δ^2-cyclohexenyl)acetate, 16423-29-3; 2-(Δ^2-cyclohexenyl)ethyl alcohol, 16452-34-9; 2-(Δ^2-cyclohexenyl)ethyl *p*-bromobenzenesulfonate, 16423-30-6; ethyl cyclohexylcyanoacetate, 3212-50-1; 2-cyclohexylethyl *p*-bromobenzenesulfonate, 16423-32-8; Δ^2-cyclohexenylacetic acid, 3675-31-8; 2-(Δ^2-cyclohexenyl)ethyl alcohol 3,5-dinitrobenzoate, 16423-40-8.

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Synthesis of 2-Methyladenosine and Its 5′-Phosphate

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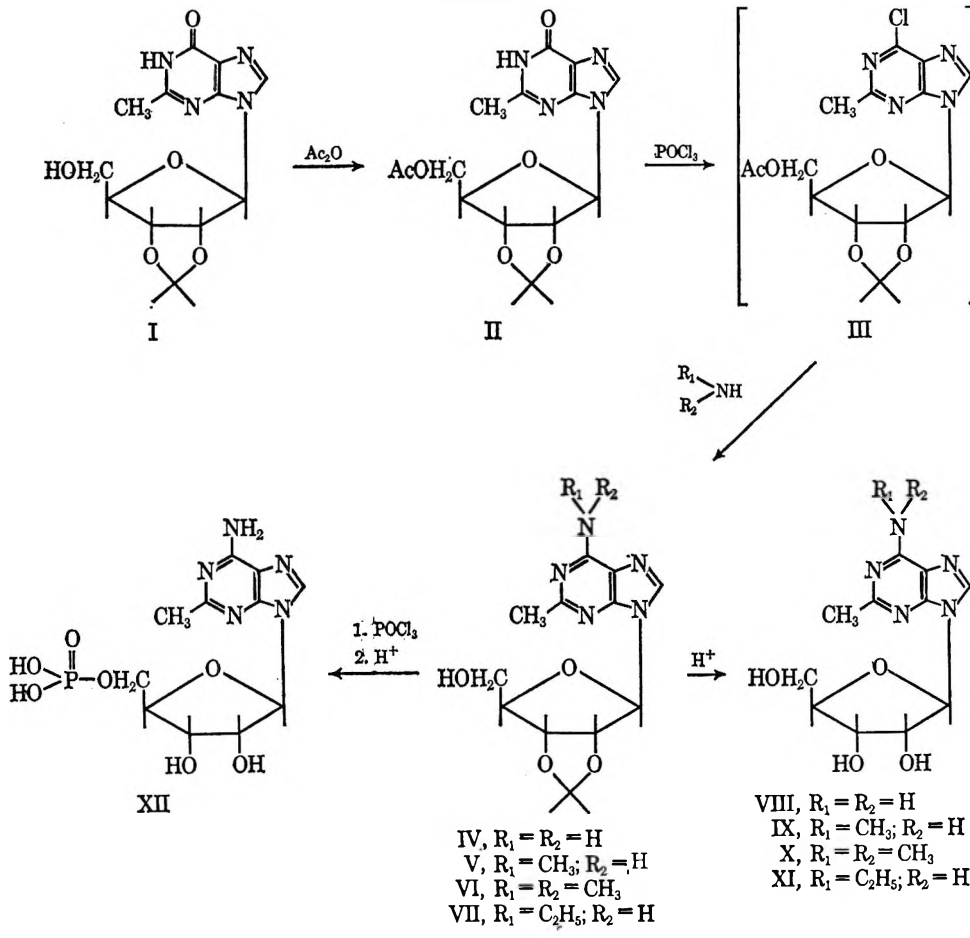
In recent years, a number of methylated purine nucleosides have been detected in transfer ribonucleic acid (RNA) as minor components, and the detection of

SCHEME I



such nucleosides has prompted many synthetic investigations. In previous papers, we have reported on the synthesis of some naturally occurring methylated purine nucleotides in connection with studies on the correlation of the flavoring activity and chemical structure of 5′-nucleotides: for example, N^2-methylguanosine,[1] N^2,-N^2-dimethylguanosine,[1] N^1-methylinosine,[2] and N^1-methylguanosine 5′-phosphates[2] were synthesized starting from 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide.

The present investigation was undertaken in order to synthesize 2-methyladenosine (VIII), its analogs, and 2-methyladenosine 5′-phosphate (XII). Previously, compound VIII was found by Littlefield and Dunn[3] to occur in RNA as a minor component, but the nucleotide XII was not isolated. The classical preparation[4] of VIII involved the condensation of a chloromercuri purine derivative with a blocked halo sugar. However, VIII was not isolated in crystalline form, and, moreover, its physical properties were not described in detail. In contrast, we have chosen 2′,3′-O-isopropylidene-2-methylinosine (I)[5] as a starting material and established a new method for preparing VIII and its analogs.

Compound I was readily acetylated (Scheme I) with acetic anhydride in pyridine to give 2′,3′-O-isopropylidene-5′-O-acetyl-2-methylinosine (II) in 77% yield, which was converted with phosphoryl chloride into 2-methyl-6-chloro-9-(2′,3′-O-isopropylidene-5′-O-acetyl-β-D-ribofuranosyl)purine (III) according to the procedure of Robins, *et al.*[6,7] Compound III was shown to be homogeneous on a paper chromatogram but could not be crystallized. Subsequent amination of III with ammonia in an autoclave at 120° for 3 hr afforded 2′,3′-O-isopropylidene-2-methyladenosine (IV) in 51% yield, from which VIII was obtained by removal of the isopropylidene group. Enzymatically prepared VIII[3] and the synthetic sample were proved to be the same compound by comparison of ultraviolet absorption spectra and R_f values. By a method developed in our laboratories,[8] IV was phosphorylated with phosphoryl chloride in trimethyl phosphate to afford the corresponding 5′-nucleotide. This material was hydrolyzed with acid to give XII, which was characterized by elemental analysis and spectral properties. The yield of XII was 31%.

Recently, numerous adenosine analogs have been detected in nature, some of which have showed significant biological activities. Noteworthy among them are tubercidin,[9] toyocamycin,[10] and puromycin.[11] It is also of interest that 2-methyladenine exhibits anti-

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tumor activity against Adenocarcinoma 755.[12] Then, 2,N^6-dimethyladenosine (IX), 2,N^6,N^6-trimethyladenosine (X), and 2-methyl-N^6-ethyladenosine (XI) as the analogs of VIII were synthesized by the same procedure as described for VIII.

Experimental Section[13]

2′,3′-O-Isopropylidene-5′-O-acetyl-2-methylinosine (II).—2′,3′-O-Isopropylidene-2-methylinosine[5] (I, 40 g) was dissolved in a mixture of pyridine (450 ml) and acetic anhydride (300 ml), and the solution was allowed to stand at room temperature overnight. After the solvent was removed *in vacuo*, 100 ml of ethanol was added and the mixture was then concentrated. This procedure was repeated several times to decompose acetic anhydride completely. The residue was dissolved in ethanol and allowed to stand at room temperature. The resulting crystals were collected by filtration and recrystallized from ethanol to give 35 g (77%) of pure crystals: mp 151°; $[\alpha]^{25}D$ −11.3° (*c* 1, water); uv, $\lambda_{max}^{pH\ 1}$ 253 mμ (ε 12,400), $\lambda_{max}^{pH\ 6}$ 251.5 mμ (ε 11,600), and $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 12,800).

Anal. Calcd for $C_{16}H_{20}O_6N_4$: C, 52.72; H, 5.53; N, 15.38. Found: C, 52.86; H, 5.67; N, 15.83.

2′,3′-O-Isopropylidene-2-methyladenosine (IV).[14]—To a stirred suspension of II (6 g) in phosphoryl chloride (30 ml) was added N,N-dimethylaniline (20 ml) and the mixture was refluxed for 3 min. The color of the solution turned to yellowish green. The reaction mixture was added to an excess of ice water with stirring and the product was extracted six times with 50-ml portions of chloroform. The combined chloroform extracts were washed with 200 ml of cold 1 *N* hydrochloric acid (to remove dimethylaniline), cold water, and 5% sodium hydrogen carbonate. The solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give a gummy product. This product, which is chromatographically homogeneous, exhibited $\lambda_{max}^{pH\ 1}$ 249.5 and 271 and $\lambda_{max}^{pH\ 13}$ 271 mμ in the ultraviolet spectra. After the above crude III was added to 50 ml of ethanol, the solution was saturated with ammonia at 0° and heated in an autoclave at 120° for 3 hr. The reaction mixture was concentrated *in vacuo* to afford a crystalline product, which was recrystallized from ethanol to give 2.7 g (51%) of pure crystals: mp 202–203°; $[\alpha]^{25}D$ −81.5° (*c* 1, water); uv, $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 12,500), $\lambda_{max}^{pH\ 6}$ 264 mμ (ε 14,300), and $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 14,200).

Anal. Calcd for $C_{14}H_{19}O_4N_5$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.11; H, 5.89; N, 21.86.

2′,3′-O-Isopropylidene-2,N^6-dimethyladenosine (V).—After 3.3 g of II was worked up as described above for IV, the crude III was aminated with 50 ml of 30% methylamine. The crude product was crystallized from water to give 2.1 g (76%) of pure crystals: mp 181°; $[\alpha]^{25}D$ −82.6 (*c* 1, water); uv, $\lambda_{max}^{pH\ 1}$ 265 mμ (ε 15,000), $\lambda_{max}^{pH\ 6}$ 271 mμ (ε 15,700), and $\lambda_{max}^{pH\ 13}$ 271 mμ (ε 16,800).

Anal. Calcd for $C_{15}H_{21}O_4N_5$: C, 53.72; H, 6.31; N, 20.89. Found: C, 53.62; H, 6.36; N, 21.15.

2′,3′-O-Isopropylidene-2-methyl-N^6-ethyladenosine (VII).—The crude III obtained from 4 g of II was aminated with 60 ml of 70% ethylamine. After the solvent was removed, the residue was dissolved in a small amount of water and allowed to stand at room temperature. The resulting crystals were filtered and crystallized from water, affording 2.1 g (54%) of the product: mp 123°; $[\alpha]^{25}D$ −78.7° (*c* 1, water); uv, $\lambda_{max}^{pH\ 1}$ 265 mμ (ε 15,300), $\lambda_{max}^{pH\ 6}$ 272 mμ (ε 16,800), and $\lambda_{max}^{pH\ 13}$ 272 mμ (ε 17,800).

Anal. Calcd for $C_{16}H_{23}O_4N_5$: C, 55.00; H, 6.64; N, 20.05. Found: C, 55.09; H, 6.66; N, 20.24.

2-Methyladenosine (VIII).—Compound IV (1 g) was added to 60 ml of water and the solution was adjusted to pH 1.5 with 1 *N* hydrochloric acid. The mixture was heated on the steam bath at 70° for 40 min with stirring to remove the isopropylidene group, cooled, and neutralized with Amberlite IRA-410 (OH^- form). The resin was removed and the filtrate was concentrated to give a crude product. Recrystallization from ethanol afforded 0.61 g (70%) of slightly hygroscopic crystals: $[\alpha]^{25}D$ −66.6° (*c* 1, water); uv,[15] $\lambda_{max}^{pH\ 1}$ 260 mμ (ε 14,000), $\lambda_{max}^{pH\ 6}$ 264 mμ (ε 14,500), and $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 15,200). The nuclear magnetic resonance spectrum in pyridine showed a singlet at 2.65 ppm due to the methyl group.

Anal. Calcd for $C_{11}H_{15}O_4N_5$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.93; H, 5.49; N, 25.07.

The following compounds were obtained by the same procedure as described for VIII. Their ultraviolet absorption spectra were as expected.

2,N^6-Dimethyladenosine (IX) was recrystallized as a crude product from ethanol. The yield was 71%: mp 179–180°; $[\alpha]^{25}D$ −67.6° (*c* 1, water).

Anal. Calcd for $C_{12}H_{17}O_4N_5$: C, 48.80; H, 5.80; N, 23.72. Found: C, 48.38; H, 5.89; N, 23.57.

2-Methyl-N^6-ethyladenosine (XI) was obtained as an analytically pure sample by recrystallization from water: yield 65%; $[\alpha]^{25}D$ −73.0° (*c* 1, water).

Anal. Calcd for $C_{13}H_{19}O_4N_5$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.55; H, 6.10; N, 22.41.

2,N,^{6}N^6-Trimethyladenosine (X).—After 3 g of II was treated as usual, the resulting III was aminated with 60 ml of 30% dimethylamine to yield 2′,3′-O-isopropylidene-2,N^6,N^6-trimethyladenosine (VI), which failed to crystallize. Then, subsequent removal of the isopropylidene group was carried out as described above. A crude product was obtained by crystallization from ethanol to give 1.4 g (56%) of pure crystals: mp 159°; $[\alpha]^{25}D$ −65.7° (*c* 1, water); uv, $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 16,700), $\lambda_{max}^{pH\ 6}$ 280 mμ (ε 19,500), and $\lambda_{max}^{pH\ 13}$ 280 mμ (ε 19,600).

Anal. Calcd for $C_{13}H_{19}O_4N_5$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.97; H, 6.54; N, 23.03.

2-Methyladenosine 5′-Phosphate (XII).—Phosphoryl chloride (2.5 ml) was mixed with 15 ml of trimethyl phosphate being cooled at −10° in a three-necked flask equipped with a thermometer and a silica gel drying tube. To this solution was added IV (2.4 g, 7.5 mmol) with stirring while maintaining the temperature below −5°, and the mixture was stirred at −5° for 2.5 hr. Within 30 min, it became clear and turned viscous. The solution was then poured into 500 ml of ice water to decompose the excess of phosphoryl chloride, adjusted to pH 1.5 with alkaline solution, and heated at 70° for 40 min. An aliquot from the solution showed two spots on a paper chromatogram. The major spot was that of XII and the other (minor) was identical with that of VIII. After cooling, the above solution was adjusted to pH 2 and passed through a column (3 × 70 cm) of 300 ml of decolorizing resin[16] to absorb XII. The column was washed with 1 l. of water and the nucleotide was eluted with 0.5 *N* ammonium hydroxide until the eluate became free from ultraviolet-absorbing material. Concentration of the eluate afforded a gummy product which was chromatographically homogeneous. After the crude product was dissolved in 50 ml of water, the solution was adjusted to pH 8.5 and a solution of barium acetate (1.55 g, 5.7 mmol) was added. The resulting precipitate, mainly consisting of barium phosphate, was removed by centrifugation. Addition of one volume of ethanol gave a precipitate of barium salt, which was collected by centrifugation, washed with ethanol, and then dried *in vacuo* at 100° for 2 hr to yield 1.24 g (31%): mp 260° dec; paper chromatography, R_f 0.02 (solvent A), 0.27 (solvent B), and 0.41 (solvent C); the moving distance in paper electrophoresis (10% acetic acid buffer, 800 V/cm, 2 hr), 3.2 cm; uv, $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 10,900), $\lambda_{max}^{pH\ 6}$ 264 mμ (ε 13,200), and $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 13,400). The infrared absorption spectrum showed absorption bands at 1100 (C–O–C) and 980 (P–O–C) cm^{-1}. The nuclear magnetic resonance spectrum in deuterium oxide showed a singlet at 2.75 ppm due to the methyl group.

Anal. Calcd for $C_{11}H_{14}O_7N_5BaP \cdot H_2O$: C, 25.68; H, 3.11; N, 13.62; P, 6.03. Found: C, 25.40; H, 3.09; N, 13.37; P, 5.68.

Registry No.—II, 16545-16-7; IV, 16526-53-7; V, 16526-54-8; VII, 16526-55-9; VIII, 16526-56-0; IX,

(12) E. Hirschberg, *Cancer Res., Suppl.*, **23**, 521 (1963).

(13) All melting points are uncorrected. Ultraviolet absorption spectra were taken with a Hitachi Type EPS-2 automatic recording spectrophotometer. The nmr spectra were measured with a Varian A-60 using tetramethylsilane as an internal standard. Paper chromatography was carried out on Toyo Filter Paper No. 51 by the ascending method. Solvent systems were A, *n*-butyl alcohol–acetic acid–water, 4:1:1 (v/v); B, *n*-propyl alcohol–ammonia (28%)–water, 20:12:3 (v/v); and C, isopropyl alcohol–saturated ammonium sulfate–water, 2:79:19 (v/v).

(14) This compound was also prepared by reaction of 5-amino-4-cyano-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)imidazole with ethyl orthoacetate followed by treatment with ammonia: Dr. T. Meguro, these laboratories, private communication, 1967.

(15) It was reported by Davoll, *et al.*[4] that the compound VIII, obtained by a chloromercuri procedure, showed $\lambda_{max}^{pH\ 1}$ 258 and $\lambda_{max}^{pH\ 13}$ 262.5 mμ.

(16) This decolorizing resin was prepared in our laboratories by copolymerization of metaphenylenediamine, resorcin, and formalin.

16526-78-6; X, 16526-79-7; XI, 16526-80-0; XII·barium salt, 16526-81-1.

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The Addition of Dinitrogen Trioxide to Norbornene[1]

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Schechter, *et al.*[2] have shown that the reaction of dinitrogen tetroxide with norbornene proceeds without skeletal rearrangement of the norbornyl system affording 22% *exo,cis*-2,3-dinitronorbornane, 12% of the *trans*-dinitro compound, and 60% of a mixture of nitronitrites. *exo* attack on the norbornyl system is favored for steric reasons; similar *exo,cis* additions have been observed in radical reactions of *p*-toluenethiol,[3] ethyl bromoacetate,[4] and hydrogen bromide[5] with norbornene. The addition of dinitrogen trioxide to olefins is generally believed to involve an extension of the free-radical mechanism applied to N_2O_4 additions,[6] so it was of interest to examine the course of adduction of norbornene with N_2O_3.

The addition of dinitrogen trioxide to norbornene can be visualized as proceeding through either 2,3, 2,7, or 2,6 addition. The 2,7 addition would be the result of Wagner–Meerwein-type rearrangement of the intermediate radical species. Hydrogen radical transfer in the intermediate would lead to 2,6 product. The course of addition was determined by employing *exo,exo*-5,6-dideuterionorbornene[7] as a substrate for N_2O_3 addition. Were the reaction to proceed without rearrangement to the 2,3 product, the 5,6-methylene protons would remain in *endo* positions in the pseudonitrosite I and nitroxime II (path A, Skeletal rearrangement to a 2,7 product would be accompanied by transformation of the 5,6-methylene hydrogens to *exo* protons in III and IV (path B, Scheme I). Hydrogen transfer in 2,6 addition would result in a deuterium attached to the nitrosated carbon atom in the pseudonitrosite V and oxime deuterium in the nitroxime VI. The results indicate that both the pseudonitrosite and nitroxime possess only *endo* hydrogens at the 5,6 positions. No rearrangement to 2,7 or 2,6 products has taken place; therefore, the reaction must have occurred *via* path A.

The nmr spectrum of the recrystallized nitroxime in deuterioacetone is in accord with structure I, that of *exo,exo*-5,6-dideuterio-3-nitro-2-norbornanone oxime. The oxime proton gives a sharp singlet whose chemical shift varies with concentration. The two bridgehead protons are observed as multiplets at δ 3.0 ppm. The three-proton is highly deshielded, being surrounded by the nitro and oximino groups, and is seen as a doublet at δ 4.8 ppm, with J = 2 cps. This proton is in an *endo* position coupling with the 7-*anti* bridge proton.[8] The bridge protons lie in different magnetic environments; their chemical shifts differ and so do their coupling patterns. A singlet peak at δ 1.4 ppm is attributable to the 5,6-*endo* protons; had they been *exo* in nature, larger coupling would be expected.

The deuterated pseudonitrosite has a high-field spectrum similar to that of the nitroxime. An unrecrystallized, but ether-washed sample of the pseudonitrosite shows a peak (area 2) at δ 5.0 ppm. This is the signal for the protons attached to the carbons bearing nitrogen atoms. This product appears to consist predominantly of the *exo,cis*-nitroso dimer II, since a *trans* configuration would result in *endo* and *exo* protons of different chemical shifts and larger coupling constants. Furthermore, *exo* protons should experience a coupling of 4–5 cps with the bridgehead protons.[8] A two-proton peak at δ 3.0 ppm is assigned to the bridgehead hydrogens and a doublet (area 2, J = 2 cps) at 1.2 ppm is assigned to the 5,6-*endo* protons. The bridge protons are manifested as signals centered at δ 1.5 and 2.3 ppm.

Catalytic reduction of the nitroxime gives a mixture of 2,3-diaminonorboranes. Conversion of the crude diamine product into the dihydrochloride followed by several recrystallizations of this salt affords *trans*-2,3-diaminonorborane dihydrochloride. This substance is identical with the salt prepared by Inglessis.[9] The signals for protons attached to nitrogen-bearing carbon atoms experience different chemical shifts as would be expected for *endo* and *exo* protons. A *cis* configuration would be more symmetrical, leading to the same chemical shift for either proton.

The N_2O_3 addition reaction probably involves initial *exo* attack by nitrogen dioxide. The steric demands of the norbornyl system then direct the combination of the intermediate radical with nitric oxide to favor the *exo,cis* product as in path A.

Experimental Section

Nmr spectra were taken in deuteriochloroform solution with a Varian A-60. Vapor phase chromatography was carried out on an FM-500. Melting points are uncorrected.

Preparation of Norbornene Pseudonitrosite.—A well-stirred solution of 1 mol of norbornene in 500 ml of a 1:1 solution of pentane–ether at −10 to 5° is treated with a mixed stream of nitric oxide at a flow rate of 80 cc/min and air at a flow rate of 40 cc/min. Completion of the reaction is evidenced by the appearance of brown gas above the surface of the reaction mixture, indicating that oxides of nitrogen are no longer being absorbed.

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) H. Schechter, J. J. Gardikes, T. S. Cantrell, and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **89**, 3005 (1967).

(3) S. J. Cristol and G. D. Brindel, *ibid.*, **76**, 5699 (1954).

(4) J. Weinstock, Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., Sept 1955, p 19-Org.

(5) H. Kwart and J. L. Nyce, *J. Amer. Chem. Soc.*, **86**, 2601 (1964).

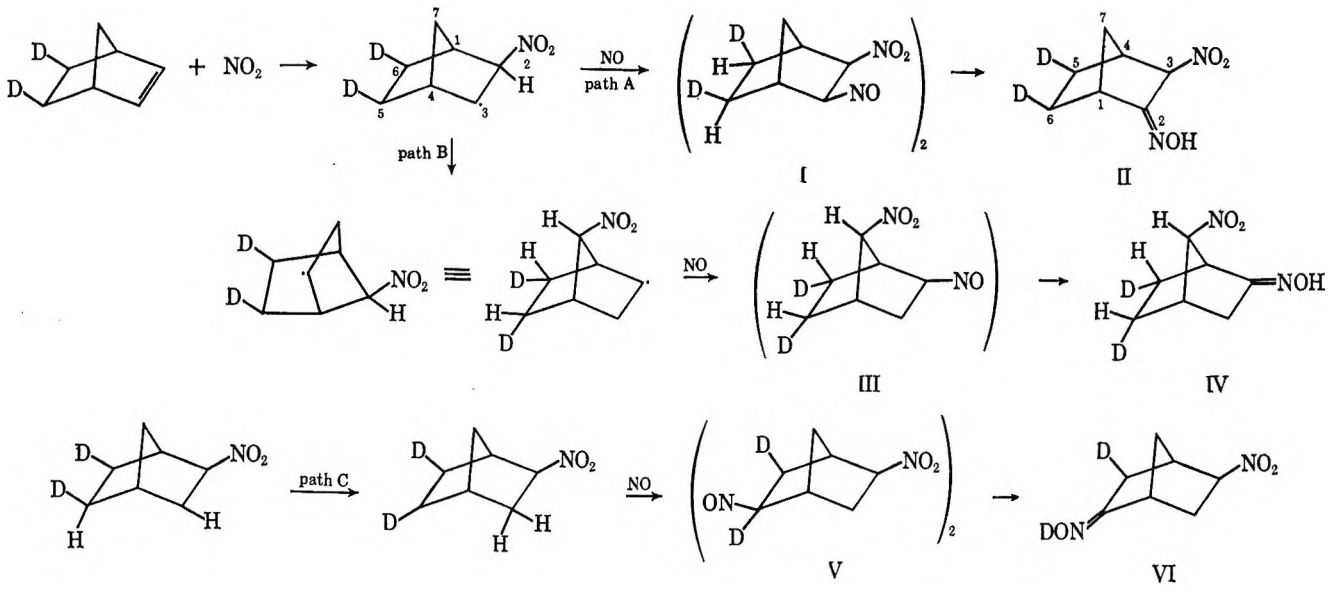
(6) H. Schechter, *Rec. Chem. Progr.*, **25**, 55 (1964).

(7) (a) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **33**, 1288 (1968); (b) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

(8) J. Meinwald, Y. C. Meinwald, and T. N. Baker III, *ibid.*, **86**, 4074 (1964).

(9) C. S. Inglessis, Ph.D. Thesis, Clark University, 1959.

SCHEME I



The crystalline product is separated by filtration, washed with ether, air dried, and recrystallized from methylene chloride–pentane. A 60% yield of white crystals, mp 135°, is obtained.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.42; H, 5.92; N, 16.47; O, 28.21. Found: C, 49.42; H, 6.13; N, 16.21; O, 28.07.

Norbornene Nitroxime.—A solution of norbornene pseudonitrosite in dioxane is refluxed under nitrogen until the green color of the nitroso monomer has completely disappeared (1–2 hr). The dioxane is evaporated leaving crude solid residue. Recrystallization from methylene chloride–pentane affords pure (75% yield) nitroxime, mp 167°.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.42; H, 5.95; N, 16.47; O, 28.21. Found: C, 49.42; H, 5.90; N, 16.14; O, 28.54.

2,3-Diaminonorborane.—Treatment of 17 g (0.1 mol) of norbornene nitroxime in absolute ethanol with 1 g of Raney nickel at 75° and 1500 psi hydrogen for 2–3 days followed by filtration of the catalyst, evaporation of the solvent, and vacuum distillation of the crude oil affords 10 g of colorless, liquid distillate, bp 100–135° (0.2 mm). Gc studies reveal that a mixture of products is present. Treatment of an ethereal solution of the crude diamine with dry hydrogen chloride affords a salt which after recrystallization from ethanol fails to melt below 300°. *Anal.* Calcd for $C_7H_{14}N_2Cl_2$: C, 42.44; H, 8.13; N, 14.15; Cl, 35.79. Found: C, 42.02; H, 8.03; N, 13.87; Cl, 35.83. The nmr spectrum in D_2O reveals absorption patterns of area 6 at δ 1.7, area 2 at 2.7 (bridgehead protons), one-proton signals at 3.3 (quartet) and 3.7 ppm (triplet) as well as exchangeable proton absorption.

The infrared and nmr spectra of the dihydrochloride and retention time of the free diamine on a Carbowax 20M–KOH column at 150° are identical with the substance prepared according to the procedure of Inglessis.[9]

***exo,exo*-5,6-Dideuterionorbornene.**—The deuterated olefin is prepared according to the procedure of Baird, Franzus, and Surridge.[7] Reaction with nitrogen oxides and subsequent conversion into nitroxime are carried out in the manner described above.

Registry No.—Dinitrogen trioxide, 16529-92-3; norbornene, 498-66-8; norbornene pseudonitrosite, 16526-91-3; norbornene nitroxime, 16526-92-4; 2,3-diaminonorbornane dihydrochloride, 16526-93-5.

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Nuclear Magnetic Resonance Chemical Shifts of Cyclopropane HCH in Unsubstituted Bicyclo[*x*.1.0]alkanes as a Function of Ring Size[1]

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In connection with product identifications in another study,[2] we required samples of several bicyclo[*x*.1.0]-alkanes (Figure 1). These compounds were prepared by methyleneation of the appropriate cycloalkene with methylene iodide and zinc–copper couple.[2-4] When we examined the nuclear magnetic resonance (nmr) spectra of these bicycloalkanes, we were impressed with the continuing upfield shift of the signal from one of the cyclopropane CH_2 protons as the size of the larger ring increased from five to ten members (Table I). The signal associated with the proton geminal to the first apparently is shifted downfield by the same change that brings about the upfield shift of the first proton in the cyclopropane CH_2 group. We cannot be certain about the regularity of the shift, however, be-

(1) (a) Presented in part at the Southeast-Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 1965, paper no. 97, and at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstracts, p S125. (b) We gratefully acknowledge partial support of this research by grants from the Petroleum Research Fund administered by the American Chemical Society (Grant No. 1817-A4) and the National Science Foundation (Grant No. GP 5749). (c) Based in part on a portion of the Ph.D. Dissertation of J. S. D., Louisiana State University, 1966. The financial assistance from the Charles E. Coates Memorial Fund, donated by George H. Coates, for preparation of the Ph.D. Dissertation of J. S. D. is gratefully acknowledged.

(2) J. G. Traynham and J. S. Dehn, *J. Amer. Chem. Soc.*, **89**, 2139 (1967).

(3) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).

(4) A commercial mixture of *cis*- and *trans*-cyclododecene was used for the preparation of bicyclo[10.1.0]tridecane. The sample of bicyclotridecane used in this study was shown by gas chromatographic analysis to be approximately 50% *cis*, 50% *trans*; only one of the isomers (presumably *cis*) gave the upfield nmr signal reported.

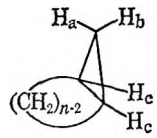

Figure 1.—*cis*-Bicyclo[*x*.1.0]alkanes: n = 5–12; x = 3–10.

cause the signal for the downfield proton in that geminal pair is obscured by the strong signals for other protons in several of the bicycloalkanes.

TABLE I

CHEMICAL SHIFTS OF CYCLOPROPANE CH_2 PROTONS IN *cis*-BICYCLO[*x*.1.0]ALKANES

Bicycloalkane	Registry no.	Chemical shift,[a] H_a	Chemical shift,[a] H_b
[2.1.0][b]		−0.4	−0.7
[3.1.0][b]		−0.02	−0.21
[4.1.0][c]		0.04	−0.47
[5.1.0]	16526-90-2	−0.02	(−0.7)
[6.1.0]	13757-43-2	0.30	(−0.4)
[7.1.0]	13758-98-0	0.42	(−0.4)
[8.1.0][d]	13757-44-3	0.48	−0.51
[10.1.0][e]		0.35	(−0.4)

[a] Center of signal, in parts per million, relative to internal tetramethylsilane; minus sign indicates downfield and parentheses indicate maximum upfield position. [b] Reference 12. [c] This compound also described by D. L. Muck and E. R. Wilson, *J. Org. Chem.*, **33**, 419 (1968). [d] The nmr spectrum of *trans*-bicyclo[8.1.0]undecane includes signals at −0.25 (cyclopropane CH_2, 2H) and −0.45 ppm (bridgehead H, 2). [e] See Reference 4.

Although there was uncertainty a few years ago about the relative magnitude of *cis* and *trans* vicinal coupling constants in cyclopropane derivatives,[5] the order $J_{cis} > J_{trans}$ seems to be firmly established and unchallenged now.[6] When both J_{ac} and J_{bc} can be discerned from the nmr spectrum, the assignment of the most upfield signal can be made with confidence.[7] When the signal for either H_a or H_b is completely obscured by the strong signals for other protons in the bicyclic hydrocarbon, however, the assignment is less clear. There has been disagreement on the shielding effects of alkyl groups on vicinal protons in cyclopropane derivatives,[6c,d,8] and the possibility of transannular end-on interactions (deshielding)[6d,9] in the medium-ring derivatives described here adds difficulty to the assignment. Whereas we were persuaded initially that the most upfield signal is associated with H_a rather than with H_b,[1c] the different viewpoints recorded in the literature since that time led us to confirm our first assignment with nuclear Overhauser effect (NOE) data.[10] Low intensity irradiation of a $DCCl_3$ solution of bicyclo[3.1.0]hexane at a frequency corresponding to the absorbance of the larger ring protons proximal to H_a but not spin–spin coupled to it led to the NOE. The shapes of the nmr signals due to H_a and H_b were essentially unchanged, but the integrated intensity of the (more upfield) H_a signal increased significantly (23%). Irradiation at other frequencies, both upfield and downfield, failed to produce the NOE. This result clearly identifies the more upfield signal with H_a. Likewise, similar irradiation produced a similar increase (25%) in the integrated intensity of the most upfield signal in the spectrum of bicyclo[8.1.0]undecane, again identifying that signal with H_a rather than H_b.

The upfield position of nmr signals for cyclopropane hydrogens (relative to other methylene hydrogens) is, of course, well known, but few chemical shifts of cyclopropane hydrogens as far upfield as some included in Table I have been reported before. The shielding of H_a reaches a maximum with the ten-membered ring, and in that system the chemical shift of H_a is nearly the same as that of the *syn* proton, shielded by the aromatic ring current, in homotropylium cation (0.6 ppm,)[11] and higher than that of the *syn* protons in unsaturated systems such as bicyclo[3.1.0]hex-2-ene,[12] bicyclo[2.1.0]-but-2-ene,[12] and bicyclo[6.1.0]nona-2,4,6-triene.[13] The signal from *cis*-bicyclo[10.1.0]tridecane is not so far upfield as that from *cis*-bicyclo[8.1.0]undecane. This result is reminiscent of other manifestations of medium ring effects.[14] Identification of the upfield signal with H_a for both common and medium ring derivatives, however, indicates that transannular, end-on interactions (which are presumably responsible for many medium ring effects[14b]) are insufficient in these bicycloalkanes to alter the relative positions of the H_a and H_b signals. The differences in shielding of H_a must be associated with a continuous change in C–C bond anisotropy effects rather than with a change in kind of interactions among these compounds. Models do not reveal any striking differences among these bicycloalkanes in proximity of H_a and the flanking methylenes, certainly not enough to provide a ready explanation of the upfield shift of the H_a signal as a function of ring size. Apparently the anisotropy effects in these saturated hydrocarbons are surprisingly sensitive to small changes in geometry.

Experimental Section

Nmr data were obtained with Varian Associates HA-60, A-60A and HA-100 instruments, with the assistance of Mr. W. Wegner. All chemical shift data are relative to internal tetramethylsilane reference and are for benzene or chloroform-*d* solutions. NOE data were obtained by a frequency sweep method with the HA-100 instrument and 40 mV irradiation; benzene was used as a reference line for field-frequency lock.[10a]

Most of the bicycloalkanes used have been described previously.[15] *trans*-Bicyclo[8.1.0]undecane was prepared in 80% yield by methyleneation[3] of *trans*-cyclodecene;[16] it distilled at

(5) (a) G. L. Closs and L. E. Closs, *ibid.*, **82**, 5723 (1960); (b) U. Schöllkopf and G. J. Lehmann, *Tetrahedron Lett.*, 165 (1962).

(6) (a) G. L. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc.*, **84**, 4985 (1962); (b) U. Schöllkopf, A. Lerch, and J. Paust, *Chem. Ber.*, **96**, 2266 (1963); (c) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); (d) W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967).

(7) On the basis of all data presently available on J_{vic} for 7-H of 7-substituted norcaranes, the more upfield signal is invariably associated with the *syn* proton (H_a in Figure 1). See also ref 6d.

(8) (a) D. E. Minnikin, *Chem. Ind.* (London), 2167 (1966); (b) D. T. Longone and A. H. Miller, *Chem. Commun.*, 447 (1967); (c) T. Ando, F. Namigata, H. Yamanake, and W. Funasaka, *J. Amer. Chem. Soc.*, **89**, 5719 (1967).

(9) (a) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *ibid.*, **87**, 5247 (1965); (b) M. A. Battiste and M. E. Brennan, *Tetrahedron Lett.*, 5857 (1966).

(10) (a) F. A. L. Anet and A. J. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965); (b) J. G. Colson, P. T. Lansbury, and F. D. Saeva, *ibid.*, **89**, 4987 (1967); (c) M. C. Woods, H. C. Chiang, Y. Nakadaira, and K. Nakanishi, *ibid.*, **90**, 522 (1968).

(11) C. E. Keller and R. Pettit, *ibid.*, **88**, 606 (1966).

(12) J. I. Brauman, L. E. Ellis, and E. E. van Tamelen, *ibid.*, **88**, 846 (1966).

(13) T. J. Katz and P. J. Garratt, *ibid.*, **86**, 5194 (1964).

(14) (a) V. Prelog, *J. Chem. Soc.*, **420** (1950); (b) J. Sicher in "Progress in Stereochemistry," Vol. 3, P. B. D. de la Mare and W. Klyne, Ed., Butterworth and Co. Ltd., London, 1962, Chapter 6.

(15) Reference 2 and references cited there.

(16) J. G. Traynham, D. B. Stone, and J. L. Couvillion, *J. Org. Chem.*, **32**, 510 (1967).

76–78° (5 mm) and its nmr spectrum included signals at −0.25 (cyclopropane CH_2, 2 H) and at −0.45 ppm (bridgehead H, 2 H).

Anal.[17] Calcd for $C_{11}H_{20}$: C, 86.8; H, 13.2. Found: C, 86.4; H, 13.1.

Registry No.—*trans*-Bicyclo[8.1.0]undecane, 15840-80-9.

(17) By R. Seab in these laboratories.

N^6,3′-O-Disubstituted Deoxyadenosine[1]

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Deoxyadenosine derivatives possessing alkali or hydrazine labile protecting groups at the N^6 and 3′-O positions are attractive intermediates for use in synthesizing oligonucleotides by the phosphotriester method.[1,2] A route to such compounds is to block the reactive 5′ oxygen of N^6-acyl- or benzoyldeoxyadenosine, introduce the desired substituent on the 3′ oxygen, and then remove selectively the protecting group on the 5′ oxygen. Since N^6-benzoyldeoxyadenosine derivatives readily undergo depurination in acidic media,[3,4] the protecting group on the 5′-oxygen atom should be one that can be removed without resort to acidic conditions. At the same time, strong alkaline conditions for removal of this group are precluded if an acyl group is to be retained on the 3′ oxygen.

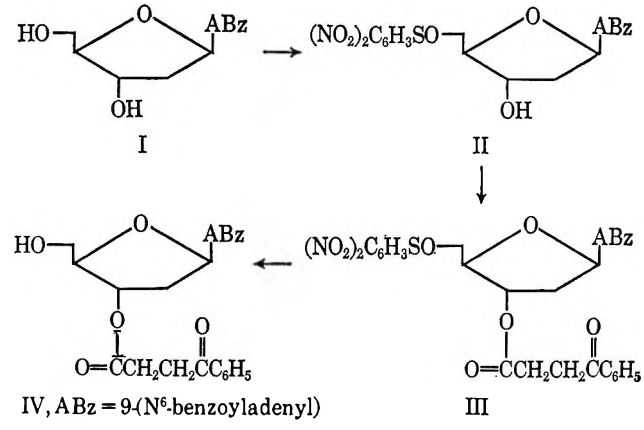
The 2,4-dinitrobenzenesulfenyl group, which protects oxygen of hydroxyl groups during acylation reactions and can be removed readily by the action of thiophenol in pyridine,[5] appeared to have the requisite properties for protecting the 5′-oxygen of deoxyadenosine derivatives. As a test of this approach we explored the synthesis of 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine *via* 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine.

Preliminary experiments were conducted with thymidine to see if the 5′ oxygen of a nucleoside with free 3′- and 5′-hydroxyl groups could be preferentially sulfenylated. At room temperature the degree of selectivity was low. However, when the reaction was carried out with slightly less than 1 equiv of 2,4-dinitrobenzenesulfenyl chloride at 0°, a 37% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)thymidine was obtained along with small amounts of the 3′-O-dinitrobenzenesulfenyl isomer (10%) and a higher sulfenylated product (~8%). The 3′ isomer has been prepared previously from 5′-O-tritylthymidine.[5]

N^6-Benzoyldeoxyadenosine underwent reaction with 2,4-dinitrobenzenesulfenyl chloride considerably more slowly than did thymidine. A suitable method for formation of the 5′-oxygen derivative was found to be treatment of N^6-benzoyldeoxyadenosine with 1.5 equiv of 2,4-dinitrobenzenesulfenyl chloride in pyridine at 20° for 1.5 hr. Under these conditions a 45% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine, a 12% yield of the corresponding 3′-O isomer, and a 13% yield of a disulfenylated derivative were obtained.

A flowsheet depicting the formation of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine (II), introduction of a β-benzoylpropionyl group at the 3′ oxygen to give III, and cleavage of the dinitrobenzenesulfenyl group to yield 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine (IV) is shown in Chart I.

CHART I



Compound III was obtained in 54% yield by reaction of II with excess β-benzoylpropionic acid and dicyclohexylcarbodiimide. The dinitrobenzenesulfenyl group could be cleaved from the 5′ oxygen cleanly with thiophenol in pyridine, as in the case of the thymidine derivatives.[5] We used hydrogen sulfide in pyridine in the preparative experiment for this purpose, however, since it was found that hydrogen sulfide effects the cleavage and the reaction mixture can be worked up more conveniently than one containing excess thiophenol.

In the case of the mono(dinitrobenzenesulfenyl) derivatives of thymidine the assignment of structure is clear as the higher melting isomer is known from independent synthesis[5] to be the 3′-oxygen derivative. Two lines of evidence point to the fact that the lower melting isomer of mono(dinitrobenzenesulfenyl)-N^6-deoxyadenosine is the 5′-oxygen derivative: (1) The lower melting isomer was obtained in preponderate amount, in accord with the observation that the 5′-oxygen of nucleoside derivatives is in general attacked more readily than the 3′-oxygen. (2) The R_f value of the lower melting isomer (in ethyl acetate on silica slides) is less than that for the higher melting isomer, in agreement with the observation that the R_f values for 5′-oxygen derivatives of nucleosides are less than the R_f values of the corresponding 3′-oxygen derivatives (*e.g.*, for the 2,4-dinitrobenzenesulfenyl, the *p*-monomethoxytrityl, and the isobutyloxycarbonyl derivatives[6] of thymidine). Proof that the β-benzoylpropionyl group in IV is joined at the 3′-oxygen, and therefore that the 2,4-dinitroben-

(1) Part XI in series on Nucleotide Chemistry. Part X: R. L. Letsinger, M. H. Caruthers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146 (1967). This research was supported by the Division of General Medical Sciences, National Institutes of Health (GM-10265).

(2) R. L. Letsinger and K. K. Ogilvie, *ibid.*, **89**, 4801 (1967).

(3) H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *ibid.*, **85**, 3821 (1963).

(4) W. Moon, S. Nishimura, and H. G Khorana, *Biochemistry*, **5**, 937 (1966).

(5) R. L. Letsinger, J. Fontaine, V. Mahadevan, D A. Schexnayder, and R. E. Leone, *J. Org. Chem.*, **29**, 2615 (1964).

(6) K. K. Ogilvie and R. L. Letsinger, *ibid.*, **32**, 2365 (1967).

zenesulfenyl group in II is joined at the 5′-oxygen, is provided by the synthesis of thymidylyl-(3′–5′)-deoxyadenosine from compound IV and 5′-O-monomethoxytritylthymidine.[7] This compound was completely hydrolyzed by snake venom phosphodiesterase, an enzyme specific for oligonucleotides possessing a terminal 3′-hydroxyl group and 3′–5′ phospho diester links.

Experimental Section

Infrared spectra were determined in potassium bromide with a Baird recording spectrophotometer. Thin layer chromatography was performed on Eastman Chromagram sheets, 6060 silica gel, with ethyl acetate; R_f values are indicated in text. Elemental analyses were made by the Micro-Tech Laboratories, Skokie, Ill.

5′-O-(2,4-Dinitrobenzenesulfenyl)thymidine.—Thymidine (2.00 g, 8.28 mmol) was dissolved in 150 ml of anhydrous pyridine and cooled to 0°. 2,4-Dinitrobenzenesulfenyl chloride (1.94 g, 7.62 mmol) in 50 ml of anhydrous pyridine was added dropwise over a period of 1 hr with stirring; then, after the mixture had stood for 4 hr at 0°, it was allowed to warm to room temperature. The mixture was diluted with 1 l. of ice–water and extracted three times with $CHCl_3$. The organic layer was washed twice with water, dried with Na_2SO_4, and concentrated. The residue was taken up in warm methanol and the solution was filtered while hot. Methanol was then distilled off and the residue was dissolved in ethyl acetate and chromatographed on silica gel (12 × 50 cm) using ethyl acetate as an eluent. The first fraction yielded 0.19 g of a yellow solid, mp 122–128°, R_f 0.85, which is probably 3′,5′-bis-O-(2,4-dinitrobenzenesulfenyl)thymidine. The second fraction contained 0.35 g (10%) of 3′-O-(2,4-dinitrobenzenesulfenyl)thymidine,[5] mp 182–184° dec, R_f 0.62. Finally, elution with 50% ethyl acetate–acetone yielded 5′-O-(2,4-dinitrobenzenesulfenyl)thymidine, isolated by stripping off the solvent, dissolving the residue in ethyl acetate, and precipitation by addition of hexane: weight 1.25 g (37%); mp 102–110°; R_f 0.43; prominent infrared bands at 2.90, 5.95, 6.28, 6.60, 7.47, and 12.08 μ. The spectrum was very close to that of the 3′-O isomer, differing primarily by absence of a shoulder at 9.0 μ.

Anal. Calcd for $C_{16}H_{16}N_4O_9S$: C, 43.64; H, 3.66; N, 12.72; S, 7.28. Found: C, 43.65; H, 3.93; N, 11.78; S, 7.06.

5′-O-(2,4-Dinitrobenzenesulfenyl)-3′-O-(β-benzyoylpropionyl)-N⁶-benzoyldeoxyadenosine (III).—To 0.366 g (1.03 mmol) of dry N⁶-benzoyldeoxyadenosine in 10 ml of pyridine at 20° was added 0.350 g (1.49 mmol) of 2,4-dinitrobenzenesulfenyl chloride in 5 ml of pyridine. After 1.5 hr the mixture was poured over 300 g of ice and allowed to stand 1 hr. The insoluble material was extracted into chloroform which, after drying over Na_2SO_4, was stripped *in vacuo*. Ethanol was added and stripped to remove traces of pyridine, and the gummy residue was dissolved in hot $CHCl_3$. Column chromatography on silica gel with ethyl acetate yielded on concentration and precipitation with hexane 0.097 g of a yellow solid, mp 115–125°, R_f 0.85, which is probably the bis-2,4-dinitrobenzenesulfenyl derivative. From the second chromatographic fraction was obtained 0.066 g (12%) of 3′-O-(2,4-dinitrobenzenesulfenyl)-N⁶-benzoyldeoxyadenosine: mp 151–153°; R_f 0.66; prominent infrared bands at 2.93, 5.82, 6.24, 6.55, 7.44, and 11.96 μ.

Anal. Calcd for $C_{23}H_{19}N_7O_8S$: C, 49.90; H, 3.46; N, 17.72; S, 5.79. Found: C, 49.64; H, 3.80; N, 17.58; S, 5.61.

Continued elution of the column yielded 0.253 g (45%) of II: mp 115–125°; R_f 0.32; prominent infrared bands at 2.95, 5.84, 6.24, 6.55, 7.44, and 11.97 μ. A mixture of 0.244 g (0.44 mmol) of compound II, 0.451 g (2.53 mmol) of β-benzoylpropionic acid, and 0.6 g (3 mmol) of dicyclohexylcarbodiimide in 2 ml of pyridine was stirred for 2 hr at room temperature, diluted with 1 ml of water, and stirred an additional hour. The insoluble dicyclohexylurea was filtered off and washed with $CHCl_3$ (50 ml) and the combined filtrate and $CHCl_3$ washings were washed with saturated $NaHCO_3$. After drying over Na_2SO_4 the solution was stripped in a rotatory evaporator, diluted with ethanol, and stripped again to a gummy residue. This material was dissolved in hot ethyl acetate and, after standing overnight, was filtered to remove the crystalline acylurea. On chromatography on a silica gel column with ethyl acetate the filtrate yielded compound III: mp 94–96°; weight 0.170 g (54% from II); R_f 0.67; prominent infrared bands at 2.98, 3.48, 5.78 (s), 5.93, 6.27, 6.60, 7.48, and 12.00 μ (w).

Anal. Calcd for $C_{33}H_{27}N_7O_{10}S$: C, 55.53; H, 3.81; N, 13.74; S, 4.49. Found: C, 55.59; H, 4.12; N, 13.63; S, 4.41.

3′-O-(β-Benzoylpropionyl)-N⁶-benzoyldeoxyadenosine (IV).—The preparation of compound III was repeated on a fourfold scale to the point where the products were dissolved in ethyl acetate and separated by chromatography. In this case, in place of the chromatographic separation, the gummy products were dissolved in pyridine and H_2S was slowly bubbled through the solution for 16 hr. Following the usual work-up procedure (stripping of the solvent, addition of ethanol, stripping of the ethanol, etc.) the solid products were chromatographed on silica gel with ethyl acetate–methanol (90/10). Compound IV was recovered by concentrating the appropriate fraction and was recrystallized from ethyl acetate: mp 111–112.5°; weight 0.532 g (57%); R_f 0.57; prominent infrared bands at 2.96, 5.76, 5.93, 6.24, 6.87, and 8.63 μ. That the 2,4-dinitrobenzenesulfenyl group was absent was shown by absence of bands at ~6.6 and 7.4 (nitro groups) and 12.0 μ (characteristic for 2,4-dinitrobenzenesulfenyl derivatives).

Anal. Calcd for $C_{27}H_{25}N_5O_6$: C, 62.90; H, 4.89; N, 13.59. Found: C, 62.96; H, 4.99; N, 13.52.

Registry No.—5′-O-(2,4-Dinitrobenzenesulfenyl)thymidine, 16243-75-7; 3′-O-(2,4-dinitrobenzenesulfenyl)-N⁶-benzoyldeoxyadenosine, 16243-76-8; III, 16281-89-3; IV, 16243-74-6.

(7) Experiments of K. K. Ogilvie, Northwestern University, Evanston, Ill.

Reactions of Phosphorus Compounds. XVI. The Reaction of Several Hydroxyphosphonium Ylides

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The preparation of 2,3-dihydro-1-benzoxepin may be readily accomplished by treating 3(O-formylphenoxy)-propyltriphenylphosphonium bromide (I) in a non-protonic solvent under basic conditions.[1] As an extension to this work, and due to the recent interest in the oxepin ring system,[2-7] we have first examined the feasibility of preparing 1-phenoxy-4-phenylbutadiene (VI) from 2-hydroxy-3-phenoxypropyltriphenylphosphonium bromide (III) and benzaldehyde. Finding this first reaction successful, we turned to the corresponding reaction of 2-hydroxy-3(2-formylphenoxy)propyltriphenylphosphonium bromide (XII) which we hoped would give 1-benzoxepin (XVII).

The salt III was allowed to react with base to form the ylide IV, and addition of benzaldehyde followed (Scheme I). The expected products of this reaction

(1) (a) E. E. Schweizer and R. Schepers, *Tetrahedron Lett.*, **15**, 979 (1963); (b) E. E. Schweizer, C. J. Berninger, D. M. Crouse, R. A. Davis, and R. Schepers, *Logothetis*, in press.

(2) (a) A. Shani and F. Sondheimer, *J. Amer. Chem. Soc.*, **89**, 6310 (1967); (b) F. Sondheimer and A. Shani, *ibid.*, **86**, 3168 (1964).

(3) E. Vogel, M. Biskup, W. Pretzer, and W. A. Boll, *Angew. Chem. Intern. Ed. Engl.*, **3**, 642 (1964).

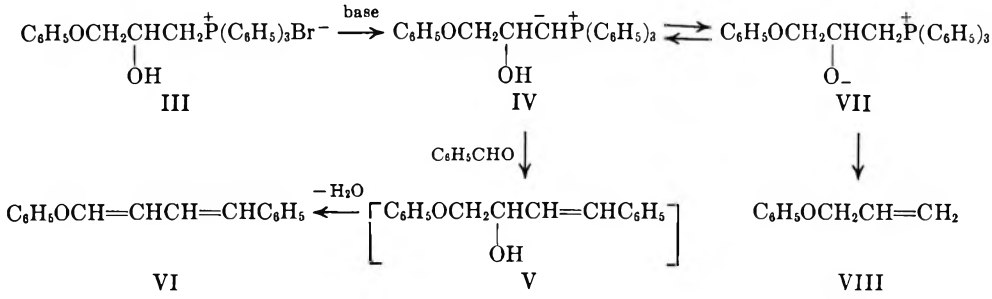
(4) H. Hoffman, *ibid.*, **4**, 872 (1965).

(5) E. Vogel, R. Schubart, and W. A. Boll, *ibid.*, **3**, 510 (1964).

(6) E. O. Fischer, C. G. Kreiter, H. Ruhle, and K. E. Schwarzhans, *Ber.*, **100**, 1905 (1967).

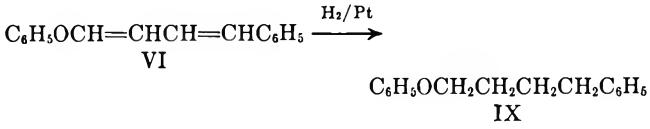
(7) E. Vogel, W. A. Boll, and H. Gunther, *Tetrahedron Lett.*, **10**, 609, (1965).

SCHEME I

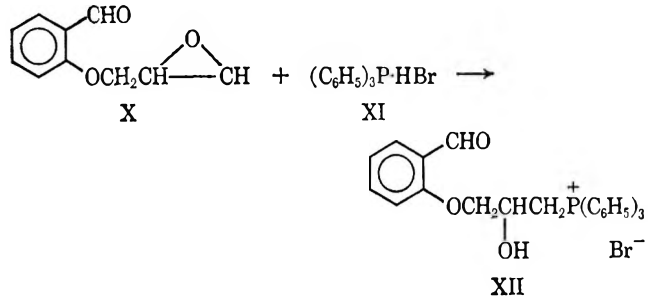


are 1-phenyl-3-hydroxy-4-phenoxy-1-butene (V) and allyl phenyl ether (VIII); however, it was found that under the reaction conditions employed most of V underwent dehydration to give 1-phenoxy-4-phenylbutadiene (VI). This reaction was carried out in two ways. If the base–solvent system used was ethoxide–ethanol, the yield of the butadiene VI was only 8.1%. If the base–solvent system used was *n*-butyllithium–benzene, the yield of the butadiene was increased to 25.5%. The major product of the reaction was allyl phenyl ether (VIII).

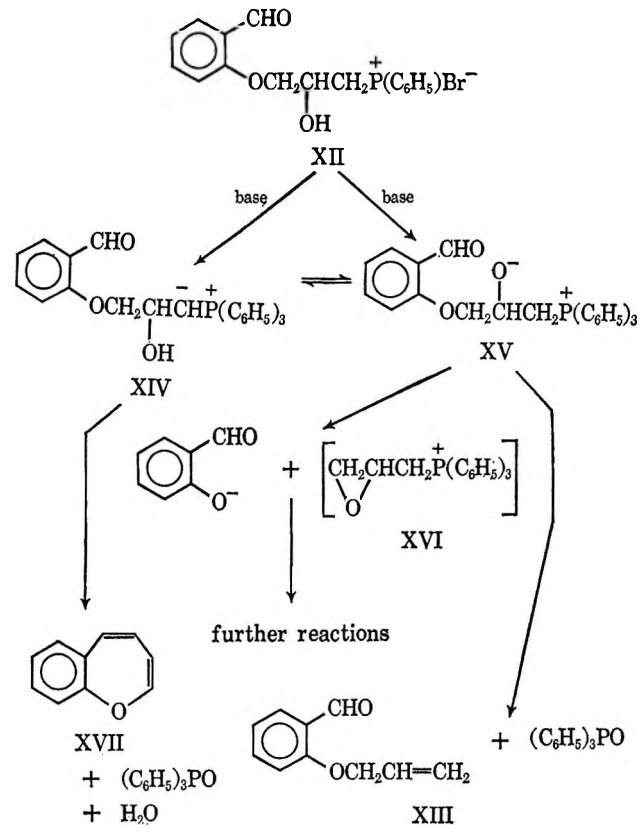
The butadiene VI was identified by its nmr and infrared spectra and by hydrogenation to 1-phenoxy-4-phenylbutane (IX) which was shown to be identical with an authentic sample.[8] Before the hydrogenation could be carried out, it was necessary to remove traces of codistilled triphenylphosphine which poisoned the



catalyst, by precipitating it as methyltriphenyl phosphonium iodide using methyl iodide in ether.



In order to prepare 1-benzoxepin (II) by an intramolecular Wittig reaction, the phosphonium salt (XII) was needed and was readily obtained by the reaction of 1,2-epoxy-3-(2-formylphenoxy)propane[9] (X) and triphenylphosphine hydrobromide (XI). The base–solvent system used to prepare the desired ylide from this salt was restricted to ethoxide–ethanol, since alkyllithium compounds would also react with the carbonyl moiety. When this reaction was carried out, 1-benzoxepin (XVII) was obtained in 5% yield. The oxepin XVII was identified on the basis of the nmr and ir spectra, which were identical with those in the literature.[2,3] The major by-products identified were *o*-allyloxybenzaldehyde (XIII) and salicylaldehyde. The reaction of ethoxide with the salt XII may be expected to initially produce either the ylide or the betaine XV. Intramolecular Wittig reaction of the ylide XIV followed by dehydration would yield 1-benzoxepine (XVII) and triphenylphosphine oxide. If the other intermediate XV were formed, decomposition of the betaine XV would give rise to *o*-allyloxybenzaldehyde (XIII); salicylaldehyde may be obtained by elimination, resulting in the salt XVI, which could undergo further reaction. The reactions of salts of type XVI have been studied by Bohlmann and Herbst.[10]



As to the possibility of interconversion between ylide XIV and betaine XV, the conversion of XV into XIV must be slower than the reactions just discussed, since we have found that reaction of 1,2-epoxy-3-(2-formylphenoxy)propane (X) with triphenylphosphine, which should proceed by way of XV, gave mainly *o*-allyloxybenzaldehyde (XIII) and absolutely no 1-benzoxepin XVII. The conversion of XIV into XV cannot be excluded, however.

(8) L. A. Walter and S. M. McElvain, *J. Amer. Chem. Soc.*, **56**, 1614 (1934).

(9) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).

(10) F. Bohlmann and P. Herbst, *Ber.*, **92**, 1319 (1959).

Experimental Section[11]

Preparation of (2-Hydroxy-3-phenoxy)propyltriphenylphosphonium Bromide (III).—In a dry 50-ml, two-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet, and a reflux condenser with drying tube was placed 20 ml of anhydrous ethanol, 1.0 g (0.039 mol) of triphenylphosphine,[12] and 9.86 g (0.04 mol) of 2-hydroxy-3-bromo-1-phenoxypropane.[13] The reaction mixture was stirred and refluxed for 40 hr in a slow current of dry nitrogen. The resulting colorless oil was poured slowly into 150 ml of anhydrous ether, the solution being shaken after each addition. If the salt did not crystallize immediately, the ether was poured off and the remaining oil was let to stand in open air. The white crystals were filtered and washed twice with fresh anhydrous ether, then boiled for several minutes in anhydrous benzene and filtered while hot in order to remove any unreacted starting materials. After washing twice more with hot benzene, the salt was dried under vacuum at 100° for 48 hr. The product (15 g) was obtained with mp 207–209° (80% yield). The nmr spectrum ($DCCl_3$) showed bands at τ 6.2 (m, 2), 5.7 (m, 2), and 4.5 ppm (m, 1).

Anal. Calcd for $C_{27}H_{26}O_2BrP$: C, 67.72; H, 5.31. Found: C, 65.79; H, 5.53.

1-Phenoxy-4-phenylbutadiene (VI).—A dry 3 l., three-necked, round-bottomed flask was provided with a mercury-sealed stirrer, a reflux condenser with drying tube, a nitrogen inlet, and a Gooch tubing connected to an erlenmeyer flask. A gentle flow of dry nitrogen was maintained throughout the reaction. Anhydrous thiophene-free benzene (2300 ml) and 20.4 g (0.21 mol) of *n*-butyllithium were added to the flask. The solution was stirred and refluxed, and 104.6 g (0.21 mol) of (2-hydroxy-3-phenoxy)propyltriphenylphosphonium bromide (III) was added cautiously through the Gooch tubing as fast as possible. If the salt was added too rapidly, the evolution of butane caused excessive frothing of the solution. During the first additions of the salt, the reaction mixture became yellow and at the end it had changed to dark red. The reaction mixture was refluxed and stirred for several minutes after the salt addition was completed. The Gooch tubing was replaced by a dropping funnel and 22.26 g (0.21 mol) of freshly distilled benzaldehyde were added dropwise. After the addition of the benzaldehyde, the original color changed to light reddish brown. The reaction mixture was refluxed and stirred for 24 hr, allowed to cool to room temperature and then filtered. The solvent was evaporated and the remaining dark red liquid was distilled at reduced pressure. The first fraction obtained, weighing 8.3 g, had bp 50–89° (0.6 mm) and was composed of mostly benzene, phenol (37.7%), allyl phenyl ether (16%), and an unidentified alcohol, as determined by vpc. The second fraction, weighing 23 g, had bp 89–185° (0.6 mm). This fraction contained the diene VI and triphenylphosphine. The solution was seeded and cooled and the phosphine was removed by filtration. After recrystallization from ethanol, 4.2 g (7.6%) of triphenylphosphine was obtained and identified by a mixture melting point with an authentic sample. The filtrate was distilled under reduced pressure giving the butadiene VI, bp 120–122° (0.08 mm), which weighed 12.2 g or 25.5% of the theoretical amount. The nmr spectrum (CCl_4) showed bands at τ 2.9 (m, 10), 4.1 ppm (m, 4). The infrared spectrum was consistent with the structure assigned.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.34. Found: C, 86.33; H, 6.53.

Hydrogenation of 1-Phenoxy-4-phenylbutadiene (VI).—Several attempts were made to hydrogenate the diene VI, but they failed owing to catalyst poisoning by the presence of trace amounts of codistilled triphenylphosphine. All fractions containing the diene were combined and diluted with anhydrous ether, and 10 ml of methyl iodide was then added slowly with stirring. The triphenylphosphine came out of solution as triphenylmethylphosphonium iodide, which was identified by mixture melting point. After cooling, the salt was removed by filtration and the ether was removed by distillation. The residue was vacuum distilled yielding the diene VI, bp 114–120° (0.07 mm). The fraction boiling from 117 to 120° (0.70 g) was hydrogenated using Adams catalyst (PtO_2) with anhydrous ethanol as a solvent. An essentially quantitative uptake of 2 mol of hydrogen per mole of compound was obtained. The solution was filtered and the ethanol was evaporated. The remaining liquid was distilled at reduced pressure yielding 0.38 g of pure 1-phenoxy-4-phenylbutane: bp 113° (0.1 mm); $n^{24}D$ 1.5506 (lit.[8] bp 144–146° (1 mm); $n^{24}D$ 1.5504).

1,2-Epoxy-3(2-formylphenoxy)propane (X).—The sodium salt of salicylaldehyde 28.8 g (0.2 mol) and 300 ml of freshly distilled epichlorohydrin were allowed to react at 118° for 24 hr. After filtering the mixture, the epichlorohydrin was removed by distillation under vacuum until the temperature rose to 60° (1 mm). The residue was short-path distilled giving 31 g of the epoxide X, bp 118–120° (0.25 mm) (lit.[14] bp 118° (0.5 mm)) which was shown to be 93% pure by vpc for an 80% yield. The nmr spectrum (neat) showed signals at δ 2.5 (m, 2), 3.1 (m, 1), 4.1 (m, 2), 6.8–7.8 (m, 4, aromatic), and 10.3 ppm (S, 1, CHO).

2-Hydroxy-3(2-formylphenoxy)propyltriphenylphosphonium Bromide (XII).—Triphenylphosphine hydrobromide[15] (XI) 34.5 g (0.1 mol) and 20 g (0.1 mol) of 1,2-epoxy-3(2-formylphenoxy)propane (X) were thoroughly mixed in a beaker and allowed to stand overnight. The gummy viscous mixture was dissolved in a minimum amount of chloroform and slowly dropped into anhydrous ether (2 l.) with vigorous stirring. A white salt precipitated. Dissolving and reprecipitation gave 42 g (80%) of the salt XII, mp 198–203°. Recrystallization from acetonitrile gave an analytically pure sample, mp 214°.

Anal. Calcd for $C_{28}H_{26}BrO_3P$: C, 64.50; H, 5.03; Br, 15.33; P, 5.94. Found: C, 64.34; H, 4.89; Br, 15.19; P, 6.01.

The nmr spectrum ($CDCl_3$) showed signals at δ 10.3 (s, 1, CHO), 4.5 (s, 1, OH), 4.6 (m, 5), and 7.0–8.0 ppm (m, 19, aromatic). The ir spectrum showed absorptions at ν^{KBr} 3100, 2700, 1670, 1430, 1380, 1235, 1160, 1100, and 940 cm^{-1}.

Preparation of 1-Benzoxepin (XVII).—Into a 500-ml, two-necked flask fitted with a condenser and a calcium chloride tube was distilled directly 300 ml of absolute alcohol, prepared by the pthalate method.[16] In this was dissolved 0.7 g of sodium metal (0.031 g-atom). When the reaction was complete, 16.5 g of the salt XII (0.032 mol) was added at once. The solution was stirred and refluxed for 9 hr. The mixture was then cooled and filtered in order to remove the precipitated sodium bromide. The ethanol was removed by distillation, and some white crystals were separated. These were removed by filtration and were shown to be triphenylphosphine oxide by comparison with an authentic sample. The remaining liquid was short path distilled under vacuum yielding 2.70 g, shown by glpc analysis to be 25% 1-benzoxepin (XVII) and 72% *o*-allyloxybenzaldehyde (XVIII). Collection of the two major products and analysis by nmr spectroscopy showed one to be 1-benzoxepin (**XVII**) (5% yield as calculated from the vpc analysis), and the other was *o*-allyloxybenzaldehyde (XIII) (40% yield). The nmr spectrum (CCl_4) of the oxepin showed signals at τ 2.50–3.2 (m, 4, benzenoid), 3.37 (d, 1), 3.79 (m, 1), 4.03 (m, 1), and 4.60 ppm (m, 1). The product XIII was identified by ir and vpc comparison (DEGS, 170°) with an authentic sample.

Reaction of 1,2-Epoxy-3-(2-formylphenoxy)propane with Triphenylphosphine.—To a solution of 5.3 g of the epoxide (XIII, 0.0296 mol) in 50 ml of dry dimethylformamide in a 100-ml flask was added 7.8 g (0.0298 mol) of triphenylphosphine. The flask was fitted with a reflux condenser and a drying tube and was placed in a silicone oil bath at 110° for 13 hr. After this time the mixture was poured into 150 ml of water, and the aqueous mixture was extracted with five 50-ml portions of ether. The combined ether layers were extracted with two 25-ml portions of water. The ether was dried over magnesium sulfate and distilled. Vacuum distillation of the residue gave 3.0 g of a material, bp 80–120° (1 mm). Vpc analysis of the mixture (20% DEGS, 170°) showed that 86% of the product was *o*-allyloxybenzaldehyde (XIII), by comparison with an authentic sample, with no 1-benzoxepin being formed. Yield of the compound XIII was 2.58 g (54%).

(11) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A60-A spectrometer with a tetramethylsilane standard. Microanalyses were done by Micro Analysis, Inc., Wilmington, Del.

(12) Obtained from Metal and Thermit Co., Rahway, N. J.

(13) Prepared according to P. Pfeiffer and K. Bauer, *Ber.*, **80**, 7 (1947).

(14) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).

(15) M. Akkar and F. Jellinck, *Rec. Trav. Chim. Pays-Bas*, **86**, 275 (1967).

(16) R. Adams and J. Johnson, "Laboratory Experiments in Organic Chemistry," The MacMillan Co., New York, N. Y., 4th ed, 1949, p 409.

Registry No.—III, 16315-61-0; VI, 16315-62-1; X, 16315-63-2; XII, 16315-64-3; XVII, 264-73-3.

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The Synthesis of (±)-Geosmin and the Other 1,10-Dimethyl-9-decalol Isomers

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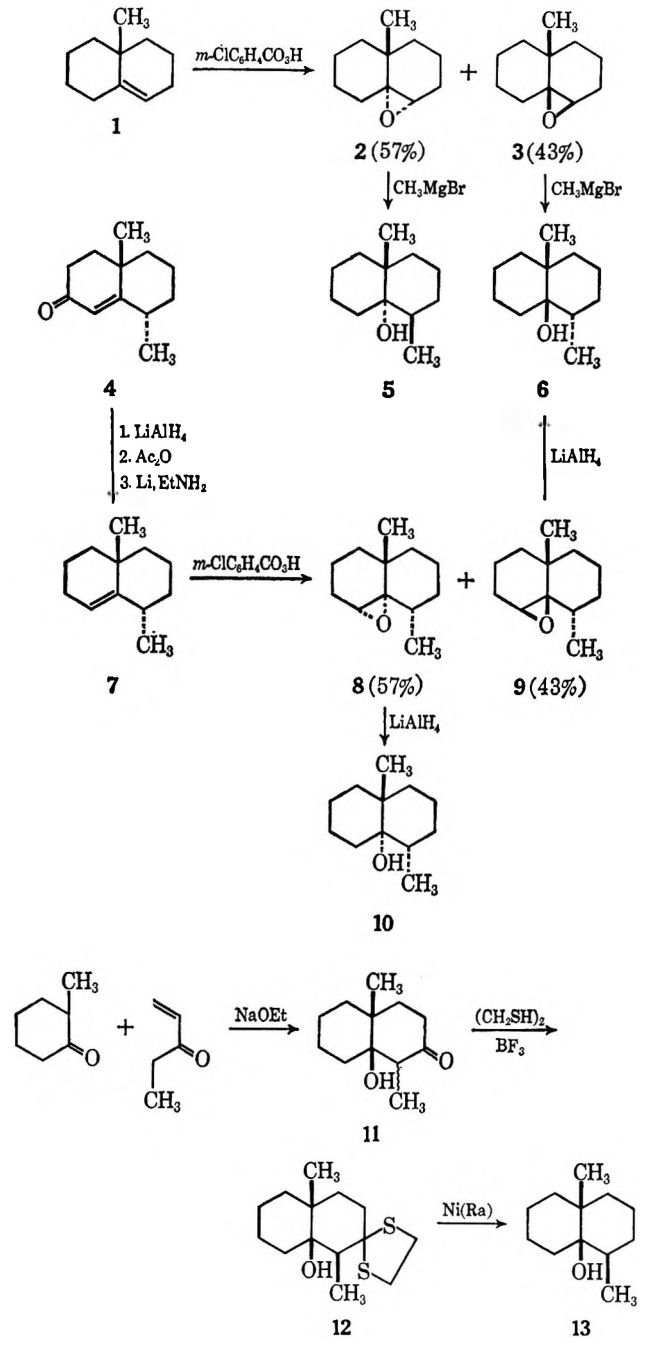
Recently, Gerber and Lechevalier[3] described the isolation of geosmin, the earthy smelling metabolite of actinomycetes microorganisms which is responsible for the characteristic odor of freshly plowed soil. Upon treatment with aqueous acid geosmin afforded a hydrocarbon[3] later identified[4] as a mixture of 1,10-dimethyl-1(9)-octalin[5] and an isomeric olefin. This finding coupled with nmr spectral evidence suggested that geosmin might be one of the isomeric 1,10-dimethyl-9-decalols.[4] In connection with some studies on olefin oxidations[5] we had prepared in racemic form decalols **5**, **6**, and **13**, three of the four possible isomers. The infrared spectra indicated that none of the three was geosmin. However, the spectra of geosmin and the *trans*-decalol **5** showed such striking similarities that we decided to attempt the synthesis of decalol **10**, the C-1 epimer of **5** and the remaining racemic 1,10-dimethyl-9-decalol isomer. In this note we describe synthetic work which pertains to these decalols and show that *trans*-1,10-dimethyl-*trans*-9-decalol (**10**) is the racemic modification of Gerber and Lechevalier's geosmin.

We previously found that the methyl octalin **1** affords a 57:43 mixture of the *trans* and *cis*-decalin oxiranes **2** and **3** upon treatment with *m*-chloroperoxybenzoic acid in benzene (Scheme I).[5] This mixture slowly reacted with methylmagnesium bromide in refluxing tetrahydrofuran to give decalols **5** and **6** which could be separated by careful chromatography on Florisil.[5] The dimethyloctalin **7** was prepared *via* reduction of octalone **4**[6] with lithium aluminum hydride, acetylation of the resulting epimeric alcohol mixture, and hydrogenolysis of the allylic acetate mixture with lithium in ethylamine, a sequence analogous to that employed for the synthesis of octalin **1**. Octalin **7**, like its desmethyl counterpart, gave a 57:43 mixture of *trans* and *cis* decalin oxiranes upon treatment with *m*-chloroperoxybenzoic acid in benzene. Reduction of this mixture with lithium aluminum hydride afforded the corresponding decalols **10** and **6** which were separated *via* careful chromatography on silica. The minor alcohol isomer was identified as *trans*-1,10-dimethyl-*cis*-9-decalol (**6**) by comparison of infrared and nmr spectra with those of an authentic sample.[5] The gas chromatographic retention times were likewise identical (peak enhancement) on several columns under a variety of conditions. This comparison defines the stereochemistry of decalol **10**, the reduction product of the predominant oxirane isomer **8**, since both oxiranes **8** and **9** originate from the same olefin. Decalol **10** was found to be identical with geosmin through spectral and chromatographic comparisons.

SCHEME I



The *cis,cis*-1,10-dimethyl-9-decalol **13** was prepared from ketol **11**, the condensation product of 2-methylcyclohexanone and ethyl vinyl ketone.[7] The crystalline thioketal derivative **12** upon desulfurization with

(1) Fellow of the Alfred P. Sloan Foundation, 1966–1968.
(2) National Institutes of Health Predoctoral Fellow, 1965–1968.
(3) N. N. Gerber and H. A. Lechevalier, *Appl. Microbiol.* **13**, 935 (1965).
(4) N. N. Gerber, Institute of Microbiology, Rutgers University, personal communication, 1968.
(5) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.* **31**, 1020 (1966).
(6) J. A. Marshall and D. J. Schaeffer, *ibid.*, **30**, 3642 (1965).
(7) *Cf.* J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964).

Raney nickel readily yielded decalol **13**. The stereochemistry of this decalol, which follows from its nonidentity with **5**, **6**, and **10**, must be preserved in the thioketal precursor **12**. Since epimerization of the C-1 methyl grouping could occur during formation of this derivative, an unequivocal stereochemical assignment to this center in ketol **11** cannot be made. However, conversion into decalol **13** does confirm the *cis* ring fusion of ketol **11** and thus supports our previous conclusions regarding the stereochemistry of aldol cyclizations leading to such ketols.[7]

The earthy odor referred to by Gerber and Lechevalier[3] is shared by all four decalols **5**, **6**, **10**, and **13**, but each is quite distinctive. The *cis*-fused isomers **6** and **13** have fragrances reminiscent of camphor and cedar and are thus somewhat more agreeable to the nose than their more pungent *trans* counterparts **5** and **10**.

Experimental Section[8]

trans-**8,10-Dimethyl-1(9)-octalin** (**7**).—To a stirred solution containing 600 mg of lithium aluminum hydride in 60 ml of anhydrous ether was added 2.50 g of octalone **4** dissolved in 5 ml of ether. After 2 hr, the mixture was treated with 1.20 ml of water and 0.96 ml of 10% aqueous sodium hydroxide and allowed to stir overnight. The crude alcohol was obtained by filtration and distillation of the ether from the filtrate.

The resulting octalol mixture was dissolved in 15 ml of pyridine and treated with 4.0 ml of acetic anhydride. After 20 hr, water (60 ml) was added and the mixture was thoroughly extracted with hexane. The combined extracts were successively washed with water, 2% aqueous sulfuric acid, and water and dried over anhydrous magnesium sulfate.

The ether was removed from the above solution and the crude product was dissolved in 125 ml of ethylamine and treated with 950 mg of lithium wire according to the procedure of Hallsworth, Henbest, and Wrigley.[9] A deep blue color persisted after 1 hr and the solution was stirred for an additional 30 min. Solid ammonium chloride was then added to neutralize the salts and decompose the excess metal. Most of the ethylamine was allowed to evaporate, water was added, and the mixture was extracted thoroughly with hexane. The combined extracts were washed successively with water, 2% aqueous sulfuric acid, and water and dried over anhydrous magnesium sulfate. The solvent was carefully removed under reduced pressure and the residue was chromatographed on 70 ml of Florisil. Elution with hexane afforded 1.34 g (65%) of octalin **7**: $n^{26}D$ 1.4960; λ_{max}^{film} 6.05 (C=C), 8.30, 9.46, 10.03, 10.69, 11.47, 12.34, 12.61 μ; $\delta_{TMS}^{CCl_4}$ 5.32 (C-1 H, poorly resolved sextet, J = 1.8 Hz), 1.05 (C-10 CH_3), 0.96 ppm (C-8 CH_3, doublet, J = 6.5 Hz).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.9; H, 12.1.

Synthesis and Reduction of Oxiranes 8 and 9.—A solution of 200 mg of octalin **7** and 720 mg of *m*-chloroperoxybenzoic acid in 15 ml of benzene was stirred at 25° for 2.0 hr. The reaction mixture was washed with 10% aqueous sodium hydroxide and saturated aqueous sodium chloride, and the benzene solution was dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure affording 220 mg of a 57:43 mixture (by gas chromatography) of isomeric oxiranes **8** and **9**: λ_{max}^{film} 9.25, 9.70, 10.68, 11.06, 11.60, 12.82, 13.18 μ; $\delta_{TMS}^{CCl_4}$ 3.0–2.80 (C-1 H), 1.05 (C-10 CH_3 of **8**), 0.58 (C-8 CH_3 of **8**, doublet, J = 6.5 Hz), 1.01 (C-10 CH_3 of **9**), 0.63 ppm (C-8 CH_3 of **9**, doublet, J = 6.5 Hz).

The crude oxirane mixture dissolved in 5 ml of anhydrous 1,2-dimethoxyethane was added to a solution of 210 mg of lithium aluminum hydride dissolved in 15 ml of 1,2-dimethoxyethane and the mixture was maintained at reflux for 4 hr. The mixture was cooled and 50 ml of ether followed by 0.42 ml of water and 0.33 ml of 10% aqueous sodium hydroxide was added. The salts were filtered after stirring overnight, and the solvent was removed under reduced pressure affording 205 mg of crude decalols **6** and **10** which displayed peaks in the gas chromatogram[10] at 36.0 min (57%, **10**) and 40.4 min (43%, **6**).

trans-**1,10-Dimethyl-*trans*-9-decalol** (**10**). (±)-**Geosmin.**—The crude decalol mixture described above was chromatographed on 40 ml of acid-washed silica. Elution with 2% ether–hexane (200 ml) afforded 82 mg of colorless oil (one peak on the gas chromatograph): bp 60° (bath temperature) at 0.3 mm; λ_{max}^{film} 2.83 (OH), 8.45, 9.42, 9.93, 10.52, 10.88, 11.29, 11.62, 12.47 μ; $\delta_{TMS}^{CCl_4}$ 1.01 (C-10 CH_3), 0.73 ppm (C-1 CH_3, doublet, J = 5.5 Hz). The infrared spectrum was identical with that of (−)-geosmin isolated by Gerber and Lechevalier.[3]

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.0; H, 12.2.

trans,**1,10-Dimethyl-*cis*-9-decalol** (**6**).—Continued elution of the above column with 2% ether–hexane (200 ml) afforded 20 mg of a mixture of decalols **10** and **6**. Elution with 3% ether–hexane (200 ml) afforded 60 mg of colorless oil: bp 60° (bath temperature) at 0.3 mm; λ_{max}^{film} 2.85 (OH), 8.61, 9.32, 9.50, 9.99, 10.33, 10.53, 11.12, 11.97 μ; $\delta_{TMS}^{CCl_4}$ 0.95 (C-10 CH_3), 0.83 ppm (C-1 CH_3, doublet, J = 6.5 Hz). The infrared and nmr spectra of this decalol were identical with those of the minor decalol isomer formed upon treatment of oxirane mixture **2** and **3** with methylmagnesium bromide.[5] The gas chromatographic retention times were likewise identical (peak enhancement) under a variety of conditions.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.0; H, 12.2.

1,10-Dimethyl-*cis*-9-hydroxy-2-decalone (**11**).[11]—A solution containing 7.8 g of 2-methylcyclohexanone and 0.85 ml of 3 *N* ethanolic sodium ethoxide was maintained at −10° and efficiently stirred while a solution of 5.9 g of ethyl vinyl ketone in 7.8 g of 2-methylcyclohexanone was added dropwise over a period of 5.5 hr. Stirring at −10° was continued for 6.5 hr after addition was complete and the organic material was isolated by extraction with ether. The combined extracts were dried and distilled affording 8.9 g (57% recovery) of 2-methylcyclohexanone, bp 55–58° (0.2 mm), and 9.3 g (68%) of ketol **11** and the corresponding conjugated ketone, bp 80–105° (0.1 mm). The higher boiling fraction was crystallized from hexane affording 4.9 g (36%) of ketol **11**, mp 70–77° (lit.[12] mp 88°). The analytical sample, mp 103°, was secured after several additional recrystallizations from hexane.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.4; H, 10.2.

Ethylene Thioketal Derivative of *cis*-1,10-Dimethyl-*cis*-9-hydroxy-2-decalone (**12**).—The procedure of Fieser was employed.[13] A solution of 1.50 g of ketol **11** in 27 ml of glacial acetic acid, 2.1 ml of 1,2-ethanedithiol, and 2.1 ml of boron trifluoride etherate was allowed to stand at ambient temperature for 2.2 hr. The solution was diluted with aqueous sodium chloride and extracted with ether. The combined extracts were washed with 10% aqueous sodium hydroxide and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The ether was distilled and the residue was crystallized from hexane affording 1.45 g (70%) of thioketal **12**, mp 119–120°. The analytical sample, mp 120.5–121°, was obtained after recrystallization from hexane and sublimation.

Anal. Calcd for $C_{14}H_{24}OS_2$: C, 61.71; H, 8.88; S, 23.54. Found: C, 61.7; H, 8.9; S, 23.4.

cis-**1,10-Dimethyl-*cis*-9-decalol** (**13**).—A solution of 461 mg of thioketal **12** in 30 ml of absolute ethanol was efficiently stirred with 15 g of freshly prepared W-2 Raney nickel at 25° for 2 hr and at reflux for 4.5 hr. The cooled mixture was carefully filtered and the ethanol was removed under reduced pressure. The residue was dissolved in ether, washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. Removal of solvent and distillation afforded 262 mg (85%) of a colorless oil: bp 55–60° (0.25 mm); λ_{max}^{film} 2.86 (OH), 8.46,

(8) (a) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere over reaction mixtures. (b) Melting points were determined on a Fisher-Johns hot stage. (c) An F & M Model 700 or Model 720 gas chromatograph was employed for analytical work (d) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(9) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1437 (1952).

(10) An 18 ft × 0.25 in. column containing 20% Carbowax 20M on Chromosorb W was employed at 146° with a helium flow rate of 100 cc/min.

(11) This experiment is abstracted from the Ph.D. Thesis of Wayne I. Fanta, Northwestern University, 1965.

(12) F. J. McQuillin, *J. Chem. Soc.*, 528 (1955).

(13) L. F. Fieser, *J. Amer. Chem. Soc.*, **76**, 1945 (1954).

9.33, 9.48, 9.88, 10.28, 10.46, 10.65, 11.18 μ; $\delta_{TMS}^{CCl_4}$ 0.96 (C-10 CH_3), 0.79 ppm (C-4 CH_3 doublet, J = 6.5 Hz).

The distillate solidified upon refrigeration, and the analytical sample, mp 40.5–41.5°, was obtained after two sublimations.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.1; H, 12.0.

Registry No.—**6**, 16423-15-7; **7**, 16423-16-8; **8**, 16423-17-9; **9**, 16423-18-0; **10**, 16423-19-1; **12**, 16423-20-4; **13**, 16452-32-7.

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The Solvolysis of *p,p'*-Disubstituted Benzhydryl Halides

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The recent series of papers by Nishida on the additivity, or lack of additivity, in the alcoholysis of mono- and disubstituted benzhydryl halides[2] prompted us to report results of a similar, though less extensive study, which had similar objectives as its aim. Our data were obtained in aqueous acetone and therefore supplement the data of Nishida.

The problem of concern is whether two identical substituents in two different benzene rings act completely independently of each other in a reaction in which a carbonium ion is developed in the transition state, when both substituents are capable of interacting with the carbonium ion. Such a situation arises in the solvolysis of appropriately substituted benzhydryl halides. Although in most disubstituted chloro and methyl derivatives additivity occurs,[2,3] Nishida has demonstrated a characteristic deviation in the case of *p,p'*-dimethylbenzhydryl chloride, and it is this deviation from additivity which our data confirm for the acetone–water system. The problem has some added current interest because multiple methyl substitution has been utilized as a probe for the structure of carbonium ion transition states.[4]

Some of the required data have been in the literature for a long time. Ingold and coworkers, in the course of their study on mass law and salt effects, studied the solvolysis of *p*-methyl- and *p,p'*-dimethylbenzhydryl chloride in 80% aqueous acetone.[5] Their data show that one *p*-methyl group increases the reactivity by a factor of 29.6, but that *p,p'*-dimethylbenzhydryl chloride reacts only 567 times as fast as the parent compound, instead of 876 times, if additivity had strictly prevailed.

Our data are reported in Table I. Because of a slight difference in solvent composition (see Experimental Section) and the great sensitivity of the rates to water content,[6] our values for the rate constants differ slightly from those of Ingold, *et al.*, but the general pattern is the same. The solvolysis of *p,p'*-dimethylbenzhydryl chloride in aqueous acetone is not only very fast, but has a very strong mass law effect in the concentration range here used. The rate constants reported, ours, as well as the literature values, were obtained by extrapolation to 0% reaction, and our data for the dimethyl derivative are only approximate. However, in the alcoholysis (ethanolysis, 2-propanolysis) of the same compound, which is not beset by these difficulties, analogous results were obtained[2] which leaves no doubt as to the over-all validity of the results.

The *p,p'*-dimethyl compound does not react as fast as it should on the basis of additivity. This is also true of *p,p'*-di-*t*-butylbenzhydryl chloride, but with the less powerful electron-releasing effect of the *t*-butyl group, the difference between observed and calculated values is less than with methyl.

The situation is similar, although reversed in an absolute sense, when the substituents have an electron-attracting effect and therefore destabilize the carbonium ion. The chlorine atom in *p*-chlorobenzhydryl chloride lowers the rate of solvolysis, but the second chlorine hinders the reaction less than the first, and *p,p'*-dichlorobenzhydryl chloride does not solvolyze as slowly as calculated. This is true also of the bromine atom, but to a somewhat lesser extent. The deviations caused by the halogens are barely noticeable in the alcoholysis but the deviations become quite pronounced when more than two substituents are present.[2]

The results confirm that in this particular system characteristic deviations from additivity occur. Nishida has shown that this can formally be expressed by assigning two different ρ values to the reactions of mono- and disubstituted benzhydryl chlorides, or by modifying the Hammett equation by the inclusion of more parameters. But the physical meaning of the deviations must be that in a system such as the benzhydryl system, the second of two identical substituents does not affect the reaction to the same extent as the first, and that their effects appear to oppose each other. Consequently, both cannot interact with the developing carbonium ion as effectively as can one alone. The result which is noted in the rate studies is that the second substituent has less effect than the first, but, because of the complete symmetry of the system, the effect of both substituents must be diminished to the same extent.

This lack of additivity is not necessarily confined to transition states. It has also been noted in the dissociation of substituted triphenylmethyl halides in

(1) Taken from the Ph.D. Thesis of M. Q. Malter, Bryn Mawr College, June, 1952.

(2) S. Nishida, *J. Org. Chem.*, **32**, 2692, 2695, 2697 (1967).

(3) Deviations from additivity in the solvolysis of benzhydryl chlorides have been observed and discussed by J. R. Fox and G. Kohnstam, *Proc. Chem. Soc.* (London), 115 (1964).

(4) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965); P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966).

(5) E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 949 (1940); M. G. Church, E. D. Hughes, and C. K. Ingold, *ibid.*, 966 (1940); M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *ibid.*, 971 (1940); L. C. Bateman, E. D. Hughes, and C. K. Ingold, *ibid.*, 974 (1940); L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *ibid.*, 979 (1940).

(6) For instance, see V. J. Shiner, Jr., and C. J. Verbanic, *J. Amer. Chem. Soc.*, **79**, 369 (1957).

Table I

RATE DATA FOR THE SOLVOLYSIS OF SUBSTITUTED BENZHYDRYL CHLORIDES

Substituents	Solvent, % acetone	Temp, °C	$k_1 \times 10^5$, sec^{-1}	k/k_H	$(k/k_H)_{calcd}$	$(k/k_H)_{obsd}/(k/k_H)_{calcd}$
H	80	0	0.277			
p-CH_3	80	0	7.70	27.8[a]		
p,p'-di-CH_3	80	0	~162	~585	773	~0.76[b]
H	80	25	6.07			
p-Cl	80	25	1.93	0.318[c]		
p,p'-di-Cl	80	25	0.840	0.138	0.101	1.37
p-Br	80	25	1.66	0.273[c]		
p,p'-di-Br	80	25	0.555	0.0914	0.0745	1.23
H	90	25	0.507			
p-CH_3	90	25	11.2	22.1[d]		
p,p'-di-CH_3	90	25	~143	~282	488	~0.58
p-t-C_4H_9	90	25	5.77	11.4[e]		
p,p'-di-t-C_4H_9	90	25	56.0	110	130	0.85

[a] Lit.[5] 29.6. [b] Lit.[5] 0.65. Ratios of 0.60 and 0.62 were found in the ethanolysis and 2-propanolysis, respectively.[2] [c] Values of 0.328 and 0.251 were observed in the solvolysis in 70% aqueous acetone for the p-chloro and p-bromo compounds, respectively: G. Kohnstam, *J. Chem. Soc.*, 2066 (1960). [d] Lit.[5] 20.6. [e] Lit.[5] 10.9 and 10.5 in 80% acetone at 25°.

liquid sulfur dioxide[7] and the ionization of substituted triphenylmethanols in concentrated sulfuric acid.[8,9]

Experimental Section

The known benzhydryl halides were prepared by literature procedures, and their melting points or boiling points agreed with those reported in the literature. p,p'-Di-t-butylbenzophenone was prepared from t-butylbenzene and carbon tetrachloride[10] and forms white crystals (ligroin) of mp 134.6–134.9° uncor.

Anal. Calcd for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.66; H, 8.89.

The 2,4-dinitrophenylhydrazone melts at 202–203°.

Anal. Calcd for $C_{27}H_{30}O_4N_4$: C, 68.33; H, 6.37. Found: C, 68.30; H, 6.02.

p,p'-Di-t-butylbenzhydrol forms white crystals (ligroin) of mp 102–102.4° uncor.

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.07; H, 9.52. p,p'-Di-t-butylbenzhydryl chloride, prepared from the above with dry hydrogen chloride, was recrystallized from ligroin and had mp 122.5–123°.

Anal. Calcd for $C_{21}H_{27}Cl$: C, 80.09; H, 8.64. Found: C, 80.06; H, 8.71.

Acetone was purified by the method of Conant and Kirner.[11] The 80 and 90% acetone were prepared by adding 200 or 100 ml of distilled water to a 1-l. volumetric flask and diluting with acetone to the mark. These solvents contain slightly more acetone than the solvents used by Ingold, *et al.*,[5] who prepared them by mixing appropriate volumes of acetone and water. Solvent batches prepared for runs at different temperatures were not comparable. Rate constants were determined in the usual way by quenching 10-ml samples in 100 ml of ice-cold acetone and titrating with standard $Ba(OH)_2$. They were calculated for each point from the integrated form of the first-order rate equation. The initial concentration of chloride was determined from an infinity titer. The concentrations ranged between 0.035 and 0.04 *M*. Runs were usually conducted in triplicate, and rate constants within one run, as well as in duplicate runs, usually agreed within a few per cent. The rate constants for p-methylbenzhydryl chloride in 80% acetone, and those for the p,p'-dimethyl compound, in both 80 and 90% acetone, fell as the reaction progressed, those of the dimethyl compound much more than the monomethyl compound, and more in 80% than in 90% acetone.[1] Rate constants were extrapolated to 0% reaction by visually fitting the best smooth line through the points. Because of considerable scatter, the values for p,p'-dimethylbenzhydryl chloride are not very precise, but the constant in 80% acetone agrees with the constant obtained similarly by Ingold, *et al.*

Registry No.—p,p'-Di-t-butylbenzophenone, 15796-82-4; p,p'-di-t-butylbenzophenone 2,4-dinitrophenylhydrazone, 16607-59-3; p,p'-di-t-butylbenzhydrol, 16607-60-6; p,p'-di-t-butylbenzhydryl chloride, 16622-59-6.

(7) N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955).

(8) N. N. Lichtin, *Progr. Phys. Org. Chem.*, **1**, 75 (1963).

(9) The argument, suggested by a referee, that the results of the solvolysis might be caused by different extents of ion pair return in mono and disubstituted benzhydryl halides, offers an alternate explanation. However, it is much less likely that this argument accounts for the results of the alcoholysis, or the data quoted at the end of the paper.

(10) The procedure was similar to that described for the preparation of benzophenone by C. S. Marvel and W. M. Sperry, "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1948, p 95.

(11) J. B. Conant and W. R. Kirner, *J. Amer. Chem. Soc.*, **46**, 232 (1924).

The Synthesis and Anionic Properties of 1,3-Dithiane 1-Oxide

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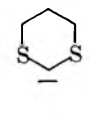
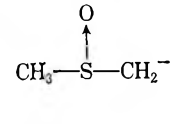
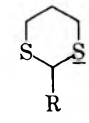
Corey and coworkers have recently developed a variety of reagents for organic synthesis utilizing the properties of sulfur (in various oxidation states) to stabilize carbanions.[2–5] The anion I derived from the title compound, 1,3-dithiane 1-oxide (II), incorporates the structural features of two of these reagents, the "dimsyl anion" (III)[2] and the dithienyl anions (IV),[3] and has been found to undergo reactions common to both.



I



III



IV

(1) A National Science Foundation Undergraduate Summer Research Participant, 1967.

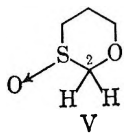
(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(3) (a) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1075, 1077 (1965); (b) E. J. Corey, D. Seebach, and R. Freedman, *J. Amer. Chem. Soc.*, **89**, 434 (1967); (c) E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968); (d) D. Seebach, N. R. Jones, and E. J. Corey, *ibid.*, **33**, 300 (1968).

(4) (a) E. J. Corey and D. Seebach, *ibid.*, **31**, 4097 (1966); (b) E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, **88**, 5656 (1966).

(5) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

1,3-Dithiane was carefully oxidized with 1 equiv of sodium metaperiodate[6] to yield (94%) a compound with the physical properties expected for 1,3-dithiane 1-oxide (II), including an interesting nuclear magnetic resonance spectrum, in which only one of the diastereomeric protons at C-2 exhibits further coupling (J_{gem} = 12 cps and J = 2.5 cps). This unusual behavior might be ascribed to conformational stability of the 1,3-dithiane 1-oxide ring, where only one proton (at lower field and presumably equatorial) is properly orientated for further coupling with a methylene proton adjacent to sulfur. Some justification for this position is found in the spectrum of another compound under investigation, 1,3-oxathiane 3-oxide (V), in which one would expect a greater amount of ring flexibility[7] and where an ABX pattern (J_{AB} = 11 cps, $J_{AX} - J_{BX}$ = 1.5 cps)[8] is observed for both the protons at position 2.

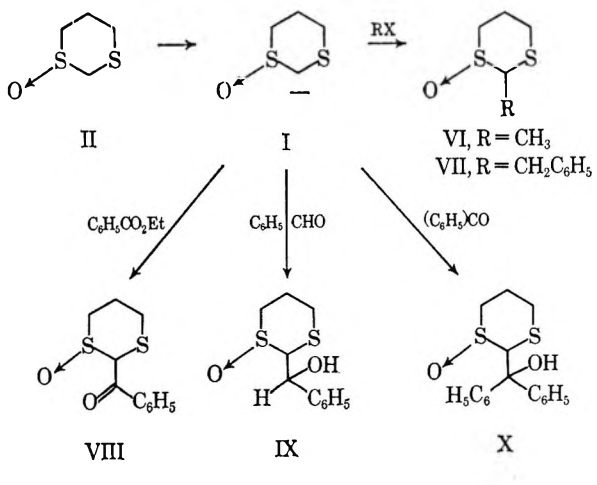


V

The optimum procedure found for rapid anion formation with minimum decomposition was to add (under nitrogen) 1 equiv of *n*-butyllithium to a cooled solution (0 to −10°) of the sulfoxide in dry tetrahydrofuran. Anion formation was rapid as evidenced by the successful reaction of the anion with benzophenone (79%) within 5 min after the final addition of *n*-butyllithium. Moreover, indications that reactions *with* the anion were also complete within minutes were found by thin layer analyses of the reaction mixtures.

1,3-Dithiane 1-oxide exhibits properties common to both sulfoxides and to dithianes in the anionic addition to benzaldehyde and benzophenone (see Chart I and Table I). Moreover, the anion can be allowed to react with ethyl benzoate to form the β-keto sulfoxide VIII (sulfoxides only) and alkylated dithianes only.[9]

CHART I



II I VIII IX X

(6) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(7) F. G. Riddell, *Quart. Rev.* (London), **21**, 373 (1967).

(8) K. C. Ramsey and J. Messick [*Tetrahedron Lett.*, **49**, 4423 (1965)] find 1,3-dioxanes have couplings (C-2) of $J_{2a} - J_{2e}$ = 6.2 cps/$J_{2e} - J_{6e}$ = 1.5 cps.

(9) For an exception, see the alkylation of β-keto sulfoxides: G. Russell, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966).

TABLE I

No.	Compound	Yield,[a] %	mp,[b] °C
II	1,3-Dithiane 1-oxide	94	87–88
VI	2-Methyl-1,3-dithiane 1-oxide	14[c]	93–94
VII	2-Benzyl-1,3-dithiane 1-oxide	24	95–96
VIII	2-Benzoyl-1,3-dithiane 1-oxide	52	134–136
IX	2-(Phenylhydroxymethyl)-1,3-dithiane 1-oxide	54	185–191 dec
X	2-(Diphenylhydroxymethyl)-1,3-dithiane 1-oxide	79	155–156 dec

[a] Yield of compound exhibiting one spot on thin layer chromatography. [b] Melting point of analytical sample. [c] Analytical sample.

The position of alkylation was confirmed to be at C-2 by comparison of the alkylated products with samples obtained by the oxidation of the corresponding methyl- or benzyl-1,3-dithiane with sodium *m*-periodate.

Like dithienyl anions (IV), the anion I possesses considerable nucleophilic character as shown by the successful benzylation with the absence of any products (*e.g.*, stilbenes) characteristic of the reaction of the "dimsyl anion" with benzyl halides.[2]

In at least one reaction, the anion I shows considerable stereoselectivity. For example, the addition product of I and benzophenone generates a second asymmetric atom at C-2, yet a single diastereomer (single spot on tlc, sharp melting point) is isolated in high yield (79%). The presence of multiple asymmetric atoms does, however, appear to present a problem with the alkylated derivatives, where the preparation of pure samples was quite difficult.

Experimental Section

Melting points were taken in capillaries, and are uncorrected. Infrared spectra were taken on a Beckman IR 10 spectrophotometer. Nmr spectra were obtained on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard. The elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. The dry tetrahydrofuran was prepared shortly before use by distillation over calcium hydride.

1,3-Dithiane 1-Oxide (II).—To a cooled solution of dithiane (2.00 g, 16.7 mmol) in methanol (125 ml) was added an aqueous solution (35 ml) of sodium metaperiodate (3.68 g, 17.5 mmol) at such a rate (approximately 30 min) to maintain the temperature at 20°. Stirring and cooling were continued for an additional 30 min. The reaction mixture was then filtered to remove sodium iodate, and the resulting solution taken to near dryness on the rotary evaporator. Extraction of the solids with chloroform produced a solution which when dried over sodium sulfate, filtered, and evaporated left the crystalline sulfoxide: 2.13 g, 15.7 mmol, 94%; mp 86–87°; ir ($CHCl_3$) 1030 cm^{-1} (S → O); nmr ($CDCl_3$), δ 3.84 [q, 2, -S (→ O)CH_2S-], 3.2 [m, 1, -CH_2S-(→O)-], 2.8 [m, 1, -CH_2S(→O)-], 2.3 (m, 4). Two recrystallizations from chloroform–cyclohexane gave the analytical sample, mp 87–88°.

Anal. Calcd for $C_4H_8S_2O$: C, 35.26; H, 5.92; S, 47.07. Found: C, 35.40; H, 6.10; S, 47.20.

Anion Generation (General Procedure).—The flask containing a solution of 1,3-dithiane 1-oxide (0.27 g, 2.0 mmol) in dry tetrahydrofuran (8 ml) was flushed with dry nitrogen, sealed with serum caps, and placed under positive nitrogen pressure. When the stirred reaction mixture reached −10° (ice–calcium chloride), *n*-butyllithium–hexane (Alpha Inorganics Inc., 2.0 mmol) was introduced dropwise with a hypodermic syringe. As the yellow color resulting from each drop of the *n*-butyllithium solution was dispersed through the solution, 1 additional drop was added. In this manner, the temperature of the reaction mixture never exceeded −5°. The resulting solution of the carbanion was used in subsequent reactions within 5–10 min.

2-Methyl-1,3-dithiane 1-Oxide (VI).—To a solution of the carbanion prepared from 0.27 g (2.0 mmol) of the sulfoxide was added methyl iodide (0.35 g (2.5 mmol) in 3 ml of tetrahydrofuran). The solution was stirred at 0° for 30 min and then

allowed to come to room temperature over a period of 60 min. The solution was evaporated and the organic products were extracted from the solid residue with chloroform. Evaporation gave a colorless oily solid. Two recrystallizations from chloroform gave analytically pure 2-methyl-1,3-dithiane 1-oxide (VI): yield 0.043 g (0.286 mmol), 14%; mp 93–94°.

Anal. Calcd for $C_5H_{10}S_2O$: C, 39.97; H, 6.71; S, 42.68. Found: C, 40.25; H, 6.89; S, 42.79.

2-Benzyl-1,3-dithiane 1-Oxide (VII).—Benzyl bromide (0.69 g, 4.05 mmol) was added to a solution of the carbanion produced from 0.500 g (3.68 mmol) of 1,3-dithiane 1-oxide (II). After stirring for an additional 4 hr, the reaction mixture was poured into water (75 ml) and acidified with hydrochloric acid. Extraction of this mixture with chloroform gave a solution that was dried over anhydrous sodium sulfate and treated with decolorizing carbon. Concentration of the solution gave an oil (0.90 g) that was purified by preparative thin layer chromatography (5% ethanol in chloroform) to give an oil that slowly crystallized: mp 51–65°; yield 0.202 g (0.888 mmol), 24%. The analytical sample (mp 95–96°) was prepared using cyclohexane–chloroform as solvent.

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.36; H, 6.23; S, 28.33. Found: C, 58.70; H, 6.32; S, 28.50.

1-Benzoyl-1,3-dithiane 1-Oxide (VIII).—To a solution of the carbanion I produced from 1.00 g of the sulfoxide (7.36 mmol) was added ethyl benzoate (0.55 g, 3.67 mmol). After stirring for 20 min the reaction mixture was poured into water (50 ml) and carefully acidified to pH 3. Extraction with chloroform produced a yellow solution which was washed with water, dried over sodium sulfate, and filtered. The chloroform was removed to leave a yellow oil (1.01 g) that was purified *via* preparative thin layer chromatography (5% ethanol in chloroform): yield 0.45 g (1.90 mmol), 52%, off-white crystals; ir ($CHCl_3$) 1050 cm^{-1}, broad (S→O), 1670 (C=O), 3430 (enol). Two recrystallizations from ethyl acetate–cyclohexane gave the analytical sample, mp 134–136°.

Anal. Calcd for $C_{11}H_{12}S_2O_2$: C, 54.96; H, 5.03; S, 26.68. Found: C, 55.21; H, 4.99; S, 26.71.

2-(Phenylhydroxymethyl)-1,3-dithiane 1-Oxide (IX).—A solution of the carbanion I in tetrahydrofuran was prepared in the usual manner from 0.50 g (3.68 mmol) of the sulfoxide. To this solution was added, over a 3-min period, a solution of benzaldehyde (0.47 g, 4.42 mmol) in tetrahydrofuran. The reaction mixture was stirred for 15 min (−5°) and the product (0.48 g, 2.0 mmol, 54%, mp 120–170°) isolated as for VII. The analytical sample (mp 185–191° dec) was prepared from chloroform–cyclohexane.

Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.51; H, 5.82; S, 26.46. Found: C, 54.71; H, 5.90; S, 26.21.

2-(Diphenylhydroxymethyl)-1,3-dithiane 1-Oxide (X).—To the solution of the carbanion (2.0 mmol) as prepared above was added a solution of benzophenone (0.34 g, 1.9 mmol) in dry tetrahydrofuran (2 ml). After stirring for 20 min, the product (0.49 g, 1.5 mmol, 79%, mp 158–162°) was again isolated as for VII. Several recrystallizations from chloroform–cyclohexane gave the analytical sample, mp 155–156° with decomposition.

Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.70; S, 20.14. Found: C, 63.86; H, 5.65; S, 20.23.

1,3-Oxathiane 3-oxide (V) was prepared by the sodium metaperiodate oxidation (see preparation of II) of 1,3-oxathiane: 78%; bp 139–141° (0.6 mm); nmr ($CDCl_3$), δ 4.63 (q, 2, $-S(\rightarrow O)CH_2O-$), 3.85 (t, 3, OCH_2-), 3.1 (m, 2, $-S(\rightarrow O)CH_2-$), 2.0 (m, 2, $-CH_2-$).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.01; H, 6.87; S, 26.84.

1,3-Oxathiane is a new compound[10] formed by the reaction of 3-mercapto-1-propanol with dimethoxymethane in boron trifluoride etherate–acetic acid.[11] Isolation of the crude product was effected by washing a chloroform solution of the reaction mixture several times with water and subsequent steam distillation from 10% potassium hydroxide. Vacuum distillation gave pure 1,3-oxathiane: 48%; bp 96–100° (100 mm.); nmr (pure liquid), δ 4.72 (S, 2, SCH_2O), 3.75 (t, 2, OCH_2-), 2.82 (t, 2, SCH_2-), 1.8 (m, 2).

Anal. Calcd for C_4H_8OS: C, 46.12; H, 7.74; S, 30.78. Found: C, 46.43; H, 7.89; S, 30.81.

Registry No.—II, 16487-10-8; VI, 16452-25-8; VII, 16452-26-9; VIII, 16452-27-0; IX, 16452-28-1; X, 16452-29-2; V, 16452-30-5.

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Graduate School of the University of Minnesota for support of this work.

(10) D. S. Breslow and H. Skolnik, in "Heterocyclic Compounds," Vol. 21, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1966, p 805.

(11) L. F. Fieser, *J. Amer. Chem. Soc.*, **76**, 1945 (1954).

The *syn-anti* Isomerism of α-*t*-Aminoalkanone Oximes

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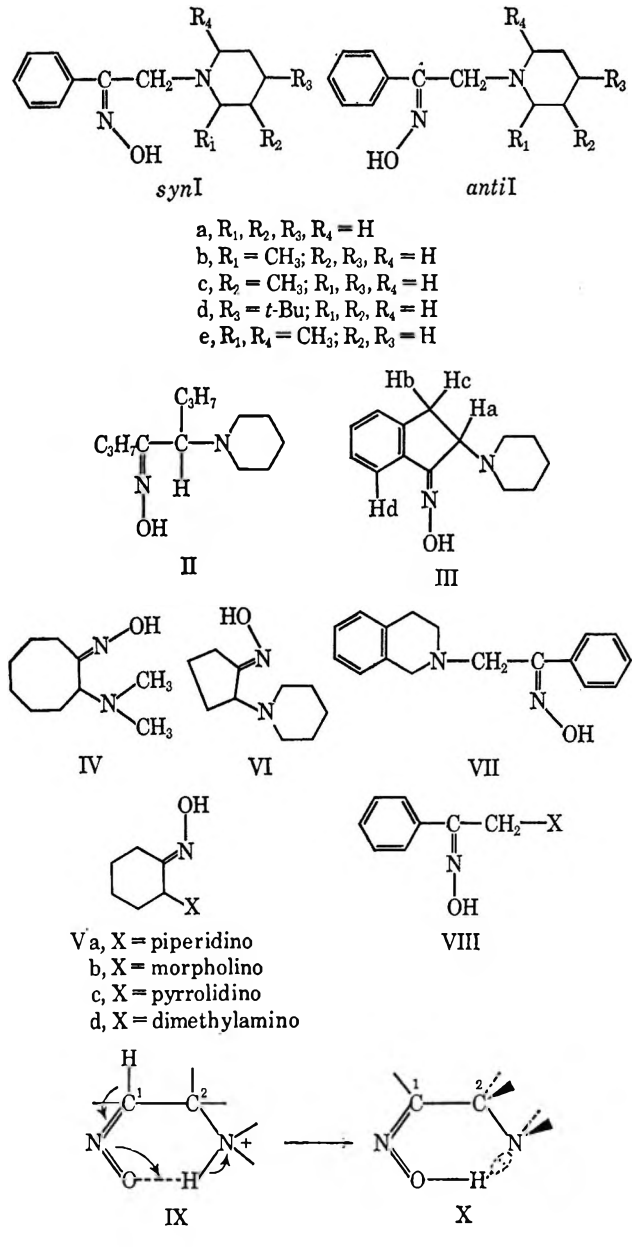
Received November 24, 1967

The formation of α-*t*-aminoalkanone oximes in the photoaddition of N-nitrosamines to olefins led us to investigate the separation and identification of *syn* and *anti* isomers in the product (Chart I).[1] These photoadditions, as carried out under acidic conditions, usually gave exclusively or preferentially one isomer.[1-4] In cases where two geometric isomers were formed and could be isolated in the pure states, the assignment of *syn* or *anti* structures was often possible from comparison of their physical properties, although the evidence was tenuous.[3,4] Where only one isomer was isolated, however, assignment was no more than a reasonable guess since there were no general rules available.[1-4] In view of recent interest in the α-substituted (methoxy, mercapto, and halogeno groups) alkanone oximes,[5-7] it is desirable to establish a method by which *syn* and *anti* isomers can be identified rapidly. To this end, a systematic study has been carried out on the α-*t*-aminoalkanone oximes and is reported in this communication. In the sequel it is shown that compounds V and VI must possess the *anti* configuration, contrary to our original suggestion.[1,3]

The compounds examined (I–VII) were available from the previous preparative work.[1-4] The compounds of VIII series were prepared by the oximation of the appropriate α-aminoacetophenone[4] and/or by a photoaddition of the appropriate nitrosamine to styrene[3] followed by extensive chromatography. The melting points of all isomers in VIII series correspond to those prepared by different routes as reported by Fischer and Grob[8] with the exception of *anti*-VIIIc which is a new compound. These compounds can be conveniently divided into two groups; those in which

(1) Y. L. Chow, *Can. J. Chem.*, **43**, 2711 (1965).
(2) Y. L. Chow, *J. Amer. Chem. Soc.*, **87**, 4642 (1965).
(3) Y. L. Chow, S. C. Chen, and C. J. Colón, *J. Org. Chem.*, **32**, 2109 (1967).
(4) Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **45**, 2559 (1967).
(5) R. L. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, **87**, 3284 (1965).
(6) M. Ohno, M. Okamoto, and K. Nukada, *Tetrahedron Lett.*, 4047 (1965).
(7) M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966).
(8) H. P. Fischer and C. A. Grob, *Helv. Chim. Acta.*, **45**, 2528 (1962).

CHART I



both isomers are available (I–IV and VIII) and those in which only one isomer is available.

The particular structural features of α-aminoalkanone oximes permit one to speculate on *syn* and *anti* configurations based on logical deduction of hydrogen bonding properties and anisotropic effects of the oximino group.[9-12] Thus if both *syn* and *anti* isomers are available, differentiation of isomers and correlation of properties with structure may be made with data obtained from techniques such as infrared and nmr spectroscopy, chromatography, and solubility and melting point determinations. Identification of some similar *syn* and *anti* isomers by means of a color test and by ultraviolet spectroscopy has been reported.[8] Both methods suffer from obvious disadvantages; namely, (i) in the former the pure sample is required and (ii) the

(9) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., Oxford, England, 1969, pp 66–71.

(10) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2327 (1963).

(11) *cf.* W. F. Trager and A. C. Huitric, *Tetrahedron Lett.*, 825 (1966).

(12) *cf.* H. Saito and K. Nukada, *J. Mol. Spectrosc.*, **18**, 1 (1965).

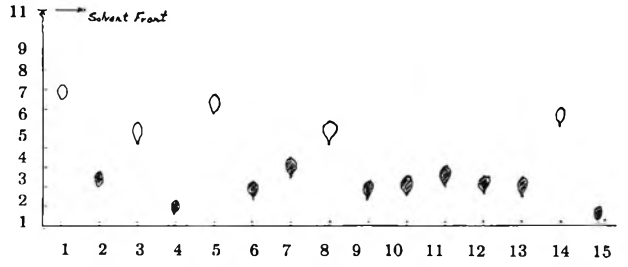


Figure 1.—The thin layer chromatograms of the oximes on alumina with 1.5% MeOH in $CHCl_3$: 1, *syn*-Ib; 2, *anti*-Ib; 3, *syn*-Ic; 4, *anti*-Ic; 5, *syn*-Id; 6, *anti*-Id; 7, *anti*-VII; 8, *syn*-IV; 9, *anti*-IV; 10, *anti*-Va; 11, *anti*-Vb; 12, *anti*-Vc; 13, *anti*-VI; 14, *syn*-II; 15, *anti*-II.

correlation is limited to α-aminoacetophenone oximes in the latter.

From the structural point of view the major difference between the *syn* and *anti* isomers of these oximes appears to be caused by hydrogen bonding. Thus the *syn* isomer should favor intramolecular hydrogen bonding, while the *anti* isomer can only undergo intermolecular hydrogen bonding. This argument is well validated by the following general observations; namely, (i) the *syn* isomer is always more soluble in nonpolar solvents (*e.g.*, cyclohexane and benzene) than the corresponding *anti* isomer, (ii) the *syn* isomer is invariably less strongly adsorbed than the corresponding *anti* isomer in column or thin layer chromatography (see Figure 1), and (iii) *syn*-III (2-piperidinoindanone oxime) is readily sublimed under conditions where *anti*-III cannot be sublimed.

Direct observation of inter- and intramolecular hydrogen bonding in the 3200–3600-cm^{-1} region employing dilution techniques does not afford an unequivocal answer since oximino hydroxyl groups of both *syn* and *anti* isomers show a broad peak at the 3250-cm^{-1} region and sharp peak at the 3590-cm^{-1} region in CCl_4 solution. It is, however, worth mentioning that the 3250-cm^{-1} peaks of *syn* isomers are usually less intense and attenuate more quickly on dilution. The usefulness of this technique is, however, severely reduced by the limited solubility of some oximes.

Nmr spectroscopy is, however, a more amenable physical method for distinguishing the *syn* and *anti* isomers owing to two salient facts; namely, (i) drastic downfield shift of the intramolecularly hydrogen bonded OH signal in comparison with an intermolecularly hydrogen bonded one[9] and (ii) the distinct anisotropic effects of the oximino group on the neighbouring proton signals.[10-12] The former point is well borne out by the downfield shift of OH signals of *syn*-oximes in comparison to those of the corresponding *anti*-oximes (Table I).

From nmr studies by various groups[8-11] the long-range shielding effects of an oximino group on α-hydrogen atoms are now fairly well understood. Thus the proton α to both the oximino and the amino group is expected to resonate at a lower field in the *syn*-oxime than in the *anti*-oxime.[10] Although the agreement displayed in Table I is excellent within each pair, a systematic correlation of the chemical shifts of the *syn* and *anti* isomers cannot be made. This failure clearly reflects the very subtle change of the magnetic environment experienced by the proton in question as controlled by a small change in conformation. Further

TABLE I

2-*t*-AMINOALKANONE OXIME

Compound	Mp, °C	OH	Chemical shifts (τ value)[a] NCH_2- or NCH-
syn-Ia	117–117.5	−3.3	6.26
anti-Ia	133–134	−0.8	6.67
syn-Ib	73–76	−2.0	6.18[c]
anti-Ib	Liquid	0.9	6.59[c]
syn-Ic	97–99	−2.0	6.29
anti-Ic	...	...	6.72[d]
syn-Id	171–174	−1.1	6.26
anti-Id	...	...	6.68[d]
anti-Ie	161–164	...	5.91[b]
syn-II	Liquid	1.3	7.06[e]
anti-II	Liquid	2.7	7.23[e]
syn-III	101–103	−2.6	5.54[f]
anti-III	171–174	−0.02	5.83[f]
syn-IV	71–73	−0.65	6.77[e]
anti-IV	84–85	0.60	7.22[e]
anti-Va	118–120	0.5	7.28[g]
anti-Vb	113–114	0.7	7.25[g]
anti-Vc	123	0.6	7.22[g]
anti-Vd	120–121[i]	0.7	7.34[g]
anti-VI	152–154	1.3	6.55[e]
anti-VII	135–136	−0.5	6.11
syn-VIIIb	146–149[h]	−2.1	6.27
anti-VIIIb	116–119[h]	0.6	6.64
syn-VIIIc	110–111	−0.5	6.13
anti-VIIIc	69–71[h]	2.0	6.51
syn-VIIId	117–119[h]	...	6.35[b]
anti-VIIId	80–83[h]	...	6.58[b]

[a] The nmr spectra were taken in $CDCl_3$ solution with internal TMS standards unless specified otherwise and melting points were recorded with a Fisher-Johns hot stage. [b] The nmr spectra were recorded in pyridine solution. [c] The coupling patterns are AB quartet where δ = 35 cps, J = 15.5 cps for *syn*-Ib and δ = 34 cps, J = 14 cps for *anti*-Ib. All other corresponding signals in I series and VIII series are singlets. [d] These values were obtained from nmr spectra of mixtures. [e] Unsymmetrical triplets. [f] The X proton of the ABX system. [g] These signals are not well-defined multiplets with the width at the half-height ranging 8–10 cps. [h] The reported melting points in ref 8 are *syn*-VIIIb 147–149°, *anti*-VIIIb 116–120°, *anti*-VIIIc 78–79°, *syn*-VIIId 118–120°, and *anti*-VIIId 82–84°. [i] This melting point was erroneously given as 111–113° in our previous publication (ref 3).

useful information obtainable from the nmr data is the chemical shifts of the proton *ortho* to the oximino group in the *syn–anti* pair of III. Here the *anti*-III has the OH group oriented *cis* to the *ortho* proton (H_d) which is therefore more deshielded than the corresponding proton in *syn*-III. Such differential shielding on *ortho* protons in *syn* and *anti* isomers is not observed in the I and VIII series possibly due to the difficulty of the benzene ring assuming a conformation coplanar with the oximino group in these compounds.

Owing to scattering of the chemical shifts in the nmr correlation and the difficulty of reproducing the exact conditions in thin layer chromatography (tlc), neither method provides a direct assignment of a *syn* or an *anti* configuration where only one isomer is available. Nevertheless, advantage is taken of the fact that a *syn* and *anti* isomeric pair shows widely separated spots in many solvent systems on a thin layer chromatogram and that the *syn* isomers show yellow spots while the *anti* show dark brown spots on interaction with iodine vapor. Since 2-piperidino- (Va), 2-morpholino- (Vb), 2-pyrrolidino- (Vc), and 2-dimethylaminocyclohexanone oximes (Vd)[13] and 2-piperidinocyclopentanone oxime (VI) are structurally very similar to 2-dimethylaminocyclooctanone oximes (IV), the tlc behavior of the lone isomer of the former group can be compared with the last pair of isomers (*syn*- and *anti*-IV) under the same conditions. The tlc results indicate that these lone isomers move with similar R_f values and show the same coloration as *anti*-IV and therefore must be assigned the *anti* configuration. It is also obvious now that the previously published nmr data[1] of V can be rationalized unequivocally with the *trans* configuration. The similar tlc comparison of the lone isomer of α-(1,2,3,4-tetrahydroisoquinolino)acetophenone oxime[4] (VII) with *syn*- and *anti*-Ia (α-piperidinoacetophenone oxime) fails to give clear-cut indication by R_f value but the coloration with iodine no doubt identifies this compound as the *anti* isomer. It should be mentioned further that due to a complication from steric factors the nmr method could not afford a distinction between *syn* and *anti* configuration[4] of Id. This assignment, however, is neatly resolved on the basis of the tlc mobilities of the two isomers.

Assignment of V and IV to the *anti* configuration brings us to consider the steric factor in the tautomerization of the corresponding C-nitroso compounds IX. The major factors controlling the thermodynamic stabilities of the *syn* and *anti* configurations of these α-amino ketoximes are (i) the steric effects attending at the vicinity of the oximino group and (ii) the strength of intramolecular hydrogen bonding between OH and the lone pair electrons of the amino moieties (see X). The mechanism of intramolecular proton transfer *via* a cyclic transition state, which gives a *syn* configuration, should possess a transition state very similar to the conformation of a *syn*-oxime. Inspection of Dreiding models reveals that for *syn* isomers of IV and V (and larger ring analogs) to assume a conformation capable of hydrogen bonding (see X) the N-alkyl groups are in the eclipsing position with the other two bonds of C-2. This nonbonded interaction no doubt counterbalances the energy gain in intramolecular hydrogen bonding to give a net destabilization of the *syn* configuration. Such destabilization is most obvious in the conformationally less flexible cyclohexanone derivative giving only *anti* isomers. As the ring sizes increase (and, therefore, the flexibility increases) to an eight-membered ring and then to the freely flexible acyclic amino oxime (such as II), the yield of *syn* isomer also increases since the nonbonded interaction can be lessened by twisting the C–N (amine) bond slightly. This twisting also causes a weakening of the intramolecular hydrogen bonding since the lone pair electrons have to rotate away from the C=N–OH plane. These two factors counterbalance each other to yield a net result of the observed *syn–anti* ratio.[3] Owing to the ring strain imposed on the conformation of a five-membered system, the oximino OH and the piperidine in VI are too far apart to make any effective intramolecular hydrogen bonding. The geometry of the transition state in this case is therefore solely decided by steric factors which favor the *anti* isomer as the product in the tautomerization. With the hope of elucidating the relative importance of these two factors, a basic equilibra-

(13) It is pertinent to point out that Fischer and Grob[8] have assigned *anti* configuration to this compound based on steric reasons.

tion of *syn*-Ic and an acid equilibration of *anti*-Id were carried out. These attempts were not successful since the desired isomerization did not occur due to unknown side reactions that prevail even under mild conditions. On an alumina (Brockman activity 1) or on a silicic acid column, isomerization of *anti*-Ic and *syn*-Ib did not take place to an extent[14] that could be detected by means of nmr spectroscopy.

It is shown now that base-catalyzed oximation of α-*t*-aminoacetophenone[4] gives predominantly the *anti* isomer of the corresponding oximes. Thus *anti* isomers of α-piperidino-, α-2-methylpiperidino-, and α-3-methylpiperidinoacetophenone oximes (*anti*-Ia, -Ib, and -Ic) are readily prepared by the oximation process eliminating laborious separation procedures required in the photoaddition route. By this oximation, however, only one isomer of VII is obtained for which *anti* configuration is assigned as discussed before.

Superficially the *anti* isomers of I–IV appear to possess higher melting points than the corresponding *syn* isomer while this trend is reversed in VIII series. The assignment of *syn–anti* isomers in VIII series have been worked out previously by Fischer and Grob,[8] the correctness of which is now further substantiated by nmr data and tlc behavior.

Experimental Section

The nmr spectra were recorded in $CDCl_3$ solution with TMS as an internal standard on a Varian A56/60 spectrometer. The tlc plates were prepared with Gelman aluminum oxide by the standard method. The melting points were recorded on a Fischer-Johns hot stage and were uncorrected.

Photoaddition of Nitrosamines to Olefins.—The photoaddition was carried out following the procedure described in a previous publication.[1] Pure samples of *syn*-VIIIc (from N-nitrosopyrrolidine and styrene), *syn*-VIIId, and *anti*-VIIId (from N-nitrosodimethylamine and styrene) were obtained in this manner.

Oximation of α-Aminoacetophenones.—The α-aminoacetophenones required were prepared fresh each time according to the procedure described.[4] The crude acetophenone prepared in this manner was taken up in 5% sodium hydroxide in methanol containing 2 equiv of hydroxylamine hydrochloride. After refluxing the solution for 20–30 min, the methanol was evaporated and the product extracted with ether. Gy this method, a mixtur of the *syn* and *anti* isomers richer in the latter was usually isolated. The pure specimens of *anti*-Ia, *anti*-Ib, *syn*- and *anti*-VIIIb, *anti*-VIIIc, and *anti*-VIIId were prepared by this method.

Equilibration of *syn*- and *anti*-Oximes.—A pure smple of *syn*-Ic (500 mg) was refluxed for 30 min in methanol (60 ml) containing sodium hydroxide (2 g). After working up in the usual manner, the recovered residue (250 mg) showed infrared and nmr spectra identical with that of *syn*-Ic.

In a methanol solution 0.5 N in hydrochloric acid, *anti*-Ib (340 mg) was dissolved and set aside at room temperature overnight. The recovered crystalline material (135 mg) was shown to be *anti*-Ib by the identical nmr spectrum.

A sample of *anti*-Ic (155 mg) was taken up in chloroform and was absorbed on an alumina column (Brockman activity) for 3 days. The recovered sample (125 mg), washed with 10% methanol in chloroform, showed infrared and nmr spectra identical with *anti*-Ic.

The same experiments performed with *anti*-Ib (340 mg) in a silicic acid column gave the unrearranged *anti*-Ib (324 mg).

Registry No.—*syn*-Ia, 16451-58-4; *anti*-Ia, 16451-59-5; *syn*-Ib, 16451-60-8; *anti*-Ib, 16451-61-9; *syn*-Ic, 16451-62-0; *anti*-Ic, 16451-63-1; *syn*-Id, 16451-64-2; *anti*-Id, 16451-65-3; *anti*-Ie, 16451-66-4; *syn*-II, 16451-67-5; *anti*-II, 16451-68-6; *syn*-III, 16451-69-7; *anti*-III, 16451-70-0; *syn*-IV, 16451-71-1; *anti*-IV, 16451-72-2; *anti*-Va, 16462-51-4; *anti*-Vb, 16451-73-3; *anti*-Vc, 16451-74-4; *anti*-Vd, 16451-75-5; *anti*-VI, 16451-76-6; *anti*-VII, 16451-77-7; *syn*-VIIIb, 16451-78-8; *anti*-VIIIb, 16451-79-9; *syn*-VIIIc, 16451-80-2; *anti*-VIIIc, 16451-81-3; *syn*-VIIId, 16451-82-4; *anti*-VIIId, 16451-83-5.

Acknowledgment.—The authors thank the National Research Council of Canada for their generous support of this work.

(14) Our earlier report[3] that *anti*-Ia was isomerized to *syn*-Ia on a silicic acid column was now shown to be wrong in that the starting material itself was a mixture of *anti*-Ia and *syn*-Ia. In general, *anti*-Ia and other *anti* isomers were isolated by column chromatographs in lesser yields than that indicated by the nmr spectra of the crude mixture. This misled us to state erroneously that *anti*-Ia was isomerized to *syn*-Ia.

Stereospecific Methods of Forming Ethers by Nucleophilic Reactions of 3α-Substituted Tropanes

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Despite the great pharmacological importance of tropine esters, little information is available on chemistry of the ethers of tropine (tropan-3α-ol). Until now, only the benzhydryl ether of tropine and some of its derivatives had been investigated.[1] This prompted the synthesis and the investigation of the properties of other tropine ethers. In the course of this investigation it became evident that the "methyl ether" of tropine described earlier[2] is actually not an O–methyl, but an N-methyl derivate, or in other words it is not an ether but a quaternary salt (methoiodide) of tropine.[3]

Willstätter[4] attempted to synthetize tropine ethers but the reaction of 3α-bromotropane with sodium ethoxide yielded tropene-2, exclusively. We also found that the conventional methods of ether-forming reactions were not applicable to the synthesis of tropine ethers.

It was possible, however, to produce various alkyl and aryl ethers of tropine and pseudotropine (tropan-3β-ol) with stereospecific reactions not previously applied to the synthesis of these compounds. The description of these methods and the stereochemistry of these reactions are the purpose of this short communication.

Tropane 3β-phenyl ether (2) can be obtained stereochemically pure from 3α-mesyloxytropane (tropine methanesulfonate) (1) and sodium phenoxide (see Figure 1).

The reaction of 1 with sodium thiophenoxide led to tropane 3β-phenyl thioether. The formation of this thioether proves that the oxygen of 2 originally came from the phenoxide anion. (For arguments for the β

(1) (a) R. F. Philips, U. S. Patent 2,595.405 (1952); (b) C. H. Nield and W. X. F. Bosch, U. S. Patent 2,782,200 (1956).
(2) Chem. Fabr. Schering, German Patent 106.492 (1900).
(3) K. Nádor, unpublished data.
(4) R. Willstätter, *Ann.*, **326**, 32 (1903).

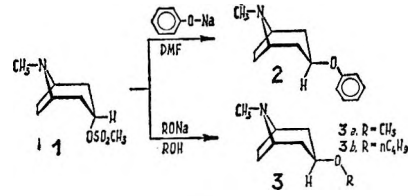

Figure 1.

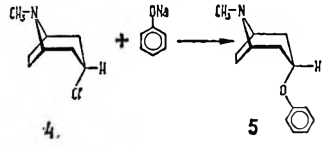

Figure 2.

configuration, see below.) Displacement and elimination of the mesylate group in **1** occurred simultaneously. This was also confirmed by the presence of tropene-2 as the by-product of the reaction.

The synthesis of tropane 3β-alkyl ethers was also carried out. The synthesis of these alkyl ethers from **1** and sodium methoxide and butoxide, respectively, gave significant amounts of tropene-2 as a by-product.

The formation of **2** occurs with the inversion of the mesyloxy group and its substitution by the phenoxy group. Although the rate of reaction depends on the concentrations of both **1** and phenoxide, it is not a pure second-order reaction. The kinetic data (see Table I)

TABLE I

RATE OF REACTION OF TROPINE METHANESULFONATE WITH SODIUM PHENOXIDE IN DMF AT 60.0° [a]

Time, sec	x/a[b]	10^2k_2,[c] l. M^{-1} sec^{-1}	10^2, k_2[d] l M^{-1} sec^{-1}
360	0.239	6.96	6.87
480	0.297	7.05	6.87
600	0.346	7.04	6.90
960	0.458	7.04	6.83
1200	0.515	7.09	6.87
1560	0.579	7.06	6.83
1800	0.617	7.16	6.90
2100	0.653	7.18	6.90
2400	0.685	7.24	6.96
3000	0.731	7.26	6.90
3600	0.768	7.35	6.96

[a] The first-order rate constant, k_1 of solvolysis of the tropine methanesulfonate in DMF at 60.0° is 1.85×10^{-5} sec^{-1}. This value was taken from another of our measurements. [b] a = 0.0125 and also all initial concentrations of both reactants are 0.0125 M. [c] Calculated from the equation $k_2^* = (1/at)[x/(a-x)]$. [d] Calculated[5] from the equation $k_2 = (k_1/a)[\alpha/(1-\alpha)]$, where $\alpha = [e^{-k_1t} + (x/a) - 1]/[(x/a)e^{-k_1t}]$.

suggest a reaction of the SN2 type with simultaneous solvolysis. The second-order rate constants (k_2*) were corrected for the solvolysis,[5] and the values of k_2 obtained are of rather good constancy. Therefore, the reaction is a combination of a bimolecular substitution and a unimolecular solvolysis.

(5) E. Tommila and I. P. Pitkänen, *Acta Chem. Scand.*, **20**, 937 (1966).

The relative configuration of the C-3 atom at **3a** and **b** was determined by cleavage with hydroiodic acid. The product of this reaction was tropan-3β-ol verified by its melting point and by its ir spectrum. Tropan-3α-ol does not react with hydroiodic acid under similar conditions.

Tropane 3α-phenyl ether was obtained from 3α-chlorotropane (**4**) in contrast with the previous observations[4] (see Figure 2). The reaction of **4** with sodium phenoxide in alcoholic solution yields **5**. Tropane 3α-phenyl thioether was also obtained stereochemically pure from **4** and sodium thiophenoxide.

Compound **4** is converted into **5** with retention of configuration (see below). This indicates that this reaction occurs by nitrogen participation *via* an SN1 process in the same way as suggested earlier by Archer[6] for the reaction of 3α-chlorotropane with potassium cyanide.

The two methods found for the synthesis of tropine ethers are stereospecific. The treatment of **1** with sodium phenoxide together with 50% tropene-2 gives nearly 50% tropine phenyl ether. The *in toto* glpc analysis of the reaction compositions has shown that the crude reaction product contained 94–96% β-phenyl ether and 4% α ether. In the case of phenyl ether synthesis from **4**, tropene-2 formation was not detected; in compliance with the gc analysis the crude reaction product contained 80% α- and 20% β-phenyl ether.

The relative configuration of the C-3 atom and the conformation of the isomers **2** and **5** mentioned above were determined by physical–chemical methods.

The ir absorption curves of both **2** and **5** show peaks at 1045 and 1245 cm^{-1}. These bands correspond to the C–O linkages. The main difference between the ir spectra of the two compounds is similar to that of the tropine–pseudotropine system.[7] In the ir spectrum of **2** there is a peak at 1009 cm^{-1}, whereas in that of **5** a peak is at 946 cm^{-1}. As a band at 1020 cm^{-1} appears in the spectrum of pseudotropine and one appears at 958 cm^{-1} in that of tropine, it can be concluded, by analogy, that the configuration of the C-3 atom of **2** is in agreement with the configuration of C-3 of pseudotropine,[8] and the configuration of C-3 of **5** is the same as in tropine. Therefore, **2** is a 3β ether and **5** is a 3α ether.

The nmr spectra of **2** and **5** are markedly different. The hydrogen resonance spectra of **2** and **5** consists of lines at 5.52 and 5.35 ppm., respectively, on the τ scale for the proton attached to the C-3 atom. The band possessing the greater τ value corresponds to the hydrogen attached axially to the C-3 atom. If the position of the hydrogen belonging to the C-3 atom is known, the relative position of the ether linkage can be deduced. These nmr studies also indicated, in agreement with the results of the ir studies, that **2** and **5** have an equatorial (β) and an axial (α) ether linkage, respectively.

Data on the conformations of **2** and **5** were obtained through the determination of their dipole moments. The dipole moments in benzene at 25.00° were 2.15 D

(6) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Amer. Chem. Soc.*, **80**, 4677 (1958).

(7) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(8) (a) G. Fodor, and K. Nádor, *J. Chem. Soc.*, 721 (1953); (b) A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.*, **74**, 5566 (1952).

and 0.94 D for **2** and **5**, respectively. For the calculation of the dipole moment[9] of the possible conformations the following bond moments were used: $\mu_{C-N} = 0.92$ D, $\mu_{C_{Ar}-O} = 1.00$ D, $\mu_{C_{Al}-O} = 1.22$ D. If it is assumed that the piperidine ring in the tropane skeleton has a chair conformation and that the methyl group is attached equatorially to the nitrogen,[10] it is possible to conclude that the conformations of the two ethers are represented by the formulas **2** and **5**; this conclusion is confirmed by the calculated dipole moment values of 2.06 and 0.96 D for **2** and **5**, respectively.

Finally, there is a typical difference between the basicity of **2** and **5**; the pK values determined in methyl Cellosolve–water solution (80:20 w/w)[11] at 25° are 8.06 and 8.42, respectively. Others[12,13] found a similar difference between the pK values of tropine and pseudotropine.

The configurations of the tropane 3α- and 3β-phenyl thioethers are based by analogy for the corresponding 3α- and β-phenyl ethers.

Experimental Section

Melting points are corrected. The given yields refer to analytically pure compounds. The infrared spectra were taken on pressed potassium bromide pellets with a Zeiss Model UR 10 spectrophotometer. Nmr spectra were measured in deuteriochloroform solution at 60 Mc/sec. using tetramethylsilane as an internal reference on an AEI spectrometer. Dipole moments measurements were taken on a Dipolmeter DM 01 instrument; a detailed account will be described in a forthcoming article. For gas chromatographic experiments an Aerograph HY-FI Model 600 apparatus was used. Elemental analyses were carried out by our microanalytical laboratory.

Tropane 3β-Phenyl Ether(2).—To 65.7 g (0.3 mol) of tropine methanesulfonate[6] in 250 ml of DMF was added 36.0 g (0.31 mol) of sodium phenoxide in 250 ml of DMF. The solution was heated on the steam bath for 3 hr. The sodium methanesulfonate was then separated by filtration, washed with ethanol and dried to give 35 g of a white crystalline product. The DMF solution was acidified with 6 N hydrochloric acid to congo red and the DMF was removed by distillation at reduced pressure. To the residue was added 200 ml of water and the solution was extracted several times with ether to remove any nonbasic material. The aqueous layer was saturated with potassium carbonate and extracted three times with 100 ml of chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate, and then the solvent and the main part of the by-product tropene-2 were evaporated at reduced pressure. The residue was distilled, bp 103° (0.06 mm), and was largely solidified, mp 42–46°. The yield of tropane 3β-phenyl ether was 28.75 g (44.2%). Several recrystallizations from petroleum ether (bp 60–80°) gave a colorless substance, mp 51°. The product was shown to be pure by gas chromatography.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.59; H, 8.91; N, 6.76.

For the hydrochloride of **2** the melting point was 282° dec from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.32; H, 8.16; N, 5.58; Cl, 13.90.

Tropane 3β-Methyl Ether (3a).—Sodium (13.8 g) was dissolved in 300 ml of methanol and 109 g (0.5 mol) tropine methanesulfonate in 500 ml of methanol was added. The solution was refluxed for 4 hr. A yield of 59 g of sodium methanesulfonate separated from the solution, a value which corresponds to the amount calculated theoretically. The remaining work-up of the preparation was the same as that for **2**. The tropane 3β-methyl ether after distillation was a colorless oil (29.2 g, 26.6%): bp 90° (15 mm); $n^{20}D$ 1.4776. The usual reaction with hydroiodic acid yielded pseudotropine, mp and mmp 107–108°.

Anal. Calcd for $C_9H_{17}NO$: N, 9.03. Found: N, 9.31.

The hydrochloride melted at 242–243° after recrystallization from ethanol–ether.

Anal. Calcd for $C_9H_{18}ClNO$: C, 56.39; H, 9.47; N, 7.31; Cl, 18.49. Found: C, 56.66; H, 9.56; N, 7.15; Cl, 18.41.

Tropane 3β-n-Butyl Ether (3b).—Its preparation from 0.3 mol of sodium n-butoxide and 43.8 g (0.2 mol) of tropine methanesulfonate in 200 ml of n-butyl alcohol was similar to that of **3a**. The tropane 3β-n-butyl ether was a colorless oil (bp 77–78° (0.4 mm); $n^{20}D$ 1.4708); the yield was 8.3 g (21%). The usual reaction with hydroiodic acid yielded pseudotropine only, mp and mmp 107–108°.

Anal. Calcd for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.27.

For the p-toluenesulfonic acid salt the melting range was 165–165.5°, from ethanol–ether.

Anal. Calcd for $C_{19}H_{31}NO_4S$: C, 61.76; H, 8.46; N, 3.97. Found: C, 61.65; H, 8.46; N, 3.85.

Tropane 3β-Phenyl Thioether.—To 43.8 g (0.2 mol) of tropine methanesulfonate was added 57 g (0.4 mol) of sodium thiophenoxide in 800 ml of DMF. The mixture was heated for 3 hr. The sodium methanesulfonate that separated from the solution corresponds to the amount calculated theoretically. The preparation was the same as for **2**. The thioether was obtained as a colorless oil (22.6 g, 48.5%): bp 144° (0.4 mm); $n^{20}D$ 1.5798.

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 72.27; H, 8.25; N, 6.37; S, 13.45.

The hydrochloride melted at 230–231° after recrystallization from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNS$: C, 62.32; H, 7.47; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 62.32; H, 7.76; N, 5.42; S, 11.57; Cl, 12.90.

Tropane 3α-Phenyl Ether (5).—Sodium phenoxide (69.6 g, 0.6 mol) and 3α-chlorotropane (47.8 g, 0.3 mol) were mixed in 200 ml of ethanol and refluxed for 16 hr. The preparation of **5** was processed similarly to that of **2**. The tropane 3α-phenyl ether (**5**) was distilled at 112–116° (0.3 mm); the yield was 31.0 g (47.6%) and solidified (mp 53°) shortly after recrystallization from n-hexane. This tropine ether was shown to be pure by gas chromatography.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.55; H, 8.99; N, 6.25.

The hydrochloride of **5** had mp 213°, from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.80; H, 8.42; N, 5.38; Cl, 13.75.

Tropane 3α-phenyl thioether was prepared from 47.1 g (0.163 mol) of sodium thiophenoxide and 25.2 g (0.16 mol) of 3α-chlorotropane in 125 ml of alcohol. After refluxing for 5 hr the mixture was processed according to the method described for **2**. The 3α thioether was obtained as a colorless oil in 33.6% yield (12.5 g): bp 125–130° (0.2 mm); $n^{20}D$ 1.5812.

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 72.31; H, 8.46; N, 6.17; S, 13.36. The hydrochloride had mp 214–216°, from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNS$: C, 62.32; H, 7.47; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 62.48; H, 7.28; N, 4.85; S, 12.03; Cl, 12.85.

Kinetic Measurement.—The course of the reaction of tropine methanesulfonate with sodium phenoxide was followed through the measurement of the conductivity of the solution. The increase of the conductivity was proportional to the change in concentration of the reactants. The conductivity was measured with a Metrohm Konduktoskop Type E 365. Further details will be published later.

Registry No.—**2**, 16487-31-3; **2**·HCl, 16487-32-4; **3a**, 16487-33-5; **3a**·HCl, 16487-34-6; **3b**, 16487-35-7; **3b**, p-toluenesulfonic acid salt, 16487-36-8; **5**, 16487-37-9; **5**·HCl, 16487-38-0; tropane 3α-phenyl thioether, 16487-39-1; tropane 3α-phenyl thioether hydrochloride, 16487-40-4; tropane 3β-phenyl thioether, 16487-41-5; tropane 3β-phenyl thioether hydrochloride, 16487-42-6.

(9) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book, Co., Inc., New York, N. Y., 1956, p 16.

(10) R. J. Bishop, G. Fodor, A. R. Katritzky, F. Sóti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc., Sect. C*, 74 (1966).

(11) W. von Simon, *Helv. Chim. Acta*, **41**, 1835 (1958).

(12) H. S. Aaron and C. P. Rader, *J. Org. Chem.*, **29**, 3426 (1964).

(13) P. F. Smith and W. H. Hartung, *J. Amer. Chem. Soc.*, **75**, 3859 (1953).

Photodimerization. II. The Structure and Isomerization of the Photodimer of Crystalline *trans*-Benzalacetone

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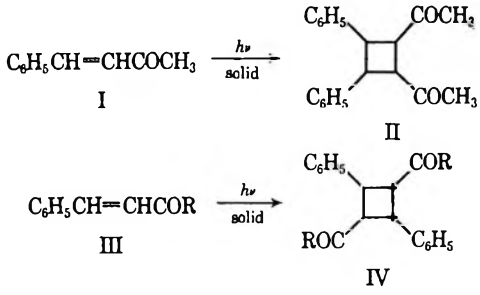
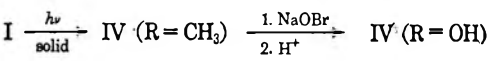
Butenandt reported[1] that the light-induced dimerization of solid benzalacetone (I) proceeded in a head-to-head fashion, leading to II. It is known, however, that various crystalline α,β-unsaturated carbonylic compounds (III, R = OH,[2] OCH_3,[3] C_6H_5[4]) produce photodimers of the α-truxillic type (IV, R = OH, OCH_3, C_6H_5).



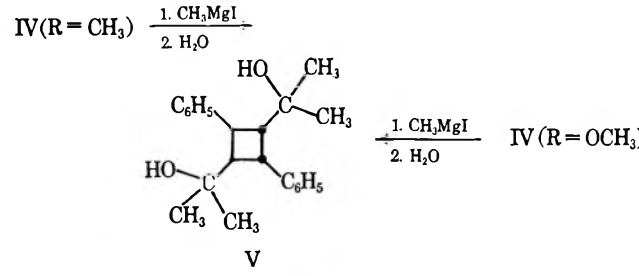
Although one cannot predict the course of a solid-state photodimerization without information concerning the crystal lattice geometry, one may expect that I should dimerize similarly in a head-to-tail fashion. We, therefore, decided to reinvestigate the structure of the photodimer of I.

Upon irradiation of a thin-layer of crystalline I for 8-hours at 10°, by means of a medium pressure ultraviolet lamp, a crystalline dimeric product, which melts at 142–143° (lit.[1] mp 142–143°), was obtained. The infrared spectrum of this dimer, compared to that of I, showed typical saturated carbonylic absorption at 1696 cm^{-1}, and the total absence of olefinic absorption.

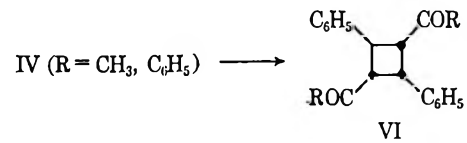
On treating the benzalacetone dimer with sodium hypobromite at 38–40° and subsequent acidification of the reaction mixture, α-truxillic acid (IV, R = OH) was obtained, indicating that the benzalacetone dimer should have structure IV (R = CH_3).



Further unambiguous proof of the correctness of structure IV (R = CH_3) was obtained by treating IV (R = CH_3) with methyl magnesium iodide. Hydrolysis of the reaction mixture led to the isolation of the crystalline derivative V (mp 114–115°). Compound V was additionally synthesized by treating dimethyl α-truxillate[5] (IV, R = OCH_3) with methyl magnesium iodide, followed by hydrolysis of the reaction mixture. Microanalysis showed V to have a molecular formula $C_{22}H_{28}O_2$. Further support for the proposed structure of V was given by its mass spectrum, which showed the molecular ion at *m/e* 324. The infrared spectrum displayed typical hydroxylic absorption (3553 cm^{-1}) and the total absence of carbonyl groups.



The benzalacetone dimer (IV, R = CH_3) appeared to be very unstable in acid or alkaline media. When IV (R = CH_3) was refluxed in ethanol containing hydrochloric acid or sodium hydroxide, complete isomerization to a crystalline product (mp 160–162°) took place. A comparison of the infrared spectra of IV (R = CH_3) and its isomer showed that the 753 and 771 cm^{-1} bands (associated with the aromatic out-of-plane C–H deformation vibration) in the spectrum of IV (R = CH_3) appeared as three bands (738, 761, and 770 cm^{-1}) in the spectrum of its isomer. This splitting is ascribed to steric interference in the isomer.[6,7] The splitting of the carbonylic absorption band (1700, 1709 cm^{-1}) in the spectrum of the isomer and the shift to higher frequency (1696 to 1709 cm^{-1}), can only be brought about by intercarbonylic electrostatic interaction.[7,8] From the spectroscopic data it seems evident that the isomer of IV (R = CH_3) must have the γ-truxillic structure VI (R = CH_3), *i.e.*, a rearrangement analogous to that of bischalkone B(IV, R = C_6H_5) to bischalkone D(VI, R = C_6H_5)[3] must have taken place.

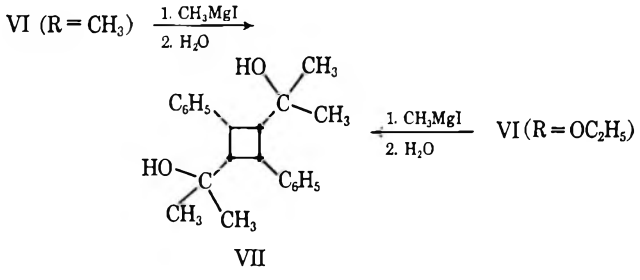


The nmr spectra of the benzalacetone dimer IV (R = CH_3) and its isomer (VI, R = CH_3) both revealed the presence of ten phenyl, six acetyl, and four cyclobutyl protons. A comparison of these two spectra with those of the corresponding truxillic acids (IV, R = OH and VI, R = OH) gave evidence for the correctness of structures IV (R = CH_3) and VI (R = CH_3). Due to the chemical equivalence of the two phenyl groups in both IV (R = CH_3) and α-truxillic acid (IV, R = OH), the signal for the phenyl protons was re-

(1) A. Butenant, *et al.*, *Ann.*, **575**, 123 (1951).
(2) H. Stobbe, *Ber.*, **52**, 666 (1919).
(3) H. Stobbe and K. Bremer, *J. Prakt. Chem.*, **123**, 44 (1929).
(4) C. Liebermann and M. Zsuffa, *Ber.*, **44**, 841 (1911); A. W. K. de Jong, *ibid.*, **56**, 818 (1923).
(5) C. Liebermann, *ibid.*, **21**, 2347 (1888).
(6) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1959, p 77.
(7) J. Dekker, P. Janse van Vuuren, and D. P. Venter, *J. Org. Chem.*, **33**, 464 (1968).
(8) R. N. Jones, P. Humphries, and K. Dobriner, *J. Amer. Chem. Soc.*, **72**, 956 (1950).

corded in each case as a sharp singlet. The splitting of the signal for the phenyl protons in the spectrum of VI (R = CH_3) and VI (R = OH) confirmed the γ-truxillic type structure of the isomer (VI, R = CH_3). The patterns of the signals for the cyclobutyl protons of IV (R = CH_3) and of VI (R = CH_3) were typical of A_2B_2 and ABX_2 systems respectively, resembling those of the corresponding α- and γ-truxillic acids (IV, R = OH and VI, R = OH).

Various attempts to convert VI (R = CH_3) into γ-truxillic acid (VI, R = OH) by means of sodium hypobromite failed, probably on account of steric hindrance. The structural and stereochemical relationship between the isomer (VI, R = CH_3) and γ-truxillic acid (VI, R = OH) was proved unambiguously by converting both the isomer (VI, R = CH_3) and diethyl γ-truxillate (VI, R = OC_2H_5)[9] by means of methyl magnesium iodide into a common crystalline derivative (VII, mp 125–126°). The mass spectrum of VII, of which the microanalysis corresponds with $C_{22}H_{28}O_2$, showed the molecular ion at *m/e* 324. The infrared spectrum exhibited typical hydroxylic absorption (3576 cm^{-1}) and the total absence of carbonyl groups.



VII

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 221 spectrophotometer. Mass spectra were obtained on a M.S. 9 mass spectrometer. Nmr spectra were recorded on a Varian A60 apparatus. Melting points were determined on a Gallenkamp (design no 889339) apparatus and are uncorrected.

A. Photodimerization of Crystalline I.—Molten benzalacetone (I, 1 g) was allowed to solidify in a thin layer in a Duran 50 test tube and irradiated for 8 hr, at 10°, by means of a medium pressure uv lamp. The reaction mixture was fractionally recrystallized from ethanol, yielding colorless needles (0.13 g) of IV (R = CH_3): mp 142–143° (lit.[1] 142–143°); ir (KBr), 3053 w, 3026 w, 2949 m, 2914 w, 1696 s, 1599 w, 1491 m, 1446 m, 1419 w, 1368 s, 1360 s, 1338 w, 1261 m, 1230 w, 1180 m, 1169 s, 1127 w, 1087 w, 1030 w, 789 w, 771 m, 753 s, 717 m, and 700 s cm^{-1}; nmr ($CDCl_3$), τ 8.37 (6 H), 6.27–5.2 (m, 4 H), and 2.7 (s, 10 H); mass of molecular ion, *m/e* 292.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.17; H, 6.896. Found: C, 81.79; H, 6.98.

B. Reaction of IV (R = CH_3) with Sodium Hypobromite.—A solution of NaOBr (0.42 g of NaOH, 0.44 g of Br_2, 2 ml of water) was added to a solution of IV (R = CH_3, 0.1 g) in dioxane (1.5 ml) over a period of 30 min. The reaction temperature was kept between 38 and 40°. The reaction mixture was stirred for a further period of 15 min, followed by the addition of 10 ml of water; 5 ml of solvent was distilled off under diminished pressure (18 mm). The reaction mixture was filtered. Acidification of the filtrate with dilute HCl led to a white precipitate. Recrystallization from aqueous ethanol yielded 0.017 g of α-truxillic acid, mp 270–273° (lit.[2] mp 273°); identification was by ir spectroscopy.

C. Isomerization of IV (R = CH_3). 1. In Acidic Medium.—Compound IV (R = CH_3, 0.1 g) was refluxed for 2 hr in ethanolic HCl (0.5 *N*, 6 ml). The reaction mixture was diluted with water (30 ml) and extracted with benzene. The extract was washed successively with 5% $NaHCO_3$ and water, and dried (Na_2SO_4). On evaporation of the solvent, a solid residue was obtained. Recrystallization from benzene–petroleum ether (bp 60–80°) yielded colorless needles of VI (R = CH_3, 0.07 g): mp 160–162°; ir (KBr), 3052 w, 3018 w, 2993 w, 2947 w, 2895 w, 1709 s, 1700 s, 1597 w, 1490 s, 1450 w, 1442 m, 1420 w, 1361 s, 1332 w, 1218 w, 1186 s, 1086 w, 1031 w, 949 w, 770 s, 761 m, 738 m, 717 w, and 698 s cm^{-1}; nmr ($CDCl_3$), τ 8.38 (6 H), 6.52–5.0 (m, 4 H), and 2.78 (d, 10 H); mass of molecular ion, *m/e* 292.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.17; H, 6.896. Found: C, 82.01; H, 7.124.

2. In Alkaline Medium.—Compound IV (R = CH_3, 0.15 g) was refluxed for 2 hr in ethanolic KOH (5%, 6 ml). The reaction mixture was diluted with water (30 ml), acidified with 1 *N* HCl, and extracted with benzene. The extract was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and chromatographed over alumina. Evaporation of the solvent produced a solid, which was recrystallized from benzene–petroleum ether (bp 60–80°) as colorless needles (mp 160–162°, 0.1 g). The ir spectrum was identical with that of VI (R = CH_3).

D. Preparation of V. 1. From IV (R = CH_3).—A mixture of IV (R = CH_3, 0.1 g) and a concentrated solution of CH_3MgI in ether (4.1 *M*, 5 ml) was stirred magnetically in a glass-stoppered 25-ml, round-bottom flask until a clear solution was obtained[10] (usually within 30 min). The reaction mixture was treated carefully with excess 0.5 *N* HCl (10 ml) and extracted with ether. The extract was washed successively with 5% $NaHCO_3$, 5% $Na_2S_2O_3$, and water and dried (Na_2SO_4). Evaporation of the solvent yielded a crystalline product (V, 0.104 g) which was recrystallized from petroleum ether (bp 50–70°) as colorless needles: mp 114–115°; ir (KBr), 3553 s, 3063 w, 3030 w, 3002 m, 2980 s, 2970 s, 2932 m, 2914 m, 1600 m, 1580 w, 1491 m, 1460 w, 1448 m, 1380 m, 1365 m, 1337 w, 1310 w, 1260 w, 1228 m, 1211 m, 1189 m, 1166 m, 1121 s, 1077 w, 1031 m, 1000 w, 958 m, 945 m, 906 m, 856 m, 827 w, 798 w, 764 s, 730 w, 700 s, and 653 w cm^{-1}; mass of molecular ion, *m/e* 324.

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.57; H, 8.69.

2. From IV (R = OCH_3).—A mixture of IV (R = OCH_3, 0.1 g) and a solution of CH_3MgI in ether (4.1 *M*, 7 ml) was treated as above to yield 0.093 g of product, mp 114–115°. The ir spectrum was identical with that of the product found in procedure D-1.

E. Preparation of VII. 1. From VI (R = CH_3).—A mixture of VI (R = CH_3, 0.1 g) and a solution of CH_3MgI in ether (4.1 *M*, 5 ml) was treated as above. Recrystallization of the product (0.105 g) from petroleum ether (bp 50–70°) yielded colorless needles: mp 125–126°; ir (KBr), 3576 s, 3065 w, 3032 w, 2977 s, 2938 m, 1600 m, 1582 w, 1490 m, 1450 m, 1364 m, 1313 w, 1271 w, 1232 w, 1201 w, 1172 m, 1125 m, 1100 w, 1083 w, 1065 w, 1045 w, 958 m, 926 w, 891 w, 851 w, 831 s, 761 s, 701 s, and 698 s cm^{-1}; mass of molecular ion, *m/e* 324.

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.65; H, 8.62.

2. From VI (R = OC_2H_5).—A mixture of VI (R = OC_2H_5, 0.1 g) and a solution of CH_3MgI (4.1 *M*, 7 ml) was treated as above to yield 0.087 g of product, mp 125–126°. The ir spectrum was identical with that of the product found in procedure E-1.

F. The nmr spectra (DMSO) of the α- and γ-truxillic acids (IV, R = OH, and VI, R = OH) showed signals at τ 6.28–5.44 (m, 4 H) and 2.62 (s, 10 H) and at τ 6.53–5.28 (m, 4 H) and 2.63 (d, 10 H), respectively. In neither case was any signals for hydroxylic protons observed.

Registry No.—IV (R = OH) 16607-21-9; IV (R = CH_3) 16607-22-0; V, 16607-23-1; VI (R = OH) 16607-24-2; VI (R = CH_3) 16607-25-3; VII, 16607-26-4.

Acknowledgment.—The authors are indebted to the Council for Scientific and Industrial Research of South Africa for financial support and for a postgraduate grant to T. G. D.

(9) C. Liebermann, *Ber.*, **22**, 2243 (1889).

(10) The reaction in which concentrated Grignard reagents are employed at room temperature (in contrast to the conventional method, in which the Grignard reaction is carried out under reflux in dilute solution) proceeds fast and practically quantitatively. This modified method was developed in our laboratory and finds its most valuable application in the case of highly insoluble substrates. The development of a clear solution indicates completion of the reaction.

Heterocyclic Amines. II. Synthesis of 3,5-Diaminopyrazole[1]

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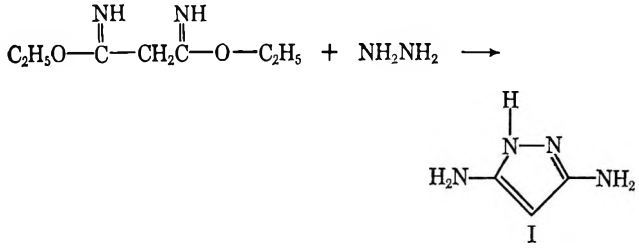
A number of unsuccessful attempts to prepare 3,5-diaminopyrazole (I) have appeared in the literature. The reaction of hydrazine with malononitrile, originally reported as a route to I,[2] has been shown by Taylor and



Hartke[3] to lead instead to 3-cyanomethyl-4-cyano-5-aminopyrazole. In another approach, an attempted Curtius reaction starting with diethyl pyrazole-3,5-dicarboxylate, provided a syrup that was incompletely characterized.[4] Finally, phenylhydrazine and phenethylhydrazine were recently reported to react with ethyl 2-cyanoacetimidate hydrochloride to form corresponding 1-substituted 3,5-diaminopyrazoles in yields of 22 and 9%, respectively.[5] However, attempts to extend this reaction to hydrazine itself were unsuccessful.[5]

Our attention was drawn to this work by a continuing interest in heterocyclic amines as potential insect-sterilizing agents.[1,6] It occurred to us that reaction of hydrazines with a suitable diimidic ester, under the mild conditions of Pinner's synthesis of amidines,[7] could lead to formation of 3,5-diaminopyrazoles.

When equimolar amounts of hydrazine and diethyl malonimidate were dissolved in warm ethanol and combined, an immediate exothermic reaction occurred. Subsequent chilling of the reaction mixture caused 3,5-diaminopyrazole (I) to precipitate in 78% yield. Analogous reactions with methylhydrazine and, utilizing a somewhat longer reaction time, with phenylhydrazine, provided the 1-methyl and 1-phenyl derivatives of I. Ultraviolet spectra of the basic and protonated forms of the products, as well as infrared and nmr spectra were consistent with pyrazole structures.

(1) Part I: J. A. Settepani and A. B. Borkovec, *J. Heterocycl. Chem.*, **3**, 188 (1966).

(2) R. von Rothenburg, *Ber.*, **27**, 685 (1894).

(3) E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.*, **81**, 2452 (1959).

(4) L. Knorr, *Ber.*, **37**, 3520 (1904).

(5) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *J. Org. Chem.*, **29**, 942 (1964).

(6) A. B. Borkovec and A. B. DeMilo, *J. Med. Chem.*, **10**, 457 (1967). For a recent review of this subject, see A. B. Borkovec, "Insect Chemosterilants," Interscience Publishers, New York, N. Y., 1966.

(7) R. L. Shriner and F. W. Newmann, *Chem. Rev.*, **35**, 351 (1944).

The predominant tautomeric form of various aminopyrazoles has been the subject of a number of recent publications.[8] Although we have not undertaken a similar determination in the present study, an nmr spectrum of I recorded in D_6-methyl sulfoxide solution [τ 4.70 (5 H), 5.42 (1 H)] is clearly inconsistent with any tautomer that does not possess an sp^2 carbon atom at position 4.

Electrophilic substitution of I occurred quite readily in aqueous bromine to provide a sample of 3,5-diamino-4-bromopyrazole.

Experimental Section

3,5-Diaminopyrazole (I).—A solution of 95% hydrazine hydrate (0.1 mol) in 50 ml of ethanol was warmed to boiling before adding 15.8 g (0.1 mol) of diethyl malonimidate[9] at such a rate that the mixture continued to reflux without external heating. Five minutes after the addition of the ester, the reaction mixture was chilled causing precipitation of 7.6 g (78%) of I. On recrystallization from isopropyl alcohol an analyical sample was obtained: mp 110°; ir (KBr), 3350, 3250, 1560, 1470, 1040, 970, and 720 cm^{-1}; uv max (95% EtOH), 217 mμ (ϵ 9400), cation 237 mμ (ϵ 18,500).

Anal. Calcd for $C_3H_6N_4$: C, 36.73; H, 6.16; N, 57.11. Found: C, 36.89; H, 6.30; N, 57.06.

3,5-Diamino-1-methylpyrazole.—To a stirred refluxing solution of 1.84 g (0.04 mol) of methylhydrazine in 50 ml of ethanol was added, under nitrogen, 6.3 g (0.04 mol) of diethyl maloimidate. Warming was continued for 5 min after the addition, and the mixture was then concentrated *in vacuo* to an oil. Crystallization from acetonitrile–ether provided 4.5 g (80%) of colorless plates, mp 51–53°. Purification was accomplished by sublimation: 75° (0.5 mm); mp 54°; ir (KBr), 3280, 3150, 1620, 1560, 1490, 1440, 1270, and 1000 cm^{-1}; uv (95% EtOH), 220 mμ (ϵ 10,500), cation 241 mμ (ϵ 18,200).

Anal. Calcd for $C_4H_8N_4$: C, 42.85; H, 7.19; N, 49.96. Found: C, 42.85; H, 7.20; N, 49.78.

3,5-Diamino-1-phenylpyrazole.—A solution of phenylhydrazine (1.08 g, 0.01 mol) and diethyl malonimidate (1.58 g, 0.01 mol) in 75 ml of methanol was refluxed under nitrogen for 12 hr. The chilled reaction mixture was acidified with 1 ml of concentrated HCl and concentrated to dryness. Three recrystallizations of the residue from ethanol–ether provided 1.3 g (62%) of 3,5-diamino-1-phenylpyrazole hydrochloride, mp 229–230° dec (mmp 229–230° dec with an authentic specimen).[5]

3,5-Diamino-4-bromopyrazole.—A solution of 1.6 g (0.01 mol) of bromine in 150 ml of water was added dropwise with stirring to 0.98 g (0.01 mol) of 3,5-diaminopyrazole dissolved in 50 ml of water. The dark reaction mixture was then warmed to 80°, treated with activated charcoal, and filtered. The pale yellow filtrate was neutralized (Na_2CO_3) and concentrated *in vacuo* to dryness. Extraction of the residue with absolute ethanol, followed by concentration and chilling afforded 1.2 g (68%) of 3,5-diamino-4-bromopyrazole, mp 133–134° dec. An analytical sample was recrystallized from ethanol–ether: mp 135–136° dec; ir, 3410, 3370, 3280, 3140, 1610, 1490, 1440, 1345, and 1020 cm^{-1}; uv (95% EtOH), 222 mμ (ϵ 9200) cation 244 mμ (ϵ 14,200).

Anal. Calcd for $C_3H_5BrN_4$: C, 20.36; H, 2.85; Br, 45.14; N, 31.65. Found: C, 20.61; H, 2.79; Br, 44.94; N, 31.70.

Registry No.—I, 16082-33-0; 3,5-diamino-1-methylpyrazole, 16675-35-7; 3,5-diamino-4-bromopyrazole, 16675-36-8.

(8) V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, *Zh. Obshch. Khim.*, **34**, 654 (1964); V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, *ibid.*, **35**, 1288 (1965); H. Dorn and H. Dilcher, *Ann. Chem.*, **707**, 141 (1967).

(9) S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.*, **71**, 40 (1949).